Clinical Study Report

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AN OPEN-LABEL, MULTI-CENTER, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY OF EVENAMIDE AS ADD-ON TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA (TRS) NOT RESPONDING ADEQUATELY TO THEIR CURRENT ANTIPSYCHOTIC MEDICATION.

Investigational Medicinal Product	Evenamide (NW-3509)
Indication studied	Treatment-Resistant Schizophrenia
Protocol number	NW-3509/015/II/2019
EudraCT number	2020-000439-32
Development Phase	Phase II
First subject enrolled	29-Jan-2021
Last subject completed	04-Nov-2023
Company/Sponsor signatory	Ravi Anand MD, Chief Medical Officer Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano), Italy
Study Duration	29-Jan-2021 to 04-Nov-2023
Date of Report	08-July-2024

This clinical study report covers the study period up to and including the 46-week visit (A separate report will be prepared for the study period beyond 46 weeks)

This study was conducted in compliance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Name of Sponsor: Newron Pharmaceuticals S.p.A.	**Individual Study Table**	**(For National Authority Use only)**
Name of Investigational Medicinal Product: Evenamide (NW-3509)		

Title of Study:

An open-label, multi-center, extension study to evaluate the long-term safety, tolerability, and preliminary efficacy of evenamide as add-on treatment up to 46 weeks in patients with treatment-resistant schizophrenia (TRS) not responding adequately to their current antipsychotic medication.

Investigators: A total of 13 Principal Investigators (9 in India, 3 in Sri Lanka, and 1 in Italy) took part in the study.

Study Centers: The study was conducted at 13 centers (9 in India, 3 in Sri Lanka, and 1 in Italy).

Publication (Reference): None

Phase of Development: II

Study Period: 29-Jan-2021 to 04-Nov-2023

Study Objectives:

Primary:

- To evaluate the long-term safety and tolerability of evenamide given orally in patients with treatment-resistant schizophrenia (TRS) not responding adequately to their current antipsychotic medication.

Secondary:

- To evaluate preliminary long-term efficacy of evenamide, based on symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S)
- To determine the long-term effect of evenamide on daily functioning, based on changes on the Strauss-Carpenter Level of Functioning (LOF) scale.

Study Design and Methods:

This was a 46-week, open-label, multi-center, extension to Study NW-3509/014/II/2019 (Study 014) designed to evaluate the long-term safety, tolerability, and preliminary efficacy of evenamide as add-on treatment in patients with TRS on a stable therapeutic dose of an antipsychotic. In Study 014, after 50 patients were randomized equally (1:1) to the 7.5 mg *bid* (n=26) and 15 mg *bid* doses (n=24) and completed their participation in the study, key safety data from these patients were reviewed by an Independent Safety Monitoring Board (ISMB). This review of the data indicated that there were no safety issues, therefore, the 30 mg *bid* dose group was initiated, and randomization was continued, with patients being randomized 1:1:2 to doses of 7.5, 15 and 30 mg *bid*. Subsequently, the Study 014 protocol was amended to discontinue the 7.5 mg *bid* dose group, and to randomize patients 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. Similarly, the Study 015 protocol was also amended (*Amendment 4, dated 18th June 2021*) to discontinue the 7.5 mg *BID* dose group.

Patients randomized to participate in Study 014 who had completed 6 weeks of open-label treatment, that were not experiencing moderate/severe side effects, and had not shown severe worsening of their symptoms of schizophrenia, and who met other entry criteria for this study were considered as eligible to receive evenamide in this open-label extension study (Study 015) for up to 46 weeks, so that the patients could receive evenamide for a total treatment period of 52 weeks (6 Weeks of Study 014 and 46 Weeks of Study 015). The duration of Study 015 was further extended by an additional 24 weeks (*Amendment 4.1, dated 30th November 2021*), and by an additional 24 weeks (*Amendment 4.2, 08th July 2022*) in India. Therefore, the total study duration will be 94 weeks; however, this clinical study report describes the data up to and including Week 46, and a separate report will be prepared for the data from the study period beyond 46 weeks.

A total of 153 subjects completed Study 014. Of these subjects, 144 consented to enter and rolled over into the extension Study 015. This includes 40 (88.9%), 41 (77.4%) and 40 (87.0%) subjects from 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* treated groups, respectively. In Study 015, 121 (84.0%) subjects completed the study through 46 weeks. This includes 40 (88.9%), 41 (77.4%) and 40 (87.0%) subjects from 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* treated groups, respectively.

Patients randomized to doses of 7.5 mg *bid*, 15 mg *bid* or 30 mg *bid* in Study 014 continued treatment in Study 015 on the same dose of evenamide that they received on the last day (Day 43) of the prior study; however, after implementation of protocol *Amendment 4, dated 18th June 2021,* the patients randomized to the 7.5 mg *bid* dose in Study 014 had their dose increased to 15 mg *bid* upon entry into Study 015, while the patients already enrolled in Study 015 at the 7.5 mg *bid* dose had their dose increased to 15 mg *bid* at their next scheduled clinic visit

Synopsis Table 1: Planned Doses by Dosing Type in each Treatment Groups

	Randomized Treatment Group (from Study 014)		
Dose Type	**Evenamide 7.5 mg *bid******	**Evenamide 15 mg *bid***	**Evenamide 30 mg *bid***
Starting Dose*	7.5 mg *bid*	15 mg *bid*	30 mg *bid*
Target Dose	7.5 mg *bid*	15 mg *bid*	30 mg *bid*
Drop-back Dose **	7.5 mg *od*	15 mg *od*	30 mg *od*

**Patients who were receiving once daily dosing at the end of Study 014 continued on once daily dosing at their current dose level in this extension study. These patients could be given an increase to bid dosing at a subsequent scheduled visit, if the Investigator felt it was warranted.*

*** If the Starting/Target Dose (bid) was not tolerated, a dose reduction to once daily (od) dosing (Drop-back Dose) was to be performed.*

**** The 7.5 mg bid dose was discontinued after the protocol amendment (Amendment 4, dated 18th June 2021) had been implemented, and any ongoing patients receiving a dose of 7.5 mg bid were switched to 15 mg bid at their next visit if already in Study 015, or at Day 1 if entering Study 015 after completion of Study 014.*

If intolerance developed, the dose could be reduced to once daily (od) dosing. If the reduced dose was well tolerated, an increase to the target dose was to be attempted at the next scheduled visit. If intolerance developed again after increasing the dose, the dose was to be reduced to once daily (od) dosing and the patient was to be continued for the remainder of the study at this reduced dose.

The dose of study medication was to be taken with food or after a meal. Any other medications were to be taken according to their usual schedule. On the day of each scheduled clinic visit, patients were reminded to take their medications at their residence according to their usual schedule, and to bring their study medication bottles with them to the clinic for adherence assessment. If no significant safety or tolerability issues were identified during the study visits, the patients were dispensed their study medication according to the planned dosing schedule. At discharge from the clinic, patients were reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

Baseline (Day 0 of Study 014)

Study 014 baseline values were used for assessing changes from baseline for safety and efficacy parameters for this extension study. The initial visit of Study 015 overlapped with the Day 43 visit from Study 014. Patients who completed Study 014 were required to provide informed consent in writing and satisfy all selection criteria for Study 015 prior to enrollment.

46-Week Extension Treatment Period

On Day 1, after all final Study 014 (Day 43) evaluations were completed, patients meeting all entry criteria were given a supply of study medication at their current dose to cover the period until the next scheduled visit. Patients were instructed to take their first dose in the evening at their residence, at least 6 hours after the last dose in Study 014 that they had received in the morning in the clinic.

Throughout the treatment period, at each scheduled visit or telephone contact, careful open-ended questioning was used to evaluate whether the patient had experiencing symptoms and/or signs suggestive of neurological side-effects, severe sedation, seizures (see *Appendix 4 of protocol version 5.0, 18th June 2021*), or any other symptoms that were dose-limiting, e.g., hypotension. In case the patient reported any of these symptoms, the patient was asked to contact the Principal Investigator, who decided, based on the symptoms/signs that had been identified, whether the patient had to come in for an evaluation, whether their dosing regimen required modification, and/or whether a concomitant medication was added. In cases where further evaluation of the patient confirmed symptoms or signs suggestive of treatment toxicity, the Investigator decided on the appropriate therapeutic and diagnostic measures. These may have included hospitalization, performance of a full neurological examination, EEG, ECG, etc.

The patient was required to return to the clinic for scheduled visits at Weeks 6, 12, 18, 24 and 36. During these visits selected safety and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. If no safety or tolerability issues were detected, the patients continued to receive their current dose. The patient was discharged from the clinic and was given a supply of study medication for the next period of dosing. After Week 24, the patient received a telephone contact from the Investigator/site staff at Weeks 30 and 41, midway between scheduled clinic visits, to inquire regarding any safety or tolerability issues that he/she had experienced, and his/her usage of any concomitant medications. Based on this report, the patient's dose could be reduced to once daily dosing, or if significant tolerability issues were noted at the current dose level, the patient was asked to return for an unscheduled visit.

The patient returned for the final evaluation at Week 46 (or at early discontinuation), at which time all final safety [vital signs (including waist circumference), 12-lead ECG, laboratory tests, ESRS-A, CDSS, physical/neurological examinations, and standard eye examination] and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. A urine drug screen was also performed.

Safety Follow-up Evaluation

For patients who were discontinued prematurely, as well as those who had completed 46 weeks of treatment in this open-label extension study and did not continue further extension treatment, a safety follow-up visit was performed

approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. Patients who did not return to the clinic for their 7-day safety follow-up visit were to be contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patients were contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

Hospitalization

Generally, patients came to the clinic for scheduled visits and returned to their home or residential care facility after all evaluations were completed. However, if the Investigator felt it was necessary for safety or other reasons, a patient could be hospitalized.

Study Population:

A total of 153 subjects completed the antecedent study, Study 014. Of these subjects, 144 consented to enter and rolled over into the extension Study 015.

Diagnosis and Main Criteria for Eligibility:
Inclusion Criteria

The patients who met all of the following inclusion criteria were eligible for enrolment into the study:

1. Patient completed 6 weeks of treatment in Study 014.
2. Patient had provided written informed consent for this extension study.
3. If female, patient was not of childbearing potential, pregnant or breastfeeding.
   For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with highly effective contraception, i.e. barrier method in combination with an oral hormonal contraceptive, or long-acting hormonal contraceptive alone (Amendment 3, dated 22nd September 2020)

Exclusion Criteria:

The presence of any of the following excluded a patient from study enrolment:

1. Patient violated any requirement of the protocol in Study 014 that would have put him/her at risk for continuing treatment with evenamide in Study 015.
2. In the Investigator's opinion, the patient had a significant worsening of risk for suicidality during Study 014.
3. Patients experiencing any moderate/severe neurological side effects, other than pre-existing EPS related to antipsychotic treatment prior to enrolling in Study 014.
4. Patient had shown significant worsening of his/her symptoms of schizophrenia between baseline and the final assessment during the 6-week treatment period in Study 014, such that continuing treatment in Study 015 is considered undesirable.
5. Patient demonstrated substantial non-compliance with dosing of the study medication in Study 014.

Identity of Investigational Medicinal Product, Mode of Administration and Batch Number: The study medication (Evenamide) was administered orally twice daily (*bid*) as 7.5-mg, 15-mg, and 30-mg dosage strengths of evenamide capsules. Information on the batches for each of the dosage strengths of evenamide capsules used in the study is provided in Synopsis Table 2.

Synopsis Table 2. Batch Information for each Evenamide Capsule Strength

Investigational Product Name	Formulation	Route	Manufacturing Authorization Holder	Strength	Batch Numbers
Evenamide (NW-3509)	Hard gelatin capsules	Oral	Newron Pharmaceuticals S.p.A.	7.5mg	17244/13 17244/19 17244/7 17244/4 17244/10 17244/16
				15 mg	17244/11 17244/42 17244/40 17244/24 17244/17 17244/5 17244/14 17244/20 17244/8
				30 mg	17244/12 17244/25 17244/43 17244/41 17244/18 17244/6 17244/9 17244/15 17244/21

Study medication with each different dosage (7.5, 15 and 30 mg of evenamide) was provided in 30 ml HDPE bottles. A 6-, 10- or 12-week supply of study medication was dispensed at the appropriate dose level for the specific visit for each patient.

Duration of Treatment: The treatment period of the study lasted up to 46 weeks, followed by a 7-day safety follow-up period for patients who did not continue further extension treatment. A separate report will be prepared for the study period beyond 46 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation and Endpoints:
Safety Evaluations – Primary Safety Objective
Safety was assessed by the following:

- Adverse events (AEs)
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature, respiratory rate, body weight, BMI, waist circumference)
- Laboratory evaluations (hematology, blood chemistry, and urinalysis; serum prolactin)
- Electrocardiogram (ECG) – 12-lead standard
- Physical examination
- Neurological examinatio
- Standard eye examination – visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and front part of eyes (eyelids, cornea, conjunctiva, sclera, and iris)
- Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)
- Calgary Depression Scale for Schizophrenia (CDSS).

All changes in safety parameters were assessed versus the baseline values of Study 014.

Preliminary Efficacy Evaluations

Preliminary Long-term Efficacy was assessed by the following measures:

- PANSS total score - mean change from baseline to endpoint
- CGI-S – mean change from baseline to endpoint
- CGI-C – proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3), and mean score at endpoint
- PANSS – Positive Symptoms total score – mean change from baseline to endpoint
- PANSS – General Psychopathology total score – mean change from baseline to endpoint
- LOF – mean change from baseline to endpoint
- PANSS – Negative Symptoms total score – mean change from baseline to endpoint.

All changes in efficacy parameters were assessed versus the baseline values of Study 014.

Safety Monitoring Board

Safety data from all patients were examined periodically by an Independent Safety Monitoring Board (ISMB). The ISMB could have requested modifications to the study design or termination of the study, if any significant safety concerns became evident, but allowed the study to continue as planned.

Statistical Methods:

Sample Size: A total of 153 subjects completed Study 014. Of these subjects, 144 consented to enter and rolled over into the extension Study 015.

Patient Characteristics: The background and demographic characteristics (age, race, ethnicity, weight, height, smoking history, education, past and current medical conditions, etc.) and disease characteristics (severity of illness, duration of illness, concomitant psychotropic medication, etc.) were collected at screening in Study 014 and were used to describe the patients enrolled in this extension study. Continuous variables were summarized by minimum, maximum, mean, median, and standard deviation, and discrete variables were summarized using frequencies and percentages.

Analysis Populations:

The Safety population consisted of all subjects who took at least one dose of study medication in this extension study. The efficacy analyses were performed on a modified intent-to-treat (mITT) population comprising all patients who had a valid Study 014 baseline value, entered into Study 015, and received at least one dose of the study medication

in this extension study, and had at least one post-baseline (Study 015) assessment for the primary efficacy measure, the PANSS total score. Analyses were conducted on randomized treatment groups, and additional analyses were performed, in which all patients' data were combined in a single evenamide treatment group for the analysis of the efficacy measures (PANSS, CGI-S, CGI-C, and LOF) in this open-label extension study. An additional mITT completers (mITT-C) population was defined, which includes subjects in the mITT population who completed the 46-week study period.

Safety Analysis:

The safety population was used for the analysis of all safety variables. The safety analysis for patients enrolled in Study 015 included all safety data collected from the time of the first dose of study medication in this study and used the baseline values of all safety parameters from Study 014 as the baseline values. All AEs were summarized by body system and preferred term. The incidence (%) of SAEs, AEs that were newly occurring or worsened after administration of study medication in this extension study (i.e., treatment-emergent AEs [TEAEs]), and AEs leading to discontinuation (ADOs), were also summarized; the severity of each AE and relatedness to study medication was assessed and presented. Changes from baseline (Study 015) at each visit and at endpoint (Week 46 or early discontinuation) for vital signs, ECG and laboratory values, and findings on the physical/neurological examinations and standard eye examination, were summarized, with abnormal and clinically notable values/findings identified. Mean changes from baseline (Study 015) in the total score and sub-scale scores on the ESRS-A, and total score on the CDSS, were presented.

Preliminary Efficacy Analysis:

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) were provided for all continuous long-term efficacy measures for actual values and changes from baseline (Study 015) at each time-point. The changes from baseline (Study 014) to endpoint (Week 46 or early discontinuation) for each of the continuous measures were analyzed using a paired t-test. For categorical variables, the number and percentage of patients in each category was presented at each time-point.

If patients showed significant worsening, the investigators were permitted to intervene with whatever measures they deemed necessary to assure patient safety, e.g., administration of rescue medication or hospitalization. Investigators were requested to perform all efficacy assessments prior to the intervention, and these served as the final assessments for analysis purposes. Subjects were allowed to continue treatment with evenamide after the intervention, and all pre and post-intervention safety and efficacy data were to be collected according to the study protocol, but post-intervention data were censored in some analyses.

Mean values and mean changes from baseline (Study 014) to endpoint (Week 46 or early discontinuation) on the PANSS total score were presented. The mean score at each visit and at endpoint (Week 46 or early discontinuation) for the CGI-S and CGI-C were presented. The distribution of patients by each category of change and the proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3) on the CGI-C was provided. Mean values and mean changes from baseline (Study 014) to endpoint on the total scores on the PANSS – Positive Symptoms sub-scale, LOF, CGI-S, PANSS – General Psychopathology sub-scale, and PANSS – Negative Symptoms sub-scale were presented.

Summary – Conclusions:

Safety Results:

- A total of 40 (27.8%) out of 144 subjects who entered in Study 015 reported at least one TEAE. Slightly less subjects in the evenamide 30 mg bid treatment group, 23.9% (11/46), reported at least one TEAE, compared with 31.1% (14/45) and 28.3% (15/53) for evenamide 7.5 mg and 15 mg bid, respectively.
- The majority of subjects who experienced TEAEs had events rated as mild - 67.5% (27/40). TEAEs of moderate intensity were reported for 25% (10/40) of subjects, while those considered severe were reported for only 7.5% (3/40) of subjects.
- One death (sudden death) of a male subject treated with evenamide 30 mg bid, for which a causal relationship could not be fully excluded, was reported.
- The number of subjects with at least one Serious TEAE reported was 2 (1.4%): the case of death described above and one subject who experienced, dilutional hyponatremia and acute symptomatic seizure, with an onset 26 days after the last dose of study medication, that were considered not related to study medication.
- Two subjects (1.4%) discontinued study medication due to a TEAE: the case of death (sudden death), and one subjects on evenamide 15 mg bid, who experienced disturbance in attention, hyperhidrosis, and somnolence (serious, severe and possibly related for the case of death; and non-serious, moderate and possibly related for the case of somnolence).
- The most frequently reported TEAEs by SOC (≥5% incidence of events in overall subjects) were 'Investigations' and 'Psychiatric disorders', with 10 (6.9%) and 9 (6.3%) subjects, respectively. No TEAE by Preferred term (PT) was reported with a frequence ≥5%.
- The most frequent TEAEs (≥2% incidence) in the overall safety population were: blood cholesterol increased, blood CPK increase, insomnia, schizophrenia, anemia, and upper respiratory tract infection, all reported with an incidence of 2.1% (3/144).
- A total of 10 (6.9%) subjects reported at least one treatment-related TEAE, which included 4 (8.9%), 4 (7.5%) and 2 (4.3%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.
- The most frequent treatment-related TEAEs by SOC (≥2% incidence of events in overall subjects) was "Nervous system disorders" with and incidence of 2.1% (3/144). No treatment-related TEAE occurred in more than one subject in any treatment group. There was no treatment-related to seizure or seizure-like TEAE.
- Very few clinical laboratory parameters' (hematology and clinical chemistry) results were deemed clinically significant by the Investigators. There were no clinically meaningful trends observed in the newly emergent clinically notable abnormalities in laboratory parameters in any of the three treatment groups.
- Vital signs data did not indicate any clinically notable effects of any of the three doses of evenamide, on blood pressure (supine and orthostatic changes), pulse rate, respiratory rate, body temperature, or body weight.
- ECG results indicated no clinically significant effects of any of the three doses of evenamide on cardiac function, including QTc interval. None of the treatment-emergent ECG abnormalities were considered as clinically significant by the Investigators.
- No clinically notable effects or trends were observed at the end of treatment compared to baseline for any of the three doses of evenamide on physical, neurological, and eye examinations, extrapyramidal symptoms (assessed by the ESRS-A), or changes in depressive symptoms (assessed by the CDSS).

Overall, the results for the safety parameters assessed in the study indicated that evenamide given orally at three fixed doses (7.5 mg, 15 mg, and 30 mg bid) in patients with treatment-resistant schizophrenia was well tolerated, without any major safety concerns, and no dose-dependent safety concern was observed.

These data do not suggest any major safety concerns with the use of evenamide, administered up to 1-year, at doses of 7.5, 15, and 30 mg bid as add-on treatment to antipsychotic medication (APs) in this population of patients with treatment resistant schizophrenia (TRS).

Efficacy Results:

Positive and Negative Syndrome Scale (PANSS)

The PANSS, a standard scale for assessing the individual symptoms of schizophrenia was used as the primary efficacy measure for the study. The analysis was done using within group comparisons (Primary Estimand: effect of continuing on the randomized dose of evenamide in the extension study, as it was administered in the core study, regardless of withdrawal from treatment; Estimator: estimate of the change from baseline in PANSS total score at Week 46 using a paired t-test for the mITT Population). Within group comparisons were performed using a paired t-test.

The baseline mean value of the PANSS total score was similar in all treatment groups. A steady improvement in the PANSS total score (lowering of score) was observed over time across study visits (Weeks 12, 24, 36 and 46) compared to baseline, reflecting a continuation of improvement in symptoms of schizophrenia. The PANSS total score in the mITT population, as assessed by the Primary Efficacy Estimand at Week 46, showed a significant mean (SD) change from baseline of -14.8 (9.12) (95% CI: -17.67, -11.83; p<0.001), -16.5 (10.47) (95% CI: -19.57, -13.35; p<0.001) and -15.0 (10.97) (95% CI: -18.51, -11.59; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by LOCF at Week 46, showed a significant mean (SD) change from baseline of -14.5 (8.99) (95% CI: -17.26, -11.65; p<0.001), -15.9 (10.24) (95% CI: -18.75, -13.10; p<0.001) and -15.2 (11.00) (95% CI: -18.53, -11.92; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Thus, the improvement (lowering of scores) in the PANSS total score from baseline over time up to Week 46 was supported by both OC and LOCF models.

The results of PANSS subscales (Positive Syndrome, Negative Syndrome, and General Psychopathology) scores within group comparisons were analyzed by using a paired t-test for the mITT Population. A significant mean (SD) change (improvement) from baseline at Week 46 was observed in all three treatment groups for each of the subscales.

'Responder' analyses were performed by summarizing the proportion of patients in each of the evenamide groups with a specified level of improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Syndrome sub-scale. By Week 46, the proportion of responders on the PANSS total score (patients who improved by at least 20% from baseline according to Rosenheck et al., 1997; Meltzer et al., 2008) increased to 20 of 42 (47.6%), 21 of 53 (39.6%) and 18 of 46 (39.1%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, compared to 10 of 42 (23.8%), 16 of 53 (30.2%), 9 of 46 (19.6%) responders, respectively, at Week 12. The proportion of patients showing meaningful improvement in positive symptoms alone, based on the responder analysis of PANSS Positive Syndrome sub-scale score, increased with time. By Week 46, the proportion of responders on the PANSS Positive Syndrome total score (patients who improved by at least 4 points from baseline) was 29 of 42 (69.0%), 36 of 53 (67.9%) and 32 of 46 (69.6%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Thus, the proportion of patients with TRS exhibiting a clinically meaningful improvement in symptoms of schizophrenia with evenamide treatment was substantial and increased over time.

Clinical Global Impression - Severity of illness (CGI-S) and Change from baseline (CGI-C)

The baseline mean value of the CGI-S was similar in all three treatment groups. A significant (p<0.001) improvement (lowering of scores) in the CGI-S was observed at all study visits (Weeks 12, 24, 36 and 46) compared to baseline in all the three treatment groups, that indicated improvement in overall severity of illness.

The results of the paired t-test performed at post-dose visits to analyze CGI-S change from baseline at Week 46 within each dose group showed a significant mean (SD) reduction from baseline of -1.1 (0.68) (95% CI: (-1.27, -0.83); p<0.001), -1.2 (0.71) (95% CI: (-1.38, -0.96); p<0.001) and -1.1 (0.69) (95% CI: -1.29, -0.86; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups. The results were confirmed by the trend for decreasing CGI-S score (improvement) and significant (p<0.001) reductions observed in different models (Primary estimand, Supportive estimand, LOCF, and Multiple imputations) of the Sensitivity Analysis on change from baseline at Week 46. Responder analysis was performed for CGI-S, by summarizing the proportion of patients in each of the evenamide dose groups with improvement in CGI-S from baseline to endpoint. Overall, in all three treatment groups combined, the proportion of "responders" for CGI-S score of at least 2-category improvement was 11.3% at Week 12, which further improved over time to 14.9%, 23.4% and 24.1% at Week 24, Week 36 and Week 46, respectively. Overall, in all three treatment groups combined, the proportion of "responders" for CGI-S score of at least 1-category improvement was greater than 70%.

A reduction in the mean (SD) CGI-C score was observed between Weeks 12 and 46, from 2.9 to 2.7 in evenamide 7.5 mg, from 2.9 to 2.8 in evenamide 15 mg, and from 2.9 to 2.8 in evenamide 30 mg *bid* treated groups. A responder analysis was done considering change in subject's condition from baseline, as indicated by the CGI-C score (CGI-C score ≤ 2 [indicating "much improved" or "very much improved"]). The proportion of responders, based on this definition, increased over time. The proportion of responders in the evenamide 7.5 mg *bid* treated group was 31% at Week 12 and 42.9% at Week 46. The proportion of responders in the evenamide 15 mg *bid* treated group was 26.4% at Week 12 and 35.8% at Week 46. The proportion of responders in the evenamide 30 mg *bid* treated group was 23.9% at Week 12 and 34.8% at Week 46.

Strauss-Carpenter Level of Functioning (LOF) scale

The mean change from baseline in the LOF total score showed statistically significant (p<0.001) improvement (increase in score) over time across study visits. The mean (SD) change from baseline in the LOF total score was 1.4 (2.03) (95% CI: 0.72, 1.99; p<0.001) at Week 12 and 1.5 (2.39) (95% CI: 0.71, 2.24; p<0.001) at Week 46 in the evenamide 7.5 mg bid treated group. The mean (SD) change from baseline in the LOF total score was 1.5 (2.70) (95% CI: 0.71, 2.23; p<0.001) at Week 12 and 2.2 (3.56) (95% CI: 1.12, 3.23; p<0.001) at Week 46 in the evenamide 15 mg bid treated group. The mean (SD) change from baseline in the LOF total score was 2.5 (3.26) (95% CI: 1.49, 3.43; p<0.001) at Week 12 and 3.6 (3.59) (95% CI: 2.45, 4.72; p<0.001) at Week 46 in the evenamide 30 mg bid treated group, indicating overall improvement in functioning.

Conclusions:

Overall, the long-term (up to 1 year) safety results indicate that evenamide given orally at three fixed doses (7.5 mg, 15 mg, and 30 mg *bid*) as add-on treatment in patients with TRS on a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine) was well tolerated, without any major safety concern. No pattern of clinically notable adverse effects, based on TEAEs, ECG parameters, laboratory abnormalities, vital signs, depressive symptoms, extrapyramidal symptoms, weight gain or metabolic syndrome, was detected, and no dose-dependent safety concern was observed.

The long-term (up to 1-year) efficacy data collected for fixed doses of evenamide of 7.5 mg, 15 mg and 30 mg *bid* show a progressive and sustained improvement in symptoms of schizophrenia as assessed by the PANSS (total score and subscales - mean change from baseline), a decrease in overall disease severity as assessed by the CGI-S score, and enhancement in patients' functionality as assessed by the Strauss-Carpenter LOF, in this population of patients with TRS. These benefits increased over time from baseline through Week 46 (1-year of treatment), and were also

supported by the results of the responder analysis of the PANSS total score, PANSS Positive Syndrome subscale score, CGI-S and CGI-C.

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3.2 LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS

µM	=	Micromolar
ACC	=	Anterior Cingulate Cortex
ADME	=	Absorption, Distribution, Metabolism and Excretion
ADO	=	Adverse Dropout (Discontinuation Due to Adverse Event)
AE	=	Adverse Event
ALP	=	Alkaline Phosphatase
ALT	=	Alanine-Aminotransferase
AST	=	Aspartate-Aminotransferase
ATC	=	Anatomical Therapeutic Chemical
AUC	=	Area Under the Plasma Drug Concentration Vs. Time Curve
bid	=	Twice Daily
BMI	=	Body Mass Index
BUN	=	Blood Urea Nitrogen
CDSS	=	Calgary Depression Scale for Schizophrenia
CGI-C	=	Clinical Global Impression – Change from Baseline
CGI-S	=	Clinical Global Impression – Severity of Illness
CI	=	Confidence Intervals
C_{max}	=	Maximum post-dose plasma drug concentration
CNS	=	Central Nervous System
ConMed	=	Concomitant Medication
CPK	=	Creatine Phosphokinase
CRF	=	Case Report Form
CRO	=	Contract Research Organization
CSR	=	Clinical Study Report
CYP2D6	=	Cytochrome P450 2D6
DBP	=	Diastolic Blood Pressure
DSM-5	=	Diagnostic And Statistical Manual of Mental Disorders – 5th Edition
ECG	=	Electrocardiogram
EEG	=	Electroencephalogram
EPS	=	Extrapyramidal Symptoms
ESRS-A	=	Extrapyramidal Symptom Rating Scale – Abbreviated Version
FGA	=	First Generation Antipsychotic Drugs
GCP	=	Good Clinical Practice
GGT	=	Gamma-Glutamyl Transpeptidase
GLP	=	Good Laboratory Practice
HBV	=	Hepatitis-B Virus
HCV	=	Hepatitis-C Virus
HDL	=	High Density Lipoprotein
hERG	=	Human *Ether-A-Go-Go* Related Gene
HIV	=	Human Immunodeficiency Virus

Hr	=	Hour(S)
Hs	=	*Hora Somni* (At Bedtime)
i.p.	=	Intraperitoneal
ICF	=	Informed Consent Form
ICH	=	International Council for Harmonization
IEC	=	Independent Ethics Committee
IP	=	Investigational Product
IRB	=	Institutional Review Board
ISMB	=	Independent Safety Monitoring Board
ITT	=	Intent To Treat
LC-MS/MS	=	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDH	=	Lactate Dehydrogenase
LDL	=	Low Density Lipoprotein
LOCF	=	Last Observation Carried Forward
LOF	=	Strauss-Carpenter Level of Functioning Scale
MBq	=	Megabecquerel (1 Mbq = 27 Microcuries)
MED	=	Minimal Effective Dose
MedDRA	=	Medical Dictionary for Regulatory Activities
MI	=	Multiple Imputation Method
Min	=	Minute(s)
MTD	=	Maximum Tolerated Dose
NMDA	=	N-Methyl-D-Aspartate
NOAEL	=	No Observed Adverse Effect Level
OC	=	Observed Cases
od	=	Once Daily
OTC	=	Over The Counter
PANSS	=	Positive And Negative Syndrome Scale
PAM	=	Prior Antipsychotic Medications
PD	=	Pharmacodynamics
PET	=	Positron Emission Tomography
PK	=	Pharmacokinetics
PNS	=	Peripheral Nervous System
PPI	=	Pre-Pulse Inhibition
Prn	=	As Needed
PT	=	Preferred Term
RBC	=	Red Blood Cells
SAE	=	Serious Adverse Event
SAP	=	Statistical Analysis Plan
SBP	=	Systolic Blood Pressure
SD	=	Standard Deviation
SGA	=	Second Generation Antipsychotic Drugs
Sig-1R	=	Human Sigma-1 Receptor
SOC	=	System Organ Class

$t_{1/2}$	=	Half-Life
T_3	=	Triiodothyronine
T_4	=	Thyroxine
TEAE	=	Treatment-Emergent Adverse Event
THC	=	Tetrahydrocannabinol
t_{max}	=	Time Of Maximum Plasma Concentration Post-Dose
TRS	=	Treatment-Resistant Schizophrenia
TSH	=	Thyroid Stimulating Hormone
TST	=	Tail Suspension Test
US	=	United States
VGSC	=	Voltage-Gated Sodium Channels
VLDL	=	Very Low-Density Lipoprotein
WBC	=	White Blood Cells

5 ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

The protocol, Investigator's Brochure, Subject Information Sheet, Informed Consent Form (ICF), and any advertisement(s) for the recruitment of subjects were reviewed and approved by an appropriately constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC), as required in Chapter 3 of the ICH E6 Guideline. A copy of the Committee's dated approval and a list of the members of the IRB/IEC was given to the Sponsor for the Sponsor's files. A copy was also included in the Final Report. Written IRB/IEC approval was obtained by the Sponsor prior to shipment of study drug or subject enrollment. Any non-administrative amendments to the protocol, ICF, or Subject Information Sheet were approved by the IRB/IEC. A list of all IRBs/IECs consulted during the conduct of this study is provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza Brazil, 2013. However, where applicable, the principles of the 1996 version of the Declaration of Helsinki were adhered to.

5.3 Subject Information and Consent

All subjects signed and personally dated an IRB/IEC approved ICF after receiving detailed written and verbal information about the reason, the nature, the required procedures, the intended duration, and the possible risks and benefits and any discomfort associated with the study.

The subject was informed that his/her participation in the study was voluntary, and he/she could refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the subject was otherwise entitled.

The language used in the oral and written information about the study, including the written ICF, was as non-technical as practical, and understandable to the subject.

The subject was given ample time to read and to understand the Subject Information Sheet and opportunity to inquire and ask for any clarification about the study before signing the ICF.

No study procedure was performed (including the screening visit) before the ICF was signed. The informed consent procedure was done according to the guidelines provided in the Declaration of Helsinki and the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP).

The subject was made aware and agreed that personal information could be scrutinized during inspection/audit by competent authorities and properly authorized persons. However, personal information was treated as strictly confidential and was not publicly available.

The Investigator assured Newron Pharmaceuticals SpA that Informed Consent was obtained by signing the Investigator Statement (Appendix 3 of the study protocol).

Original signed Informed Consent Forms were filed with the Investigator's File. The sample ICF is provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted by 13 Principal Investigators at 9 sites in India, 3 sites in Sri Lanka, and 1 site in Italy.

A list of Investigators and other important participants in the study, their affiliations, and copies of their curricula vitae, are provided in Appendix 16.1.4 of the CSR. Appendix 16.1.5 contains the signature of the Sponsor's responsible medical officer, indicating that this clinical study report accurately describes the conduct and results of this study. The study administrative structure is described in Table 6-1.

Table 6-1: Study Administrative Structure

Sponsor: Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano) Italy Tel: +39-02-6103461	**Contract Research Organizations (CRO):** Lead CRO CliniRx Research Pvt Ltd Patriot House, 4th Floor, 3, Bahadur Shah Zafar Marg New Delhi-110002 India CRO for Sri Lanka Remedium One Pvt Ltd 41/10, Guildford Crescent Colombo 7, Sri Lanka (Amendment 1, dated 13th Feb 2020) CRO for Italy Pharma D&S Via dei Pratoni, 16, 50018 Scandicci (FI) Italy (Amendment 2, dated 5th Jul 2020)
ISMB Committee Members: R. Krishnan, M.D. (Chairman of the ISMB) CEO of the Rush University System for Health Rush University Medical Center Rush Ambulatory Behavioral Health	**Adverse Event Reporting:** Rodolfo Giuliani Head of Medical Affairs & Drug Safety Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3

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Abbreviations: CSR = Clinical Study Report; ISMB = Independent Safety Monitoring Board.

7 INTRODUCTION

Additional information is included in the protocol available in Appendix 16.1.1 and the Investigator's Brochure..

7.1 Overview

Evenamide (NW-3509) is an orally available new chemical entity that specifically blocks voltage-gated sodium channels (VGSCs) in a state-dependent manner, with a higher affinity for the inactivated state of the channel, and modulates sustained repetitive firing, without inducing impairment of the normal excitability. Evenamide normalizes glutamate release induced by aberrant sodium channel activity, without affecting basal glutamate levels, due to its inhibition of VGSCs. VGSCs play an essential biophysical role, transmitting electrical signals through action potential generation and propagation in the peripheral (PNS) and central nervous systems (CNS). There is growing evidence indicating that gene mutations, changes in gene expression, or inappropriate modulation of these channels can lead to electrical instability of the cell membrane and exaggerate spontaneous activity of neurons (hyper-excitability), as is observed during pathological states such as epilepsy, pain, and psychiatric disorders (Chahine et al, 2008).

In schizophrenia, VGSC blockers are frequently used as "add-on" therapy to antipsychotics, with their success being attributed not only to their mood-stabilizer effects, but also to their enhancement of the onsetof antipsychotic action, increasing the overall efficacy of the antipsychotic drugs (Casey et al, 2003; Citrome, 2003; Tiihonen et al, 2003). Based on its effect on VGSCs, evenamide used in combination with current neuroleptics should improve their efficacy, allowing a reduction of their dosage, and thereby reducing associated side effects (e.g., metabolic syndrome, tardive dyskinesia, and extra-pyramidal symptoms [EPS]).

7.2 Pharmacology

It is hypothesized that there is a dysfunction of the glutamatergic and dopaminergic systems in schizophrenia and bipolar disorders. Current antipsychotic drugs target the dysregulation of mesolimbic and mesocortical dopaminergic/serotoninergic systems. However, this approach to treating the symptoms of schizophrenia still appears to be inadequate, with a very high proportion (74%) of patients discontinuing their antipsychotic (first or second generation) due to intolerance, inadequate benefit, or both, within 18 months of starting treatment (Lieberman et al, 2005). This suggests a failure to modulate other important mechanisms that are critical for anti-psychotic benefit.

Data from treatment non-responders indicate that dopamine synthesis capacity is unaltered in patients in the first episode (Jauhar et al, 2018), thus explaining the failure of dopamine antagonists to benefit patients with treatment-resistant schizophrenia (TRS). Studies also indicate that first-episode psychosis patients who respond poorly to treatment have elevated glutamate levels in the

anterior cingulate cortex (ACC) compared to those who respond well (Egerton et al, 2012). Higher levels of glutamate in the anterior cingulate gyrus are found in treatment-resistant, but not treatment-responsive patients, compared to healthy volunteers (Demjaha et al, 2014; Mouchlianitis et al, 2016).

Aberrant electrical connectivity in schizophrenia that leads to abnormal cortical activity and glutamate transmission largely contributes to the pathophysiology of this psychiatric disorder; however, it is not targeted by existing therapies. Evenamide normalizes glutamate release induced by aberrant sodium channel activity (veratridine-stimulated), without affecting basal glutamate levels, due to its inhibition of VGSCs. The minimal effective dose in an *in vivo* microdialysis study in rats was 2.5 mg/kg i.p., which overlaps with the effective doses in preclinical models of psychiatric illnesses.

Evenamide appears to be highly selective in its effects on VGSCs. Radio-ligand binding assays demonstrated that evenamide showed less than 20% inhibition against a panel of > 130 receptors, ion channels, transporters and kinases when tested at 10 µM, i.e., at concentrations many folds higher than likely to be achieved in humans. Acute treatment with doses of evenamide (2.5 mg/kg po) active in preclinical models did not alter monoamines (dopamine, serotonin, norepinephrine) or their metabolite levels in the brain, while functional electrophysiology studies did not detect any significant activity of evenamide on other ion channels, such as voltage-gated Ca^{2+} channels and N-methyl-D-aspartate (NMDA) receptor channels, up to extremely high concentrations (IC_{50} >100µM). Evenamide showed an affinity for the human sigma-1 receptor (Sig-1R) in a radioligand binding assay in the range of 0.49-1.11 µM. However, evenamide showed antagonistactivity at the Sig-1R only at concentrations 140 times the anticipated maximum therapeutic exposure of 0.02 µM.

The potential benefits of evenamide were demonstrated in a battery of animal models predictive of efficacy in psychiatric diseases, including models of schizophrenia, mania, psychosis, depression, compulsivity and aggressiveness, and cognition. Evenamide was effective when administered alone and in combination with marketed antipsychotics.

In the schizophrenia model of impaired sensorimotor gating and information processing (Pre-Pulse Inhibition [PPI] deficit), evenamide was effective, irrespective of whether the impairment was spontaneous or induced by amphetamine, NMDA-receptor antagonists (MK-801, PCP or ketamine), or sleep deprivation. The minimal effective dose (MED) in reversing PPI deficits ranged from 0.5 mg/kg i.p. (sleep deprivation model) to 1.25 mg/kg p.o. (MK-801/ amphetamine-induced deficits).

The potential anti-manic and antipsychotic effects of evenamide were demonstrated in the mouse models of amphetamine + chlordiazepoxide- and amphetamine-induced hyperactivity, respectively, at MEDs of 5-20 mg/kg p.o. Antidepressant activity was evaluated using the tail

suspension test (TST) in mice (MED 10 mg/kg p.o.), and effects on aggressive behavior were evaluated in the resident-intruder paradigm (MED 0.25 mg/kg i.p.). The marble burying test was used to evaluate compulsive behavior (MED 20 mg/kg p.o.).

A key feature of these experiments was that sub-threshold doses of evenamide added to ineffective doses of typical (haloperidol) or atypical (risperidone) antipsychotics in models of schizophrenia (PPI deficit), mania (amphetamine + chlordiazepoxide hyperactivity), and psychosis (amphetamine-induced hyperactivity) demonstrated significant efficacy of the combination.

In the rat model of PPI deficit induced by amphetamine (2.5 mg/kg, s.c.), ineffective doses of evenamide (0.625 mg/kg and 1.25 mg/kg p.o.) in combination with sub-threshold doses of haloperidol (0.05 mg/kg i.p.) or risperidone (0.05 mg/kg i.p.) produced a reversal of the PPI deficit. The combination of haloperidol (0.3 mg/kg i.p.) and inactive doses of evenamide (10 and 20 mg/kg p.o.) also significantly increased PPI compared to haloperidol alone in a model of spontaneous PPI deficit in C57BL/6J mice.

The above experiments suggest that evenamide, when added to sub-therapeutic doses of antipsychotics, may confer antipsychotic efficacy, or augments their effects, thus indicating that doses of antipsychotic drugs can be reduced, which should result in a reduction in their dose-dependent side-effects.

Consistent with the NMDA receptor (NMDAr) hypofunction hypothesis of schizophrenia, the NMDAr antagonists (ketamine, PCP) are known to produce a hyper-glutamatergic activity in the brain that correlates with induced schizophrenia symptoms in both animals and humans (Lieberman et al, 2008; Moghaddam and Javitt, 2012). Evenamide monotherapy (minimal dose 5 mg/kg) showed effects similar to clozapine in reversing ketamine- or PCP-induced worsening of the PPI in the rat, thus implying a mechanism affecting glutamatergic transmission.

The mean effective dose of evenamide when used as monotherapy across different PPI deficits is 6 mg/kg; this corresponds to a mean plasma concentration of 100 ng/ml in the rat. However, a series of add-on studies have demonstrated that lower/ineffective doses of evenamide (producing plasma levels approx. 20 ng/ml in the rat) are sufficient to effectively counteract the PPI deficit induced by different sources, when combined with ineffective doses of first or second-generation antipsychotics including clozapine (Anand. et al, ECNP abstract, 2018). These preclinical data, in addition to the significant benefits noted with evenamide produced in schizophrenic patients provides a rationale for the evaluation of evenamide in patients with TRS not responding to therapeutic doses of atypical antipsychotics provide support for the evaluation of patients with TRS.

Extrapolated plasma concentrations of evenamide at the minimal effective doses (0.65 mg/kg – 1.25 mg/kg p.o., given as add-on to antipsychotics) in schizophrenia models range from 10 to 20 ng/ml. Physiological PK/PD modelling, using input information of evenamide LogP, solubility,

permeability, *in vitro* clearance, plasma protein binding, and effective concentrations in animal models of PPI, indicated that a steady state plasma concentration of 20-40 ng/ml would likely be effective in humans.

In summary, preclinical data indicate that evenamide, through modulation of the firing abnormalities, has the potential to normalize the aberrant spread of excitatory transmission and the excessive release of glutamate that occur as a consequence of the hypothesized dysfunction of the glutamatergic and dopaminergic systems in schizophrenia. As evenamide was administered in conjunction with $5HT_2/D_2$ blocking antipsychotics, it may add to or synergize with these drugs to bring about a combined therapeutic effect on glutamate release and dopaminergic and serotoninergic systems, thus modulating these major neurotransmitter systems that have been associated with schizophrenia symptoms.

7.3 Safety Pharmacology

Evenamide was evaluated for its potential to induce exaggerated pharmacology, i.e., CNS side effects in a range of *in vitro* and *in vivo* safety pharmacology and respiratory studies [modified Irwin study in rats, rotarod test, spontaneous locomotor activity, rat whole body plethysmography]; effects on the cardiovascular system [cardiac channels Na^+ 1.5, Ca^{2+} 1.2 and hERG, canine Purkinje fibers and telemetry in the conscious dog], as well its potential to induce phospholipidosis *in vitro*. The safety pharmacology studies did not reveal any findings that pose a risk for humans; the most conservative safety margin is greater than x20; this is based on the lowest efficacious concentration in any of the add-on experimental paradigms (i.e., 20 ng*h/ml in the rat and risperidone PPI model), and the most conservative No Observed Adverse Effect Level (NOAEL) dose in any of the species tested (i.e., 5.0 mg/kg/*bid* in the 4 weeks dog study C_{max} = 414 ng/ml). A single-dose study in healthy male volunteers did not detect any pattern of treatment–related adverse changes at doses up to and including 30 mg (mean C_{max} = 93 ng/mL; range 65.3-113 ng/mL). Similarly, multiple doses of 15, 20 and 25 mg *bid* were well tolerated in patients with schizophrenia (Study 002 – see details below under Clinical Studies).

7.4 Pharmacokinetics and Metabolism

The pharmacokinetics of evenamide following intravenous and oral administration had been studied in mice, rats, dogs and cynomolgus monkeys. Generally, in all species, evenamide was rapidly absorbed, with maximal concentrations reached within 0.25 to 1.25 hours following oral dosing and was cleared with a terminal half-life of 0.5 to 1.5 hours. The oral bioavailability was 18% in mice, 7% in rats, 15-30% in dogs, and 20% in cynomolgus monkeys.

In the rat evenamide showed high penetration into the brain; the concentration ratio brain/plasma was 13 at 0.25 hours after oral dosing and 5.7 at 1 hour. The clearance of evenamide was similar

in both plasma and the brain (1.5-2.0 hours). Plasma protein binding was 91.0% in rats and 94.2% in humans.

In the 4-week rat toxicity study, exposure to evenamide was higher in females than in males, and increased in a dose over-proportional manner. Accumulation ratios were >1 in both sexes. In the 4-week dog study, no gender effect was noted, and no accumulation was seen. The kinetics were linear over the dose range of 2.5 to 10 mg/kg/*bid*.

In the first Phase I study, single oral doses of 1, 2, 5, 10, 20 and 30 mg of evenamide were administered to 6 healthy subjects per dose level. Absorption was rapid and t_{max} was reached between 0.75 and 2.0 hours. C_{max} and AUC-values kept increasing with increasing doses. The mean terminal elimination half-life observed in the six cohorts ranged between 1.6 and 4.0 hours.

Based on the short half-life, a *bid* dosing schedule was used in the multiple ascending dose study in patients with schizophrenia (Study 002). In 'Study 002', all patients randomized to evenamide started at a dose of 15 mg *bid*, and had subsequent weekly dose increases to 20 and 25 mg *bid*, based on tolerability. Peak plasma concentration [C_{max}; mean (SD)] of 40.4 (20.4), 65.7 (31.3) and 94.1 (51.3) ng/ml were achieved after the first administration of doses of 15, 20 and 25 mg, respectively, with a t_{max} of 1-2-hr and a half-life of 2.2-2.5 hr.

Although there was no data available on the effect of food on plasma concentrations of evenamide, because of the rapid rise to C_{max} a recommendation was made to dose with food or after a meal.

In vitro, evenamide was extensively metabolized in rat, dog, minipig, cynomolgus monkey and human hepatocytes; metabolic stability was highest in dog and human. Metabolic reactions included demethylation, di-demethylation, hydroxylation (major), di-hydroxylation, oxidation (major) and various combinations thereof, as well as glucuronidation. The number of metabolites detected was 16 in rat, 15 in minipig, 12 in monkey, 8 in dog and 5 in human hepatocytes.

In vitro inhibition studies demonstrated direct or time-dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 (IC_{50} >100 µM). No notable induction of CYP1A2 or 3A4 mRNA was observed upon incubation with human hepatocytes up to 50 µM. A moderate inductive effect on CYP2B6 was observed, although this was not fully concentration-dependent. Considering human exposure at a dose of 30 mg, the unbound fraction in human plasma (0.058) and the lack of co-medications predominantly metabolized by CYP2B6, the risk of clinically relevant CYP induction caused by evenamide is considered to be low.

Evenamide is not a substrate for MDR1 (P-gp), BCRP, OATP1B1, OATP1B3, OATP1A2 or OATP2B1. It did not notably inhibit MDR1, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT3, MATE1 or MATE2-K (IC50 >50 µM). IC_{50} values were calculated against OATP1A2 (15.51 µM), OCT1 (17.55 µM) and OCT2 (26.00 µM) but considering human C_{max} at a dose of 30 mg and the unbound fraction in human plasma (0.058), the risk of clinically relevant

transporter inhibition by evenamide was calculated as low. Evenamide was not a time-dependent inhibitor of OATP1B1 or OATP1B3.

7.4.1 Clinical Pharmacology Study NW3509-007

An ADME (mass balance) study (NW3509-007) evaluating the metabolism of evenamide in humans has been completed. Six healthy male subjects received a single oral dose of 25 mg of (^{14}C) NW-3509, with radioactivity of no more than 12.2 MBq, in this non-randomized, single-site, open-label, non-controlled single oral dose Phase I trial. Two subjects were CYP2D6 poor metabolizers. Excreta and plasma were collected for 6 days after dosing. The total radioactivity in urine, feces, plasma, and whole blood was measured, and evenamide was measured in plasma by a specific LC-MS/MS assay. Only one AE of mild intensity was reported (catheter site bruising) and assessed as unrelated to the study drug. There were no clinically significant findings in any laboratory assessments, vital signs, urinalysis, ECGs, or physical examinations. The oral administration of [^{14}C] NW-3509 25 mg capsule was considered safe and well tolerated under the conditions in the study.

An average of 113% of the radioactivity administered was recovered in excreta over a 144-hour sampling period, with the majority of radioactivity (approximately 111% of the dose) recovered in the urine. Exposure to evenamide accounted for approximately 5% of circulating plasma total radioactivity based on AUC(0-inf), indicating extensive biotransformation of evenamide following oral administration; this proportion was not notably different in the two CYP2D6 poor metabolizers. There was limited distribution of radioactivity into blood cells. This study detected a major metabolite of NW-3509, (3-butoxy-phenyl) -acetic acid, representing approximately 68% of circulating radioactive material, and a glucuronide of hydroxyl NW-3509, representing 10% of circulating drug-related material. The (3-butoxy-phenyl)-acetic acid was not a major urinary metabolite, has been detected in both rat and dog chronic studies, and has been shown to be devoid of any activity at 89 CNS targets in *in-vivo* studies.

7.4.2 Toxicology studies

The toxicology program conducted to date consists of the following: single dose pharmacokinetic studies in mice, rats, dogs and monkeys; repeat dose 4- and 13-week oral studies in rats and dogs; chronic oral studies in rats (26-weeks) and dogs (39-weeks); phototoxic potential and mutagenicity studies (Ames test, chromosome aberration test *in vitro*, micronucleus test in female rats). Embryo-fetal developmental toxicity studies in rats and rabbits and a fertility and early embryonic development study in rats have also been conducted.

7.5 Clinical Studies

7.5.1 Study NW3509A/001/I/2011 (Study 001)

Study 001 was a single dose, randomized, placebo-controlled, independent, sequential cohort (9 subjects in each cohort) study performed to determine the safety, tolerability, and the maximum tolerated dose (MTD) of escalating single oral doses of evenamide (1, 2, 5, 10, 20 and 30 mg; n=6 at each dose) or placebo (n=3 in each cohort) in healthy male volunteers. The safety, tolerability and plasma level data at each dose were evaluated by an Independent Safety Monitoring Board before proceeding to the next higher dose. A decision was made to terminate dose escalation at 30 mg, based on limitations of the available dosage strengths (1, 2.5 and 5-mg capsules). The plasma levels (C_{max}) in healthy volunteers at the 20 and 30 mg doses exceeded levels that were efficacious (i.e., 20-40 ng/mL) in preclinical pharmacology experiments.

7.5.2 Study NW3509A/002/II/2015 (Study 002)

Study 002 was a Phase IIa, 4-week, randomized, double-blind, placebo-controlled, multicenter study (US, 2 centers; and India, 3 centers) designed to investigate the tolerability, safety and preliminary evidence of efficacy of evenamide as an add-on treatment in 89 patients (evenamide, N=50; placebo, N=39) with a DSM-5 diagnosis of schizophrenia, who had responded previously to treatment with risperidone or aripiprazole, but were worsening on a stable dose of these drugs [risperidone, N=70 (78.7%);aripiprazole, N=19 (21.3%)]. The starting daily dose in this trial was 15 mg *bid*, which was increased at weekly intervals to 20 and 25 mg *bid*, contingent on tolerability, for a maximum of 27 days of treatment.

Evenamide was generally safe and well tolerated at doses of 15, 20 and 25 mg *bid*. Despite the limitations of the study design (i.e., small sample size, unequal randomization, short duration [4 weeks], limited to milder patients to enable them to provide meaningful feedback on side-effects, outpatient treatment), there was a strong signal for efficacy for evenamide, based on results for the Positive and Negative Syndrome Scale (PANSS) total and Positive Symptoms sub-scale, as well as global assessments of disease severity and change from baseline (Clinical Global Impression of Severity of illness [CGI-S] and Change from baseline [CGI-C]), and an assessment of daily function (Strauss-Carpenter Level of Functioning Scale [LOF]).

7.5.3 Study NW-3509/008/II/2019 (Study 008)

Study 008 was a 4-week, double-blind, placebo-controlled, multi-center study in patients with schizophrenia evaluating the safety, tolerability, including EEGs, and preliminary efficacy of multiple fixed doses of 7.5 and 15 mg *bid* of evenamide as add-on to a single atypical antipsychotic.

A total of 138 patients were randomized to treatment in the study, with a mean (SD) age of 37.6 (10.73). The majority of patients were male (76.1%), and of Asian race (81.9%). The most common atypical antipsychotics that patients were taking concomitantly were risperidone (35.5%),

olanzapine (29.7%) and clozapine (16.7%).

Based on results from this study, the Sponsor and the ISMB concluded that evenamide, at doses of 7.5 and 15 mg *bid* given for 28 days, was well-tolerated and not associated with any evidence of symptoms/signs suggestive of seizures, EEG changes or dose-limiting AEs. These results support evaluation of higher doses of 30 mg *bid* in the current study. *(Amendment 4, dated 18th June 2021)*

7.5.4 Study NW-3509/010/I/2019 (Study 010)

This was a Phase 1, randomized, partially blinded, placebo- and positive (moxifloxacin 400 mg) -controlled, 4-way balanced crossover study to assess the effect of single oral therapeutic (30 mg) and supratherapeutic (60 mg) doses of evenamide on the QT/QTc interval in healthy male and female subjects. The trial was designed in line with the recommendations for evaluation of QT/QTc interval prolongation outlined in the ICH E14 guidelines.

A total of 56 healthy subjects were enrolled in the trial; of these 42 (75%) were males. The mean (SD) age was 34.4 (9.95) years, 40 of the subjects were Caucasian, while 7 were Black and 6 were Asian, and the average body weight was 72.76 (range: 50.0−99.8) kg.

Overall, 54 subjects completed all four dosing cycles of the study, while one subject who was diagnosed with Covid-19 missed 2 dosing cycles, and one subject who experienced laboratory abnormalities completed the third cycle, but the study was completed prior to his fourth dosing cycle.

The primary analysis did not find any correlation between plasma concentrations of evenamide and its major metabolite, (3-butoxy-phenyl) -acetic acid, and QTc intervals. Analysis of individual dQTcF values at t_{max} of evenamide and (3-butoxy-phenyl)-acetic acid for each of the two dose levels found that the median dQTcF was less than 0, indicating a small dose-dependent reduction of the QTcF. There were no QTcF observations associated with the evenamide or placebo treatments that exceeded 450 msec. There was only one dQTcF observation greater than 30 msec (associated with placebo treatment) and none exceeded 60 msec. The median maximum increase on moxifloxacin was 17.3 msec, and there were two dQTcF observations >30 msec associated with moxifloxacin treatment.

These results strongly suggested that evenamide would be devoid of the risk of QTc prolongation and arrhythmias. *(Amendment 4, dated 18th June 2021)*

7.5.5 Study NW3509/011/I/2019 (Study 011)

Study 011 was a randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and PK of a single oral dose of 60 mg of evenamide in 9 healthy adult male subjects (evenamide n=6 and placebo n=3).

Subjects ranged in age from 34 to 45 years (mean, 39.6 ± 4.1 years) and were mostly White

(88.9%). The mean weight was 79.2 kg ± 12.0 kg (mean BMI of 24.5 ± 2.0 kg/m^2).

Peak plasma levels of evenamide (in a range of 68.8-248 ng/mL) occurred 45-90 minutes after dosing, and the plasma half-life of evenamide was determined as between 2.15 and 4.07 hours. Peak plasma levels of (3-butoxy-phenyl)-acetic acid (evenamide's major metabolite), in a range of 519-930 ng/mL, consistently occurred 120 minutes after dosing (except for one subject with t_{max} at approximately 4 hours). The plasma half-life of (3-butoxy-phenyl)-acetic acid was determined as between 3.96 and 6.13 hours.

Four subjects reported 6 AEs. One AE (mild abdominal discomfort) was reported in evenamide-treated subjects and was considered not related to the study drug. Five AEs were reported in the placebo-treated subjects (nausea in 2 subjects, and vomiting, feeling hot and headache in 1 subject each). Of the 5 AEs in the placebo-treated subjects, 3 AEs were considered possibly related to the study drug (nausea, headache, and feeling hot). All AEs resolved.

No deaths, SAEs, other significant AEs, or discontinuations due to AEs were reported during this study. No clinically significant changes were noted in laboratory tests, vital signs, ECG parameters, cardiac, or physical and neurological examinations. No suicidal ideation, or seizure checklist finding was identified at any time point for any subject during the study.

Evenamide was generally safe and well-tolerated in Study 011 at a dose of 60 mg. Following review of unblinded safety data from this study, the ISMB indicated that other evenamide studies could proceed as designed, with a maximum dose of 30 mg *bid*. *(Amendment 2, dated 5th Jul 2020)*

8 STUDY OBJECTIVES

The objectives of the study are as follows:

8.1 Primary Objective:

- To evaluate the long-term safety and tolerability of evenamide given orally in patients with treatment-resistant schizophrenia (TRS) not responding adequately to their current antipsychotic medication.

8.2 Secondary Objectives:

- To evaluate preliminary long-term efficacy of evenamide, based on symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S).
- To determine the long-term effect of evenamide on daily functioning, based on changes on the Strauss-Carpenter Level of Functioning (LOF) scale.

9 INVESTIGATIONAL PLAN

9.1 Study Design

Study 015 was a 46-week, open-label, multi-center, extension of Study NW-3509/014/II/2019 (Study 014) designed to evaluate the long-term safety, tolerability and preliminary efficacy of evenamide as add-on treatment in patients with TRS on a stable therapeutic dose of a single antipsychotic. In Study 014, after 50 patients were randomized equally (1:1) to the 7.5 mg *bid* (n=26) and 15 mg *bid* (n=24) doses and completed their participation in the study, key safety data from these patients were reviewed by the ISMB. This review of the data indicated that there were no safety issues; therefore, the 30 mg *bid* dose group was initiated, and randomization was continued, with patients being randomized 1:1:2 to doses of 7.5, 15 and 30 mg *bid*. Subsequently, the Study 014 protocol was amended to discontinue the 7.5 mg *bid* dose group, and to randomize patients 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. Similarly, the Study 015 protocol was also amended *(Amendment 4, dated 18th June 2021)* to discontinue the 7.5 mg evenamide *bid* dose group.

Patients randomized in Study 014 who completed 6 weeks of open-label treatment, did not experience moderate/severe side effects, did not show severe worsening of their symptoms of schizophrenia and met other entry criteria for this study were eligible to receive evenamide in this open-label extension study (Study 015) for an additional 46 weeks, for a total treatment period with evenamide of up to 52 weeks. In India, the duration of this extension study was further extended up to Weeks 70 *(Amendment 4.1, 30th November 2021)* and 94 *(Amendment 4.2, 08th July 2022).* A separate report will be prepared for the study period beyond 46 weeks.

Patients randomized to doses of 15 mg *bid* or 30 mg *bid* in Study 014 continued in Study 015 on the same dose of evenamide that they received on the last day (Day 43) of the prior study, while patients randomized to the 7.5 mg *bid* dose in Study 014 had their dose increased to 15 mg *bid* upon entry into Study 015, following the approval of the Protocol *Amendment 4.0 18th June 2021.* Prior to this amendment patients initially randomized to 7.5 mg *bid*, who were still on treatment in Study 014, completed this study at their current dose (i.e., 7.5 mg *bid*), and titrated up to 15 mg *bid* upon entry into Study 015. Patients already enrolled in Study 015 at the 7.5 mg *bid* dose had their dose increased to 15 mg *bid* at their next scheduled clinic visit. In all such cases, up-titration of the dose was performed following patients' signature of a revised version of the ICF. Dose reductions to once daily dosing were performed at any time if intolerance developed.

Patients who completed 6 weeks of treatment in Study 014 provided informed consent in writing and fulfilled all the selection criteria prior to getting enrolled in this extension study. The baseline safety and efficacy evaluations in Study 014 served as the baseline assessments for this extension study.

On Day 1, after all final Study 014 (Day 43) evaluations had been completed, patients meeting all entry criteria were given a supply of study medication at their current dose to cover the period until the next scheduled visit. Patients were instructed to take their first dose in the evening at their residence, at least 6 hours after the last dose in Study 014 that they received in the morning at the clinic. Patients were required to return to the clinic for scheduled visits at Weeks 6, 12, 18, 24 and 36. During these visits selected safety and efficacy evaluations were performed. If no safety or tolerability issues were detected, the patient was discharged from the clinic and continued on their current dose. After Week 24, a telephone contact was made with the patient by the Investigator/site staff at Weeks 30 and 41, midway between scheduled clinic visits, to inquire regarding any safety or tolerability issues that he/she may have experienced, and use of any concomitant medications. Based on this report, the patient's dose may have been reduced to once daily dosing, or the patient may have been asked to return for an unscheduled visit, if necessary.

Patients returned to the clinic for all final safety and efficacy evaluations at Week 46 (or at early discontinuation). For patients who completed 46 weeks of open-label treatment and did not continue treatment in the further extension period (i.e., up to Week 70, and up to Week 94), as well as those who discontinued prematurely, a safety follow-up visit was performed 7 days after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. Patients who did not return to the clinic for their 7-day safety follow-up visit were contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patients were contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any SAEs within 30 days after the final dose (this information was collected through a telephone contact).

An overview of the study design is provided in Table 9-1.

Table 9-1 Summary of Study Design

Period	Pre-Treatment	46-Week, Open-Label, Treatment Period						Post-Treatment	
Visit	**Baseline[#]**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 36**	**Final [$] (Week 46 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	0/1	43	85	127	169	253	323	7 days after last dose	30 days after last dose
Duration	1 day	42 days	42 days	42 days	42 days	84 days	70 days	7 days	30 days
Treatment/ Procedures	Informed consent; confirmed I/E criteria. First dose of evenamide taken on Day 1 (PM) at residence	Selected safety assessments (AEs, vital signs, ECG and Conc. Medication)	Selected safety and all efficacy assessments	Selected safety assessments (AEs, vital signs, ECG and Conc. Medication)	All safety and all efficacy assessments	Selected safety and all efficacy assessments	Last dose of study medication; all final safety and efficacy assessments; serum prolactin; urine drug screen; serum pregnancy test.	Safety evaluations (vital signs and AEs) performed 7 days after last dose of study medication	Contact patient 30 days after last dose of study medication to assess occurrence of any SAEs
Telephone Contact					Week 30 (AEs and Conc. Medication)	Week 41 (AEs and Conc. Medication		If patient does not return for scheduled visit, contact to assess AEs	Information can be collected via telephone contact

[#] *Study 014 baseline values, were considered for safety and efficacy evaluations for this extension study; however, the Day 43 final evaluations overlapped the initial evaluations for Study 015, and all assessments were to be completed on the same day.*

[$] *Final evaluation for patients who discontinued prematurely.*

**Performed for patients who discontinued prematurely, and those who completed 46 weeks of treatment but did not continue in the next additional treatment period (i.e., up to Week 70).*

9.2 Discussion of Study Design, Including Choice of Control Groups

This was a 46-week, open-label, multi-center, extension to Study NW-3509/014/II/2019 (Study 014) designed to evaluate the long-term safety, tolerability, and preliminary efficacy of evenamide as add-on treatment in patients with TRS on a stable therapeutic dose of an antipsychotic. In Study 014, after 50 patients were randomized equally (1:1) to the 7.5 mg *bid* (n=26) and 15 mg *bid* doses (n=24) and completed their participation in the study, key safety data from these patients were reviewed by an Independent Safety Monitoring Board (ISMB). This review of the data indicated that there were no safety issues, therefore, the 30 mg *bid* dose group was initiated, and randomization was continued, with patients being randomized 1:1:2 to doses of 7.5, 15 and 30 mg *bid*. Subsequently, the Study 014 protocol was amended to discontinue the 7.5 mg *bid* dose group, and to randomize patients 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. Similarly, the study 015 protocol was also amended *(Amendment 4, dated 18th June 2021)* to discontinue the 7.5 mg *bid* dose group.

An open-label study design was chosen for this extension study, as the antecedent study (Study 014) was also open-label. This allowed the treating physicians to optimize each patient's dose of evenamide and concomitant medications, as they were aware of the dose that the patient was receiving. The inclusion of three parallel evenamide dose groups of 7.5 mg *bid* (discontinued part way through the study), 15 mg *bid*, and 30 mg *bid* (added after it was introduced in Study 014 following review by the ISMB of safety data from the 7.5 and 15 mg *bid* doses) allowed determination of dose dependency for the incidence of adverse events, as well as changes from baseline in other safety parameters and efficacy measures.

Patients randomized to participate in Study 014 who completed 6 weeks of open-label treatment, were not experiencing moderate/severe side effects, had not shown severe worsening of their symptoms of schizophrenia, and who met other entry criteria for this study were considered eligible to receive evenamide in this open-label extension study (Study 015) for 46 weeks, *(Amendment 4, dated 18th June 2021)* for a total treatment period with evenamide of up to 52 weeks. The duration of this extension study was further increased, contingent on the availability of data from other studies to support the additional treatment.

Patients randomized to doses of 15 mg *bid* or 30 mg *bid* in Study 014 continued in Study 015 on the same dose of evenamide they were receiving on the last day (Day 43) of the prior study, while patients randomized to the 7.5 mg *bid* dose (49 patients) in Study 014 had their dose increased to 15 mg *bid* upon entry into Study 015. Patients already enrolled in Study 015 at the 7.5 mg *bid* dose had their dose increased to 15 mg *bid* at their next scheduled clinic visit. If intolerance developed, the patient was dropped back to once daily (*od*) dosing.

The dose of study medication was taken with food or after a meal. Any other medications were taken according to their usual schedule. On the day of each scheduled clinic visit, patients were reminded to take their medications at their residence according to their usual schedule, and to bring their study medication bottles with them to the clinic for adherence assessment. In case no

significant safety or tolerability issues were identified during the study visits, the patient was dispensed their study medication according to the planned dosing schedule. At discharge from the clinic, patients were reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

Patients who completed 6 weeks of treatment in Study 014, satisfied all the selection criteria and provided informed consent in writing prior to being enrolled in this extension study. Study 014 baseline values were considered for safety and efficacy evaluations for this extension study.

On Day 1 after all final Study 014 (Day 43) evaluations had been completed, patients meeting all entry criteria were given a supply of study medication at their current dose to cover the period until the next scheduled visit. Patients were instructed to take their first dose in the evening at their residence, at least 6 hours after the last dose of Study 014 that they received in the morning in the clinic. Throughout the treatment period, at each scheduled visit or telephone contact, careful open-ended questioning was used to evaluate whether the patient was experiencing symptoms and/or signs suggestive of neurological side-effects, severe sedation, seizures, or any other symptoms that could be dose-limiting, e.g., hypotension. In case the patient reported any of these symptoms, the patient was asked to contact the Principal Investigator, who decided, based on the symptoms/signs that had been identified, whether the patient had to come in for an evaluation, whether their dosing regimen needed to be modified, and/or whether a concomitant medication had to be added. In cases where further evaluation of the patient confirmed symptoms or signs suggestive of treatment toxicity, the Investigator decided on the appropriate therapeutic and diagnostic measures to be taken. These may have included hospitalization, performance of a full neurological examination, EEG, ECG, etc.

Patients were required to return to the clinic for scheduled visits at Weeks 6, 12, 18, 24 and 36. During these visits selected safety and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. If no safety or tolerability issues were detected, patients continued their current dose. The patient was discharged from the clinic and given a supply of study medication for the next period of dosing. After Week 24, the patient received a telephone contact from the Investigator/site staff at Weeks 30 and 41, midway between scheduled clinic visits, to inquire regarding any safety or tolerability visit issues that he/she had experienced, and his/her usage of any concomitant medications. Based on this report, the patient’s dose could be reduced to once daily dosing, or if significant tolerability issues were noted at the current dose level, the patient was asked to return for an unscheduled visit.

The patient returned for the final evaluation at Week 46 (or at early discontinuation), at which time all final safety [vital signs (including waist circumference), 12-lead ECG, laboratory tests, Extrapyramidal Symptom Rating Scale – Abbreviated Version (ESRS-A), Calgary Depression Scale for Schizophrenia (CDSS), physical/neurological examinations, and standard eye examination] and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. A urine drug screen was also performed.

For patients who discontinued prematurely, as well as those who completed 46 weeks of treatment in this open-label extension study and did not continue treatment in the further extension period (i.e., up to Week 94 in India), a safety follow-up visit was performed approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. Patients who did not return to the clinic for their 7-day safety follow-up visit were contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patient was contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose *(Amendment 4, dated 18th June 2021).*

9.3 Selection of Study Population

Only patients who participated in Study 014 and met all selection criteria for this open-label extension study were considered eligible for enrollment. A total of 153 subjects completed the antecedent study, Study 014. Of these subjects, 144 consented to enter and rolled over into the extension Study 015.

In cases where the Investigator was uncertain of a subject's eligibility for the study (e.g., selection criteria, coexistent medical conditions, or concomitant therapy), the Medical Monitor from the CRO monitoring the study was contacted to confirm the appropriateness of the inclusion of the patient.

Each patient enrolled in the antecedent study (Study 014) had received a six-digit subject number, with the first three digits specifying the center number and the last three digits the subject at the center. This same subject number was used throughout Study 015 to identify the patient. The subject number was entered in the eCRF and the same appeared in the header of each eCRF page.

9.3.1 Inclusion Criteria

The patients who met all of the following inclusion criteria were eligible for enrollment into the study:

1. Patient completed 6 weeks of treatment in Study 014.
2. Patient had provided written informed consent for this extension study.
3. If female, patient was not of childbearing potential, pregnant or breastfeeding.

   For inclusion, female patients must have been post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with highly effective contraception, i.e. barrier method in combination with an oral hormonal contraceptive, or long-acting hormonal contraceptive alone (Amendment 3, dated 22 September 2020).

9.3.2 Exclusion Criteria

The presence of any of the following excluded a patient from study enrollment:

1. Patient violated any requirement of the protocol in Study 014 that would have put him/her

at risk for continuing treatment with evenamide in Study 015.

2. In the Investigator's opinion, the patient had a significant worsening of risk for suicidality during Study 014.
3. Patient was experiencing any moderate/severe neurological side effects, other than pre-existing EPS related to antipsychotic treatment prior to enrolling in Study 014.
4. Patient had shown significant worsening of his/her symptoms of schizophrenia between baseline and the final assessment during the 6-week treatment period in Study 014, such that continuing treatment in Study 015 was considered undesirable.
5. Patient demonstrated substantial non-compliance with dosing of the study medication in Study 014.

9.3.3 Removal of Subjects from Therapy or Assessment

Only patients from Study 014 who met all of the inclusion criteria and none of the exclusion criteria were eligible for enrollment into this extension study. In addition to violations of inclusion and exclusion criteria, other reasons for not enrolling a patient include a major protocol deviation, lost to follow-up, voluntary withdrawal, and study termination; the primary reason was noted on the applicable Case Report Form (CRF).

If the subject was withdrawn from the study, all efforts were made to complete and report the observations as thoroughly as possible, including post-treatment evaluation at the time of the subject's withdrawal, with an explanation of why the subject was withdrawing from the study. Dropouts were not replaced.

Interrupting or permanently discontinuing a subject's treatment with the study medication was considered if any of the following occurred:

- The subject experienced any moderate/severe hypersensitivity or allergic reaction, that could be linked to the study medication;
- The subject experienced an AE sufficiently severe, in the opinion of the investigator, that it contraindicated continuing treatment with the study medication;
- The subject was not compliant with taking the study medication or concomitant antipsychotic medication, or the required safety assessments;
- The subject's schizophrenia symptoms worsened to such an extent that, despite therapeutic measures such as multiple administrations of rescue medication for 7 days or more, the patient continued to worsen, and/or required hospitalization.

Subjects whose treatment had been interrupted could restart study medication if the AE that led to stopping the medication had been resolved. If the AE reappeared upon restart, the study medication was to be discontinued. Subjects who discontinued treatment, but agreed to continue in the study, were to return for scheduled visits for assessment of selected safety (AEs, vital signs) and efficacy

(PANSS, CGI-S and CGI-C) parameters.

The criteria for a subject to discontinue from the study prior to Week 46 are listed below. A subject considered for discontinuation from study participation if:

- The subject experienced any moderate/severe hypersensitivity or allergic reaction, which was clearly linked to the study medication;
- The subject's schizophrenia symptoms worsened to such an extent that, despite therapeutic measures such as multiple administrations of rescue medication for 7 days or more, the patient continued to worsen, and/or required hospitalization;
- The subject experienced an AE sufficiently severe, in the opinion of the investigator, that it contraindicated continuing in the study;
- The subject wished to withdraw; in this instance, a specific reason (e.g., subject was unwilling to attend the scheduled clinic visits) was to be recorded by the Investigator;
- The subject was afflicted with a systemic illness, unrelated to the study medication, during the study treatment period, for which a prohibited concomitant medication was required and could put the patient at risk for further participation in the study;
- The subject was not adhering to the protocol requirements, and continued participation posed a significant risk to the subject's health;
- The subject was lost to follow-up, i.e., the subject did not return to the clinic, and attempts to contact the subject were unsuccessful. For the subject considered as 'lost to follow-up,' the site must have made at least 3 unsuccessful attempts to contact the patient and/or his/her caregiver by registered mail; attempts to contact the subject were to be fully documented.
- The Sponsor, Institutional Review Board/Ethics Committee (IRB/EC), or regulatory agency terminated the study.

For subjects who discontinued from the study prematurely, the date of discontinuation was entered on the Study Completion/Termination CRF, and one of the following reasons for discontinuation was selected:

- Adverse event,
- Major protocol deviation,
- Withdrawal of consent,
- Lost to follow-up,
- Lack of efficacy,
- Other (specify) – e.g., pregnancy, logistical issues, termination of study by Sponsor, etc.

For patients who discontinued the study prematurely (i.e., before completing the 46-week open-

label treatment period), the reason for discontinuation was entered in the CRF. All patients who discontinued prematurely were asked to return for a final evaluation, at which time all Week 46 assessments were to be performed. Patients who discontinued prematurely were also requested to return for the safety follow-up assessment 7 days after their last dose of study medication.

Record of Study Participants

The investigator maintained a confidential record of all study participants, including all patients from Study 014 who completed the study and were considered for this extension study, but were not actually enrolled. The confidential record included sufficient information so that it was possible to contact the study patient.

9.4 Treatments

9.4.1 Treatment Administered

The test drug (evenamide) was provided by the Sponsor in the form of capsules at dosage strengths of 7.5, 15 and 30 mg (after the 30-mg dose was introduced in Study 014) for oral administration. All study medication, together with relevant documentation, was supplied to the pharmacy at the investigational site.

The bottles of study medication were unblinded and had the dosage strength specified on the label. The appropriate doses were dispensed on Day 1 according to the dose that the patient was receiving at the end of Study 014. The Principal Investigator, study coordinator, nurses, and other site staff, as well as the patients, were aware of what was administered to the patient; however, the blinded safety and efficacy rater was not aware of the treatment assignment (blinded rater). Special care was taken so that the blinded rater was not accidentally unblinded once the patient entered Study 015, including ensuring that he/she was not present during dosing in the clinic, and did not see the medication bottle or notes in the chart that would have revealed the treatment assignment.

The first dose of study medication on Day 1, which was the same day as Day 43 of Study 014, was taken by the patient in the evening at his/her residence, at least 6 hours after the last dose in Study 014 that the patient received in the morning in the clinic. The oral doses of evenamide taken by the patient according to their treatment assignment in Study 014 are summarized in Table 9-2.

The study medication was administered as capsules of 7.5, 15 and 30 mg dosage strengths of evenamide. Doses were administered as 1 capsule *bid* given at approximately 8:00 AM and 8:00 PM (these dosing times were flexible; however, the two doses were supposed to be taken at least 6 hours apart). Patients were instructed to take one capsule from the bottle of study medication at each dosing time.

Table 9-2: Capsules Administered for Planned Doses of Study Medication

	Randomized Treatment Group (from Study 014)		
Dose Type	**Evenamide 7.5 mg *bid******	**Evenamide 15 mg *bid***	**Evenamide 30 mg *bid***
Starting Dose*	7.5 mg *bid*	15 mg *bid*	30 mg *bid*
Target Dose	7.5 mg *bid*	15 mg *bid*	30 mg *bid*
Drop-back Dose **	7.5 mg *od*	15 mg *od*	30 mg *od*

** Patients who were receiving once daily dosing at the end of Study 014 were continued on once daily dosing at their current dose level in this extension study. Doses of these patients might have been increased to the target bid dose at a subsequent scheduled visit if the Investigator felt it was warranted.*

*** If the Starting/Target Dose (bid) was not tolerated, a dose reduction to once daily (od) dosing (Drop-back Dose) was performed.*

**** The 7.5 mg bid dose was discontinued, and any patients who were receiving a dose of 7.5 mg bid were switched to 15 mg bid. (Amendment 4, dated 18th June 2021)*

Dosing during the 46-week Open-Label Treatment Period

The planned dose levels used in the study are shown in Table 9-2 above. Patients randomized to doses of 15 mg *bid* or 30 mg *bid* in Study 014 were continued in Study 015 on the same dose of evenamide they received on the last day (Day 43) of the prior study. Patients randomized to the 7.5 mg *bid* dose in Study 014 also continued on this dose in Study 015 up to the implementation of Amendment 4, dated 18th June 2021, where their dose was increased to 15 mg *bid* at their next scheduled clinic visit (Table 9-2); patients enrolled in Study 015 after the implementation of this amendment had their dose increased to 15 mg *bid* upon entry into Study 015. All the doses of evenamide were to be given once daily, if tolerability issues had previously necessitated a dose reduction. Dose reductions to once daily dosing could be performed at any time if intolerance developed. If the reduced dose was well tolerated, an increase to the target dose was to be attempted at the next scheduled visit. If intolerance developed again after increasing the dose, the dose was to be reduced to once daily (od) dosing and the patient continued for the remainder of the study at this reduced dose.

The dose of study medication was to be taken with food or after a meal. Any other medications were to be taken according to their usual schedule. On the day of each scheduled clinic visit, patients were reminded to take their medications at their residence according to their usual schedule, and to bring their study medication bottles with them to the clinic for adherence and drug accountability assessment. If no significant safety or tolerability issues were identified during the study visits, the patients were dispensed their study medication according to the planned dosing schedule. At discharge from the clinic, patients were to be reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

Overdose

The maximum single dose of evenamide given to a subject in a clinical study is 60 mg. This dose was administered to 6 healthy volunteers in Study NW-3509/011/I/2019 and 55 healthy volunteers in Study NW-3509/010/I/2019, which was designed to assess effects on the QTc interval on the ECG. In both studies, a single dose of 60 mg was well tolerated. In Study NW-3509/010/I/2019 there were no serious or severe AEs or AEs leading to withdrawal, and the most common TEAEs at the 60 mg dose were headache and dizziness, reported in 12.7% and 9.1% of subjects, respectively. No effects of the 60-mg dose on QTc or other ECG parameters were noted in Study 010. Doses greater than 60 mg have never been administered to any human subject.

In Study NW-3509A/002/II/2015, in which multiple doses of evenamide up to 25 mg *bid* were administered to patients with schizophrenia for up to 27 days, there were 3 reports of overdose for patients on evenamide, based on capsule counts of returned medication. None of these overdoses were associated with adverse events. Therefore, in case of an accidental overdosage, conservative management of symptoms and signs was advised *(Amendment 4, dated 18th June 2021)*.

Procedure followed in India for reporting overdose

If the investigational site staff administering the study medication or the study Pharmacist (based on pill counting) reported that a subject took more than the requisite number of capsules (i.e., the patient actually ingested the additional capsules) or a higher dose than was assigned, this was to be considered an overdose and was to be reported immediately to the Investigator. Any instance of overdose, whether symptomatic or not, was to be communicated to the CRO within 24 hours and was to be fully documented as a Serious Adverse Event. Details of any signs or symptoms and their management were to be recorded including details of any antidote(s) administered. *(Amendment 1, 13th February 2020)*.

Procedure followed in Italy, and Sri Lanka for reporting overdose

If the investigational site staff administering the study medication, the caregiver, or the subject reported that a subject inadvertently took more than the requisite number of capsules or a higher dose than was assigned, this was considered an overdose and was to be reported immediately to the Investigator. In addition, if the study Pharmacist noted a significant discrepancy, based on pill counting of returned medication (i.e., 2 or more fewer capsules were returned than expected, based on the dosing period), indicating that the patient may have had taken more than twice the number of capsules prescribed as an individual dose, the Investigator attempted to determine the possible cause for the discrepancy. For example, the missing medication might have been lost, damaged, diverted to another patient, or mistakenly discarded. If the cause of the discrepancy was identified and was not the result of the patient deliberately taking more capsules than prescribed, the event was not considered an overdose.

Any instance of a suspected overdose (based on pill counting), that was asymptomatic and for which there was no explanation, was considered a ‘medication error,’ and was not reported as a

Serious Adverse Event. Any confirmed overdose, whether symptomatic or not, was to be communicated to the CRO within 24 hours and fully documented as a Serious Adverse Event. Only symptomatic overdoses were to be submitted to Regulatory Authorities as expedited safety reports. Details of any signs or symptoms accompanying the overdose and their management were to be recorded, including details of any antidote(s) administered. The patient was to be reminded of the importance of taking the medication according to the dosing schedule, and not discarding any of the medication or giving it to other individuals. *(Amendment 1, dated 13th February 2020).*

9.4.2 Identity of Investigational Product(s)

The supplies for the study consisted of evenamide capsules with each different dosage (7.5, 15 and 30 mg) provided to each site in 30 ml HDPE bottles with a child-proof screw cap. The 30 mg capsules were used only if the 30 mg *bid* dose was introduced in the antecedent study, Study 014, following review by the ISMB of key safety data from the 7.5 and 15 mg *bid* doses. Each bottle contained a 1-week supply of study medication for twice daily (*bid*) dosing, plus additional medication in case of loss/damage (e.g., 1-week supply: 14 capsules + 2 extra capsules for 1 extra day of dosing = 16 capsules). One bottle was dispensed for each week of dosing prior to the next scheduled visit. The bottles were properly labelled with the below information:

- Protocol No. NW-3509-015-II-2019,
- Investigator's name and contact information (provided on separate label based on country-specific requirements),
- Quantity of capsules,
- Evenamide dosage strength (7.5, 15 or 30 mg),
- Expiry date,
- Storage conditions (typically room temperature, which was between 15°C and 25°C),
- Cautions required by regulatory authorities,
- Name of study sponsor and contact information,
- Patient's subject number (entered by site),
- Date of dispensing (entered by site).

Capsules containing evenamide were dispensed for the planned doses of 7.5 mg, 15 mg or 30 mg, which were administered orally twice daily (or once daily if the patient has had a dose reduction). The packaging of the medication for each dose level is presented in Table 9-3. Each patient received the appropriate number of bottles, each containing 16 capsules (designated for one week of dosing) for each dosing period, i.e., 6 bottles at Baseline (Day 1) and at Weeks 6, 12 and 18; 12 bottles at Week 24; and 10 bottles at Week 36. Two extra capsules were provided in each bottle for each week of *bid* dosing in case of lost or damaged medication, or a delay in the patient returning for a scheduled visit. This extra medication was sufficient to cover the allowable window on each scheduled visit (see Section 11.4.10 of the protocol); however, if it was known that a patient was

delayed further in returning for his/her visit, and might run out of medication, additional medication was to be dispensed to the patient to cover this period. Patients who had their dose reduced to once daily dosing received half the number of bottles of study medication that was used for twice daily dosing at the current dose and were instructed to take only one capsule per day in the morning.

Table 9-3: Drug Packaging According to the Planned Dosing Schedule by Treatment Group

Study Days	Planned Doses (*bid* dosing)				Dose Reductions (od dosing)			
	No. of Bottles*	Evenamide			No. of Bottles*	Evenamide		
		7.5 mg *bid***	15 mg *bid*	30 mg *bid*		7.5 mg *od***	15 mg *od*	30 mg *od*
Day 1	6	96 caps x 7.5 mg	96 caps x 15 mg	96 caps x 30 mg	3	48 caps x 7.5 mg	48 caps x 15 mg	48 caps x 30 mg
Week 6	6	96 caps x 7.5 mg	96 caps x 15 mg	96 caps x 30 mg	3	48 caps x 7.5 mg	48 caps x 15 mg	48 caps x 30 mg
Week 12	6	96 caps x 7.5 mg	96 caps x 15 mg	96 caps x 30 mg	3	48 caps x 7.5 mg	48 caps x 15 mg	48 caps x 30 mg
Week 18	6	96 caps x 7.5 mg	96 caps x 15 mg	96 caps x 30 mg	3	48 caps x 7.5 mg	48 caps x 15 mg	48 caps x 30 mg
Week 24	12	192 caps x 7.5 mg	192 caps x 15 mg	192 caps x 30 mg	6	96 caps x 7.5 mg	96 caps x 15 mg	96 caps x 30 mg
Week 36	10	160 caps x 7.5 mg	160 caps x 15 mg	160 caps x 30 mg	5	80 caps x 7.5 mg	80 caps x 15 mg	80 caps x 30 mg

**16 capsules/bottle*

*** The 7.5 mg dosage strength had been discontinued and was no longer dispensed. (Amendment 4, dated 18th June 2021)*

In the clinic, supplies of the study medication were stored under room temperature conditions (that is between 15 and 25°C), in a secure locked area. During outpatient treatment, patients were requested to store the medication at room temperature. All unused study medication and medication bottles were returned to Newron or its designee at the end of the trial or destroyed by the study site upon authorization by Newron. The destruction of unused medication was documented in accordance with ICH E6(R2) GCP guidelines.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subject Number

Each patient enrolled in the antecedent study (Study 014) received a six-digit subject number, with the first three digits specifying the center number and the last three digits the subject at the center. This same subject number was used throughout Study 015 to identify the patient. The subject number was entered in the eCRF and appeared in the header of each eCRF page, as well as being displayed in the listings for the CSR.

Patient Randomization

- Eligible subjects were randomized into 3 dose groups (7.5 mg *bid*,15 mg *bid* and 30 mg *bid*) in Study 014 and entered into Study 015 after completing 6 weeks of treatment in Study 014 (more details can be found in the overall design section).
- Note that, after implementation of protocol Amendment 4, subjects randomized to 7.5 mg *bid* had their dose of evenamide increased to 15 mg *bid*. There were 13 such cases and most of the up-titrations occurred close to Week 46. Therefore, the 7.5 mg *bid* dose group can also be considered as a 7.5 mg to 15 mg *bid* dose group in this study.

9.4.4 Selection of doses in the Study

The doses of evenamide selected for this study were based on preliminary evidence of safety and efficacy derived from animal models; a safety study in healthy volunteers (NW-3509A/001/I/2011 [Study 001]), which evaluated single doses of evenamide from 1 to 30 mg; an early 4-week safety and efficacy study (NW-3509A/002/II/2015 [Study 002]) in which patients with schizophrenia showing partial response to an atypical antipsychotic were treated with multiple ascending doses of 15, 20 and 25 mg *bid*; and a safety study in healthy volunteers (NW-3509/011/I/2019 [Study 011]), which evaluated a single 60-mg dose of evenamide. Additionally, results are available from two recently completed studies, Study NW-3509/008/II/2019 (Study 008), a 4-week study in patients with schizophrenia that evaluated doses of 7.5 and 15 mg *bid*, and Study NW-3509/010/I/2019 (Study 010), a crossover study in healthy volunteers that evaluated the effects of single doses of 30 mg and 60 mg on the QTc interval on the ECG. *(Amendment 4, dated 18th June 2021)*. The starting dose of 15 mg *bid* was very well-tolerated in 'Studies 002 and 008'. In the prior clinical studies, both the 30-mg and 60-mg single doses and the 25-mg *bid* doses of evenamide were well tolerated and not associated with any dose-related CNS events. This study evaluated the tolerability and safety of a maximum dose of 30 mg *bid*, with precautions to ensure the safety of patients enrolled in the trial.

In the multiple escalating dose study in patients with schizophrenia (Study 002), doses of 15, 20 and 25 mg *bid* were associated with mean (SD) C_{max} values of 40.4 (20.4), 65.7 (31.3) and 94.1 (51.3) ng/mL after the first administration of each dose. These levels should be within an effective range, as pharmacology studies indicate that a C_{max} plasma concentration of 20-40 ng/mL is effective in animal models predictive of antipsychotic efficacy.

Safety Ratio (SR) calculations for NW-3509 at the highest clinical dose of 30 mg (C_{max} 93.3 ng/mL, AUC 350 ng.hr/mL, Study 001) are presented in Section 7.3 of Study Protocol, included in Appendix 16.1.1.

9.4.5 Timing of Dosing for Each Patient

Evenamide has a short half-life ranging from 1.6 to 4 hours in volunteers (Study 001), and 2.2 to 2.5 hours in schizophrenic patients receiving multiple doses of 15 to 25 mg *bid* (Study 002).

Therefore, based on the above findings, twice daily (*bid*) dosing has been used in the current study, with a decrease to once daily (*od*) dosing permitted if intolerance develops. The doses tested in the current study were 7.5, 15 and 30 mg *bid*. These doses were expected to be safe as single doses of 30 mg (Study 001 and Study 010) and 60 mg (Study 010 and Study 011), as well as multiple doses of 25 mg *bid* (Study 002), were well-tolerated. The inclusion of the 7.5 mg *bid* dose allows determination of the minimally effective dose, while having three parallel dose groups allows a pilot assessment of dose dependency for safety and efficacy responses.

9.4.6 Blinding

This was an open-label, rater-blinded study; therefore, the Investigator and study staff, except for the blinded rater assessing safety and efficacy, were aware of the patient's treatment assignment.

If the blinded rater accidentally became aware of the treatment assignment for an individual patient, the Investigator was to document this in the patient's records, and to also provide a reason for the unblinding and the extent of the unblinding.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Background Antipsychotics

Any medication, in addition to the study medication, that was administered during the study from the start of the screening period through to the final evaluations on Week 46 was recorded in the eCRF (including over the counter [OTC] medications). Patients and their caregivers were instructed to contact the Investigator for approval prior to taking any medications, including OTC medications, while residing at home or in a residential care facility and prior to their final evaluation on Week 46.

Restrictions specified in the exclusion criteria were followed on concomitant medications being taken upon entry into the Screening period and during the treatment period of the study.

The psychotropic medications which were allowed for the treatment of insomnia on an "as needed" basis at the doses specified are as follows:

- zolpidem (2.5-10 mg/day, P.O.)
- zolpidem CR (12.5 mg/day, P.O.)
- zaleplon (5-20 mg/day, P.O.)
- zopiclone (7.5-15 mg/day, P.O.)

In addition, quetiapine, at a maximum dose of 150 mg *hs*, was permitted as a soporific in patients who had been taking it throughout Study 014. Patients were also allowed to start quetiapine (at doses up to 150 mg *hs*) for sleep post-baseline in Study 015. This could have been provided as a maintenance dose, if needed. Also, valproic acid was permitted, if used as a maintenance treatment.

Drugs that could increase the risk of seizures, e.g. bupropion, were not allowed to be administered. *(Amendment 1, dated 13th Feb 2020)*

9.4.7.2 Rescue Medication

"Rescue medication" in this clinical study is every pharmacological intervention used by the investigator to treat "an exacerbation of schizophrenia." This treatment included, as per protocol, a dose increase of the current antipsychotic medication, administration of a prohibited medication, or addition of a different antipsychotic medication.

In certain cases (e.g., dose increases of the concomitant antipsychotic by more than 25%) efficacy evaluations were to be performed before the start of dosing.

If a patient had an exacerbation of schizophrenia during the treatment period of the study that required additional pharmacological intervention, the Investigator was allowed to increase the dose of the patient's antipsychotic (if not currently at their maximum tolerated dose) or administer any other antipsychotic or other medication required to treat the episode.

If the dose of the patient's antipsychotic was increased by more than 25%, or the rescue medication administered was a drug prohibited by the protocol (e.g., a mood stabilizer), and use of the medication was not temporary (5 days or less), all final (Week 46) efficacy evaluations were to be performed prior to the start of dosing with the new treatment. Despite this intervention, the patient continued in the study and returned for all scheduled efficacy and safety evaluations.

At screening and during the treatment period, a patient was to be on a stable dose of one antipsychotic medication, which was recognized from its start date (preceding the screening date).

A dose change of the current antipsychotic (reduction due to an AE, or an increase in dose because of worsening symptoms) was identified by the stop date for the original dose and an entry for the new dose.

If a new antipsychotic was initiated, with a start date after baseline, that was considered "rescue medication" and had an indication of "worsening psychosis" or "worsening of schizophrenia symptoms".

A table was provided to summarize the dose of rescue medication taken during the study (Table 14.1.4.3). A subject data listing of the rescue medication details was also presented for the Safety Population.

In efficacy outputs the following rules were applied to subjects who received rescue medication, as applicable:

- Data collected post rescue medication was flagged in the listings and a footnote added to explain, if applicable.
- In the summary tables, data collected after rescue medication for PANSS total score, CGI-S and CGI-C was censored, i.e., treated as missing values.

Since this was an exploratory study, data collected after initiation of rescue medication was not censored for efficacy analyses purposes.

9.4.8 Treatment Compliance:

The study drug was only dispensed to subjects in accordance with the protocol. Monitoring of drug accountability records and information on medication dispensed to subjects in the study were done periodically by a monitor. A pill counting method was utilized to ensure dosing compliance at the subject level.

The compliance related methodological details are captured in Section 9.7.1.4 of this report.

9.5 Safety and Efficacy Variables

9.5.1 Safety and Efficacy Measurements Assessed and Flow Chart

Baseline (Day 43 of Study 014 / Day 1 of Study 015)

Patients who completed 6 weeks of treatment in Study 014 were required to provide informed consent in writing for Study 015 and satisfy all the selection criteria prior to being enrolled in this extension study. Study 014 baseline values were used for evaluating changes from baseline for safety and efficacy parameters for this extension study.

46-Week Extension Treatment Period

On Day 1, after all final Study 014 (Day 43) evaluations had been completed, patients meeting all entry criteria were given a supply of study medication at their current dose to cover the period until the next scheduled visit. Patients were instructed to take their first dose in the evening at their residence, at least 6 hours after the last dose in Study 014 that they received in the morning in the clinic. Throughout the treatment period, at each scheduled visit or telephone contact, careful open-ended questioning was used to evaluate whether the patient was experiencing symptoms and/or signs suggestive of neurological side-effects, severe sedation, seizures, or any other symptoms that could be dose-limiting, e.g., hypotension. In case the patient reported any of these symptoms, the patient was asked to contact the Principal Investigator, who decided, based on the symptoms/signs that had been identified, whether the patient had to come in for an evaluation, whether their dosing regimen required modification, and/or whether a concomitant medication had to be added. In cases where further evaluation of the patient confirmed symptoms or signs suggestive of treatment toxicity, the Investigator decided on the appropriate therapeutic and diagnostic measures to be taken. These may have included hospitalization, performance of a full neurological examination, EEG, ECG, etc.

Patients were required to return to the clinic for scheduled visits at Weeks 6, 12, 18, 24 and 36. During these visits selected safety and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. If no safety or tolerability issues were detected, patients continued receiving their current dose. The patient was discharged from the clinic and given a supply of study medication for the next period of dosing. After Week 24, the patient received a telephone contact from the

Investigator/site staff at Weeks 30 and 41, midway between scheduled clinic visits, to inquire regarding any safety or tolerability issues that he/she had experienced, and his/her usage of any concomitant medications. Based on this report, the patient's dose could have been reduced to once daily dosing, or if significant tolerability issues were noted at the current dose level, the patient could have been asked to return for an unscheduled visit.

The patient returned for the final evaluation at Week 46 (or at early discontinuation), at which time all final safety [vital signs (including waist circumference), 12-lead ECG, laboratory tests, ESRS-A, CDSS, physical/neurological examinations, and standard eye examination] and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. A urine drug screen was also performed.

Safety Follow-up Evaluation

For patients who discontinued prematurely, as well as those who completed 46 weeks of treatment in this open-label extension study but did not continue further extension treatment, a safety follow-up visit was performed approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. Patients who did not return to the clinic for their 7-day safety follow-up visit were contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patient was contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

The study flow-chart with the schedule of evaluations performed at each visit in the study is provided in Table 9-4. Detailed schedules of evaluations along with a narrative description of activities at each visit, are provided in the Study protocol in Appendix 16.1.1.

Table 9-4: Schedule of Evaluations

Visit Assessment	Final Visit of Study 014 [A]	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 41	End of study (Week 46) [D]	7 Day Safety follow-up [E]	30 Day Safety Follow-up [F]
Study Day	**0/1**	**43**	**85**	**127**	**169**	**211**	**253**	**288**	**323**	**330**	**353**
Informed consent	X										
Inclusion/Exclusion Criteria	X										
Vital Signs [B]	X	X	X	X	X		X		X	X	
Physical Examination	X				X				X		
Neurological Examination	X				X				X		
Electrocardiogram (12-lead ECG) [C]	X	X	X	X	X		X		X		
Standard Eye Examination	X				X				X		
Laboratory (Hematology, Biochemistry, Urinalysis)	X		X		X		X		X		
Serum prolactin	X								X		
Urine Drug Screen	X								X		
Serum Pregnancy Test [1]	X				X				X		
ESRS-A	X		X		X		X		X		
Study drug dispensing and accountability	X	X	X	X	X		X		X[J]		
Concomitant Medication and Significant Non-Drug Therapies	X	X	X	X	X	X	X	X	X		
Adverse events	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[F]
Seizure Checklist	X										
PANSS	X		X		X		X		X		
CGI-S	X		X		X		X		X		
CGI-C			X		X		X		X		
LOF	X		X		X		X		X		
CDSS	X				X				X		
Telephone Contact						X[H]		X[H]		(X) [E]	X

Study Completion									X		

[A] *Day 0 of Study 015 is identical to Day 43 of Study 014, and the values from the Day 0 (Study 014) safety and efficacy evaluations were used as the baseline values for Study 015.*

[B] *Vital signs were performed at baseline (Day 0), at Weeks 6, 12, 18, 24, 36 and 46, and at the 7-day safety follow-up visit. Vital signs were taken once in 3 positions (sitting for 5 minutes, within 1 minute of standing and after 3 minutes of standing). Waist circumference was also measured at baseline (Study 014) and at Week 46. Height that was measured at screening of Study 014 was used for calculating BMI.*

[C] *A 12-lead ECG was performed at baseline (Day 0) and at Weeks 6, 12, 18, 24, 36 and 46.*

[D] *All Week 46 evaluations were to be performed when a subject discontinued from the study prematurely.*

[E] *Performed 7 (±2) days after the last dose of study medication for patients who discontinued prematurely. If the patient had not attended the clinic visit, a call was made to the patient (or caregiver) to encourage attendance; or if unavailable, adverse event information was collected via the telephone.*

[F] *The patient was contacted minimally 30 days after the last dose of study medication to assess the occurrence of any SAEs. This information could have been collected through a telephone contact.*

[G] *Assessed adverse events that occurred since the prior visit or contact, including symptoms and signs suggestive of seizures*

[H] *Patients being treated as outpatients were contacted by telephone at Weeks 30 and 41; adverse events, including symptoms and signs suggestive of seizures, and concomitant medication use were assessed. If the patient reported significant intolerance, a dose reduction was to be performed, and he/she could have been asked to return to the hospital for an unscheduled visit for evaluation and appropriate workup.*

[I] *A serum pregnancy test was performed for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or were surgically sterilized, at Baseline and Weeks 24 and 46. (Amendment 4, dated 18th Jul 2021)*

[J] *At Week 46, only accountability of returned study medication was performed. No additional study medication was dispensed to the subjects who have completed the study at Week 46, and were not continuing further extension treatment. However, additional study medication was dispensed, as per protocol, to those subjects who continued the study beyond 46 weeks (Amendment 4.1 dated, 30th November 2021, Amendment 4.2, dated 8th July 2022).*

9.5.1.1 Safety Assessments

The assessment of safety was based on the following:

a) Vital signs (systolic/diastolic blood pressure, pulse, body temperature, respiratory rate, body weight, BMI, waist circumference),

b) Laboratory tests (hematology, blood chemistry, and urinalysis; serum prolactin),

c) 12-lead standard ECG,

d) Physical examination,

e) Neurological examination,

f) Standard eye examination – visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and front part of eyes (eyelids, cornea, conjunctiva, sclera, and iris),

g) ESRS-A,

h) CDSS,

i) Subjective reporting of any AE by the subject,

j) Objective observation of any AE by the Investigator,

k) Seizure Checklist.

The investigator was asked to comment on any clinically significant abnormal test results.

9.5.1.1.1 Adverse Events

Adverse events (AEs) evaluations were performed at Baseline, and at each visit of the study. Every untoward medical event was collected from the time when the patient signed the informed consent till the end of the safety follow-up period, i.e., 7 days post final dose of study drug. All AEs were recorded in the CRF. In addition, all the patients were followed up for 30 days after their last dose of study medication for the occurrence of any Serious AE.

In the CRF, AEs were classified as serious or non-serious with description of signs and symptoms along with onset date and time. The intensity of the event, relationship with the study drug, action taken in relation to the AE, action taken with the study drug, and subject outcome (stop date/time in case the outcome was recovered) were recorded as a part of data collection.

The details on AEs/SAEs definitions, data collection, relationship to study drug, intensity, action taken in relation to the adverse event, action taken with the study medication, outcome, reporting of SAEs and safety reporting to Investigators, IRBs, ECs, and Regulatory Authorities is detailed in Section 13 of Study 015 protocol presented in Appendix 16.1.1.

9.5.1.1.2 Reporting of Overdose

If the investigational site staff administering the study medication, the caregiver, or the subject reported that a patient inadvertently took more than the requisite number of capsules, then it was to be considered as “overdose” and reported immediately to the Investigator.

The details regarding reporting of overdose in India, Italy, and Sri Lanka are mentioned in Section 9.4.1.

9.5.1.1.3 Management of Pregnancy

Women of child-bearing potential, who were not using a highly effective contraception method were not eligible for the study. Use of contraception was to be initiated at least 28 days before the first dose and continued until 30 days after stopping study medication. As a further precaution, a serum pregnancy test was performed for all women of child-bearing potential, as well as those who were post- menopausal (age 50 or older with confirmed amenorrhea for >12 months) or who had been surgically sterilized, at Baseline (Day 0 of Study 014), Week 24 and Week 46 (or at early discontinuation). Additional serum or urine pregnancy tests were performed, as needed, based on local requirements.

If a patient became pregnant during the study, she was to be discontinued from the study immediately. The Investigator was to report all pregnancies, within 24 hours of discovery or notification by the patient, to the CRO by email or by fax using the Pregnancy Reporting Form. The timelines and other reporting requirements were the same as for a Serious AE. The patient (or caregiver/legal guardian/representative) was instructed to notify the Investigator within 24 hours if it was determined, after completion of the study, that the patient had become pregnant, either during the treatment phase of the study or within 30 days of completing the study. Whenever possible, a pregnancy was to be followed to term and for 1 year after delivery of the baby, and any premature terminations reported. The status of the mother and child was to be reported to the CRO or NEWRON within 24 hours after delivery, and one year later. *(Amendment 4, dated 18th June 2021)*

9.5.1.1.4 Vital Signs

Vital signs assessments were performed at all scheduled evaluations. Vital signs included body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. In addition, waist circumference was measured at Week 46 or at early discontinuation visit. Height, measured at the screening visit in Study 014, was used to calculate BMI. For all vital signs assessments, pulse and blood pressure was measured after the subject had been in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing.

If a change *of clinical relevance* from pre-dose to post-dose was observed, the vital signs assessment was to be repeated as often as needed, at the discretion of the Investigator. Findings were documented on the Vital Signs section of the CRF.

9.5.1.1.5 Clinical Laboratory Evaluations

Blood and urine samples were collected at the visits specified in the schedule of evaluations (Table 9-4). Evaluations of the hematology, blood chemistry and urinalysis analytes listed in Table 9-5 were performed every 12 weeks and at the final evaluation (Week 46 or early discontinuation). In addition, measurement of serum prolactin was performed at the final visit. A serum pregnancy test was performed at Week 24 and at the final visit (Week 46 or early discontinuation) for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or had been surgically sterilized.

Table 9-5: Summary of laboratory analytes

LABORATORY ANALYTES			
Hematology	**Blood Chemistry**		**Urinalysis**
Hematocrit	Sodium	Triglycerides	pH
Hemoglobin	Potassium	AST	Specific gravity
RBC count	Chloride	ALT	Protein
WBC count	Bicarbonate	Alkaline phosphatase	Glucose
Differential WBC count	Calcium	GGT	Ketones
Platelets	Glucose	LDH	RBC, WBC, casts
	BUN	Total cholesterol	Nitrites
	Creatinine	HDL, LDL, VLDL	Bilirubin
	Total bilirubin	CPK	Hemoglobin
	Albumin	Total protein	
Special Diagnostic Tests			
- Urine drug screen (Baseline [Day 0 of Study 014] and final visit) - Serum prolactin (Baseline and final visit) - Serum pregnancy test (Baseline, Week 24, and final visit) - for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or have been surgically sterilized			

A urine drug screen was performed at the final visit. The following substances were analyzed in the urine drug screen (performed at the study site): amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol (THC), cocaine, methylenedioxy-methamphetamine, opiates, oxycodone, phencyclidine, and propoxyphene). Additional urine drug screens were performed during the study if substance abuse was suspected.

The Investigator was to review the laboratory values at the final Day 43 evaluation in Study 014 to ensure that the subject met the protocol's inclusion/exclusion criteria. Abnormal tests at baseline were repeated, if necessary. The Investigator reviewed post-dose laboratory values within 24 hours of receipt of the laboratory report. After the review was completed, the Investigator signed and dated each laboratory report.

The laboratory provided normal reference ranges for the laboratory tests on the laboratory results report. A value was considered **normal** when it fell on or within the upper and lower limits of the reference range. A value was considered **abnormal** when it exceeded the upper or lower limit of the reference range. The laboratory flagged all abnormal and clinically notable values on the laboratory report, and provided the normal reference ranges for each parameter, and verified that the result was not due to pre-analytical problems (e.g., sample taken improperly, sample stored incorrectly, sample labeled incorrectly) or to analytical problems (e.g., machine not accurately calibrated, technical problems with equipment or reagents, or deterioration of analyte).

The Investigator evaluated any *change of clinical relevance* from pre-dose to post-dose in a laboratory test as to whether it met the definition of an adverse event, and repeated, if needed, any clinically significant abnormal laboratory test. Any laboratory abnormality that required intervention, led to a reduction in the dose of the study medication or concomitant antipsychotic, or if symptomatic was recorded on the Adverse Events CRF.

9.5.1.1.6 Electrocardiogram (ECG)

All subjects had a standard 12-lead ECG performed as specified in the schedule of evaluations (Table 9-4).

To ensure consistency in the data analysis across subjects, all ECGs were sent to a central ECG monitoring service for review and interpretation; however, the 'real-time' review and interpretation of the 12-lead ECGs, done for determination of a subject's eligibility for enrollment in the trial, as well as post-dose safety monitoring, was performed by a physician at the investigational site. One copy of the ECG tracing was retained in the subject's records, one was retrieved by the monitor, and a third was provided to the central ECG reader for analysis. The ECG interpretation from the central reviewer was reviewed by the Investigator, initialed, and dated, and a copy inserted in the subject's records. The interpretation by the central reader was done for all statistical analyses.

Each ECG tracing had the following information entered on it:

- Study number,
- Subject's number and initials,
- Date and time ECG obtained.

If clinically significant abnormalities were found, the subject's ECG was to be repeated at regular intervals until it returned to normal. Any ECG abnormality that required intervention, led to a reduction in the dose of the study medication or concomitant antipsychotic, or was symptomatic was recorded on the Adverse Events CRF.

Details of the procedures related to the centralized ECG monitoring service were provided in a separate manual prepared by the ECG Vendor (Appendix 16.1.10).

9.5.1.1.7 Physical Examinations and Neurological Examinations

A physical examination was performed at Week 24 and at the final visit (Week 46 or at early discontinuation). The findings were entered on the Physical Examination section of the CRF. The physical examination included an examination of general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system. Genital, urinary tract and rectal examinations were not done on a routine basis.

A neurological examination was performed at Week 24 and at the final visit (Week 46 or at early discontinuation). The findings were entered on the Neurological Examination section of the CRF. The neurological examination included the following: evaluation of mental status, cranial nerves, muscle strength and tone, reflexes, the sensory system, coordination and gait.

9.5.1.1.8 Standard Eye Examination

A standard eye examination, comprising assessments of visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and the front part of the eyes (eyelids, cornea, conjunctiva, sclera and iris) was performed at Week 24 and at the final visit (Week 46 or at early discontinuation). The examination was performed by a

physician at the site who had the appropriate experience and training. If a clinically significant abnormality was noted that required expert follow-up, an Ophthalmologist or Optometrist was to be consulted.

9.5.1.1.9 Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)

The ESRS is a 33-item scale designed to examine changes in motor function associated with pharmacologic treatment (Chouinard G et al, 1980; Chouinard G et al, 2005). It has a 'subjective' part (12 items, 0 - 4 rating) and a part scored 'objectively' based on observation and examination (parkinsonism: eight items, dystonia: two items, dyskinesia: seven items; all scored on a 0 - 6 scale described for each item separately in terms of frequency and severity, some subdivided for body-parts). There are three global scales assessing dyskinesia, parkinsonism and dystonia, and a Hoehn and Yahr stage estimation of parkinsonism. It has been validated in many studies including add-on therapy and drug withdrawal studies for atypical antipsychotics. An abbreviated version of the ESRS, the ESRS-A, was used in this study and was performed every 12 weeks and at the final visit (Week 46 or at early discontinuation).

9.5.1.1.10 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a nine-item, observer-rated, semi-structured, goal-directed interview, validated for diagnosing depression in patients with schizophrenia. Each item is scored between 0 and 3 based on operational criteria. A total score of 6 or above is considered predictive of a major depressive episode. Internal reliability as well as inter-rater reliability is high (Addington D et al, 1993). In the current study, the CDSS was performed at Week 24 and at the final visit (Week 46 or at early discontinuation) to assess depressive symptoms.

9.5.1.1.11 Seizure Checklist

If any of the following symptoms and signs that are suggestive of a seizure were observed in a patient or reported by a patient/caregiver, appropriate diagnostic measures (e.g., EEG) and follow-up were to be performed:

- *Seizure*
- *Fit*
- *Jerk*
- *Jerky movements*
- *Startle*
- *Convulsion*
- *Absence seizure*
- *Gazing*
- *Staring*
- *Fall*
- *Fainting*
- *Syncope*
- *Auditory/visual aura*
- *Myoclonus*
- *Automatism*
- *Unconsciousness*
- *Biting of tongue*

9.5.1.1.12 Metabolic Syndrome

Most antipsychotics cause significant cardio-metabolic and endocrine side effects, including weight gain, insulin resistance, dyslipidemia, and hypertension (Henderson DC et al, 2015; Riordan H et al, 2011). Up to 50% of patients treated with antipsychotics develop these complications comprising ametabolic syndrome. Criteria for metabolic syndrome, according to the International Diabetes Federation (2006), include central obesity plus any 2 of the following 4 factors: elevated triglyceride level, reduced HDL cholesterol, elevated blood

pressure, and elevated fasting plasma glucose or previously diagnosed type 2 diabetes. Since all patients enrolled in this study received an antipsychotic, and many had an extensive treatment history with multiple other antipsychotics, several parameters were evaluated to assess the presence of metabolic syndrome at screening, and to monitor its progress over the course of the study to assess any potential effects of evenamide. These parameters included waist circumference, tests that were part of the routine laboratory panel (e.g., plasma glucose, triglycerides, HDL, LDL) and vital signs (e.g., weight, BMI, blood pressure) performed at each visit.

9.5.1.1.13 Independent Safety Monitoring Board

An independent board of knowledgeable experts appointed by Newron safeguarded subjects participating in evenamide trials by reviewing unblinded safety data on an ongoing basis during the conduct of the new trials (Phases I-III) that constitute the evenamide schizophrenia development program, including the current 'Study 015'. The main reasons for Newron to constitute the formation of this Independent Safety Monitoring Board (ISMB) were: 1) the limited human safety data generated to date for evenamide, 2) high base rates of major safety events in the underlying population, and 3) susceptibility of the study population to safety risk because of their underlying diseases.

The ISMB was comprised of at least 3 voting members. All these members were clinicians who had extensive experience in the treatment of patients with mental disorders and may have participated in other ISMBs. Ravi Anand, MD, Newron's Chief Medical Officer, served as the Sponsor's representative and primary contact for the ISMB. A non-voting consultant statistician was assigned to help the committee with any special analyses.

The purpose of the ISMB was to review the accumulating safety data from the subjects in the studies in an advisory capacity and to protect additional subjects from harm in the advent of an unanticipated safety signal. The role of the ISMB was to increase the effectiveness of safety monitoring by supplementing usual activities performed under the Sponsor's study-specific safety monitoring plan, in this case by enabling unblinded safety reviews for cases in which decisions about study conduct require knowledge of treatment assignment information.

For 'Study 015', the ISMB, based on their review of the safety data, made recommendations to the Sponsor /Newron regarding study modification/or amendment (e.g., increase safety monitoring), study termination (e.g., the evenamide safety profile is unacceptable), or continuation of the study as designed. In Study 014, the ISMB reviewed key safety data from the first 50 patients randomly assigned (1:1) to evenamide 7.5 or 15 mg *bid* and determined whether it was safe to proceed with dosing of patients at 30 mg *bid*. The ISMB provided recommendations to continue the trial as designed, or with modification, including amendments to the protocol for discontinuation of the evenamide 7.5 mg *bid* dose group from the study, dosing of patients with 30 mg *bid* doses, and the modification of the randomization to a 1:3 ratio for the 15 mg *bid* and 30 mg *bid* dose groups, respectively *(Amendment 4, dated 18th June 2021)*.

The current study protocol was subject to amendment mandated by the emerging (unblinded) safety profile of evenamide, if necessary. The Sponsor's representative made the decision to

accept the ISMB's recommendation and request for access to unblinded study data in order to make an informed decision.

The ISMB reviewed data from all patients enrolled at specified intervals throughout the trial. The CRO and Sponsor compiled subject data by treatment group and provided it to the ISMB at regular intervals. The ISMB had access to safety data, including adverse events, dropouts, SAEs, clinically significant abnormal laboratory tests, vital signs, and ECGs. The ISMB was notified for the occurrence of any fatal/life threatening event within 24 hours of Newron becoming aware, and other SAEs within 72 hours. The ISMB also received detailed information on any adverse dropouts occurring in the study. The ISMB was empowered to review all the safety data on an ongoing basis, with special emphasis on SAEs and deaths, in addition to the standard safety parameters. Details of the ISMB charter (separate document) were available to regulatory authorities and IECs/IRBs upon request.

9.5.1.2 Efficacy Assessments

Patients were instructed to take the morning dose of study medication at their residence on the day of each scheduled clinic visit. Patients took their concomitant antipsychotic and other medications at their residence according to their usual schedule. To ensure consistency of ratings for key efficacy measures, e.g. PANSS and CGI-C/S, these assessments were performed at the approximately the same time relative to the morning dose of study medication, if possible, during the scheduled clinic visits at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation).

Efficacy-related Endpoints

Long-term preliminary efficacy was assessed by the following measures:

- PANSS total score - mean change from baseline to endpoint
- CGI-S – mean change from baseline to endpoint
- CGI-C – proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3), and mean score at endpoint
- PANSS – Positive Symptoms total score – mean change from baseline to endpoint
- PANSS – General Psychopathology total score – mean change from baseline to endpoint
- LOF – mean change from baseline to endpoint
- PANSS – Negative Symptoms total score – mean change from baseline to endpoint.

9.5.1.2.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al, 1987) is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The 30 symptoms are each rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale, which has been shown to be sensitive to medication treatment, provides a balanced representation of positive and negative symptoms, and gauges their relationship to one another and to global psychopathology. In addition to a total score, this assessment yields separate sub-scores on a Positive Syndrome Scale, a Negative Syndrome Scale, and a General Psychopathology Index. The PANSS interview process typically takes between 30 and 40 minutes to complete. The PANSS was conducted at

Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation), and was used as the primary efficacy measure in the trial. The same physician (an MD, clinical psychologist, or other clinician with extensive training and experience) performed the ratings of the PANSS, CGI-C and CGI-S.

9.5.1.2.2 Clinical Global Impression (CGI)

The CGI (Guy W (Ed)) is the general name for 2 scales: the CGI-Severity (CGI-S) measures global severity of illness at a given point in time, and the CGI-Change (CGI-C) measures change from the baseline state (baseline from Study 014) at each post-baseline visit. In this study, the ratings of the CGI-S and CGI-C were performed by the same blinded clinician who performed the rating of the PANSS. The CGI rater had access to the PANSS data, as well as the results of safety assessments and the ratings on other efficacy measures. Whenever possible, the CGI scales were completed by the same clinician for every assessment; if this was not possible, the rating clinician reviewed the subject's presentation (along with review of clinical notes) with the rater who completed the initial evaluation.

The CGI rating scale permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S is performed, in which the Investigator rates the severity of a subject's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). At subsequent visits, the Investigator assesses the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at baseline in Study 014 using the CGI-C, a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating "no change". The CGI-S and CGI-C assessments were conducted at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation).

To ensure that the assessments of the CGI-S and CGI-C were done consistently, the CGI rater performed a complete assessment of the patient at baseline, including positive and negative symptoms, global psychopathology, functioning and mental state. Investigators were provided with a guide to ensure that all domains were assessed. A summary of the baseline interview (baseline assessment of Study 014) was written as a narrative that covered the dimensions of symptomatology, so that it could be referred to when assessing response at subsequent visits. This narrative remained at the site and was readily available to the rater(s) for subsequent ratings. The narrative was to be reviewed prior to completing any future CGI-C rating. At each subsequent visit, the rater was requested to write a brief paragraph describing the justification for the rating on the CGI-S and CGI-C. Further details are provided in Section 12.3.2 of the Study 015 protocol presented in Appendix 16.1.1.

9.5.1.2.3 Strauss-Carpenter Level of Functioning (LOF) Scale

The LOF has been widely used as an instrument to evaluate clinical outcome in patients with schizophrenia (Strauss and Carpenter, 1977). The LOF is a semi-structured, clinician-administered scale containing nine items and requires approximately 15 to 20 minutes for completion. The individual items fall into four domains, with higher scores on a 5-point scale (0 - 4) reflecting better functioning. The subscales are: Social contacts (frequency and quality of social contacts), Work (quantity and quality of useful work), Symptomatology (absence of symptoms and recent hospitalization), and Function (ability to meet basic needs, fullness of

life, and overall level of function). Subscale scores were calculated as the mean scores for items in each scale. A total score was calculated as the sum of the raw scores across the nine items. Inter-rater reliability has been demonstrated, and the instrument has been shown to be sensitive to subtle changes in functioning and treatment effects over time. The LOF was conducted at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation).

9.5.1.2.4 Rater Training

All raters in this study were required to have demonstrated competence in administering scales used in clinical trials. Raters were trained and certified for the PANSS and CGI-S/C using the Newron specialized website and its training program. The same rater performed both the PANSS and CGI assessments and performed all ratings for a given patient throughout the study.

To ensure the sensitivity and reliability of all individual assessments, it was requested that the same blinded rater was to conduct the PANSS and the CGI-S/C ratings on an individual patient at every visit. It was recognized that, because of scheduling, ill health, etc., it would sometimes not be possible to meet this condition; however, every reasonable effort was made to ensure uniform conditions across evaluations for all ratings.

If a rater was not present to conduct a scheduled assessment, another qualified rater who was familiar with the patient and was present for the rating at the prior visit was to conduct the assessment. For the CGI-S/C, the substitute rater was to carefully review the notes or recording from the baseline evaluation prior to interviewing and rating the patient.

Details of the rater's qualifications and certification for the PANSS and CGI ratings for the study are presented in Section 12.3.4 of the Study Protocol presented in Appendix 16.1.1.

9.5.2 Appropriateness of Measurements

All safety and efficacy assessments used in this study were standard (i.e., widely used and generally recognized as reliable, accurate, and relevant). Adverse events (AEs) were assessed throughout the study and included an assessment of CNS symptoms and signs, with a particular focus on identifying any seizure-like events. Other standard safety assessments were performed at baseline, following the first dose, and periodically throughout the study. In addition, the ESRS-A was used to evaluate potential treatment-related movement disorders. Depressive symptoms were assessed using the CDSS. A standard eye examination was included to assess any potential ocular effects of evenamide. Assessment of efficacy was a secondary objective of this study. The efficacy of evenamide in treating the symptoms of schizophrenia was assessed using the PANSS, CGI-S, CGI-C, and LOF.

9.5.3 Primary efficacy variable

The PANSS, which was used as the primary efficacy measure in this study, has been used as the primary measure in many antipsychotic trials. Additionally, the PANSS Positive Symptoms sub-scale was used as a secondary efficacy measure, as the effect of evenamide is expected to be primarily on the positive symptoms of schizophrenia, based on the findings in a previous study (Study 002). The Negative Symptoms and General Psychopathology sub-scales were also analyzed separately as secondary measures.

9.6 Data Quality Assurance

This study was conducted in accordance with the Declaration of Helsinki and the ICH E6 Guideline (Good Clinical Practice). To ensure compliance, the Investigator agreed, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation, including subjects' hospital files (the source documents), by authorized individuals. The Investigators made all pertinent records, including source documentation, available for inspection by regulatory authorities and auditing by the Sponsor. This information was considered confidential. Documentation of inter-laboratory standardization methods and quality assurance procedures are presented in Appendix 16.1.1.

9.6.1 Data collection

9.6.2 Electronic Case Report Form

All the subject data generated during the study was recorded on the electronic Case Report Form (eCRF) for all subjects who signed Informed Consent. It was the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The eCRFs were considered complete when each eCRF has been reviewed and electronically confirmed by the Investigator, indicating his/her assurance of the accuracy of all recorded data. As requested, copies of the eCRFs were made available to the appropriate regulatory agencies.

9.6.2.1 Study Monitoring

CliniRx Research Pvt Ltd., India was selected by the Sponsor as lead CRO to oversee the conduct of the trial. The Sponsor transferred all local responsibilities to CliniRx, which was responsible for the selection of local CROs. An appropriate representative of the CRO (Study Monitor) maintained contact with the Investigator and visited the site to discuss and/or to address any study related matter. An initiation visit (pre study) was made by the study monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Investigator allowed the study monitor to perform periodic, interim monitoring visits. The purposes of these visits (on-site) were:

- To verify that written informed consent was obtained prior to each subject's participation in the study,
- To assess the progress of the study,
- To review the compliance with the study protocol
- To determine whether all AEs were appropriately reported,
- To determine whether the Investigator was maintaining the essential documents,
- To discuss any emergent problem,
- To check the eCRF for accuracy and completeness,
- To validate the contents of the eCRFs against source documents,

- To assess the status of drug storage, dispensing, and retrieval (by an independent unblinded study monitor with no other involvement with the study and who did not have access to the eCRFs or other study documents).

Violations and deviations from the protocol were notified to the study monitor as soon as possible. Site staff also registered these in a site-specific log. Minor and major protocol deviations were pre-specified as agreed between the clinical and medical operational teams in the Protocol Deviation Classification Sheet. Protocol deviations were reviewed by the Sponsor and CRO medical representatives.

The study monitor performed a closeout visit at the time when all eCRFs were completed and all queries answered.

9.6.2.2 Audits and Inspections

There were no audits conducted during the study.

9.7 Statistical Methods

9.7.1 Statistical & Analytical Plan

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the analysis and reporting of data collected under Newron Pharmaceuticals S.p.A. clinical study protocol NW-3509/015/II/2019 *(Amendment 4.1 dated 30th November 2021 for India and, Amendment 4.3 dated 18 July 2022 for Sri Lanka and Italy)*. Complete details of the statistical methods were outlined separately in the SAP presented in Appendix 16.1.9 of this clinical study report (CSR).

All data collected in this study was documented using summary tables, patient data listings and figures. Results are displayed in this report for each dose level of evenamide, and in some cases for all evenamide dose groups combined.

Continuous Variables (e.g., Height) were summarized using descriptive statistics, specifically the number of data points (n), mean, median, standard deviation (SD), minimum and maximum.

Categorical Variables (e.g., Sex) were summarized by counts and percentages. The percentages were derived based on the total number of subjects in each dose group within the specified population.

Decimal places in data presentations

The mean and median were reported to an additional 1 decimal place, and the standard deviation (SD) and confidence intervals (CI) were reported to an additional 2 decimal places, compared to the original result. Minimum and maximum were reported to the same decimal place as in the original result, unless otherwise specified. Percentages were presented to 1 decimal place; except percentage was not presented when the count was zero, and 100% was presented as an integer. The values were rounded to the specified decimal places as above. P-values were rounded to 3 decimal places; p-values smaller than 0.001 were presented as ‘<0.001’, and greater than 0.999 were presented as ‘>0.999’.

Long Text Handling

For data fields for free text entry, long texts were retained in listings, except for the vital signs listing, where "reason not done" was not displayed. However, details were found in the study datasets.

Data Derivation

The following definitions and derivations are applicable for Study 015 eligible subject's baseline data listings and report preparation.

Baseline

The protocol stated that the final Day 43 safety and efficacy evaluations in Study 014 would serve as the baseline assessments for this extension Study 015. However, from a statistical perspective the date of first dose of evenamide (i.e., in-clinic administration on Day 1 of Study 014) has been considered as the anchor date, and this is also supported by protocol clarification document dated 13-Oct-2023. Therefore, relevant baseline assessments of Study 014 are retained, and Day 43 data have been ignored for the analysis of changes from baseline.

Anchor Date

First Dose Date of Study 014 (i.e., Day 1) was considered as the first dose date for safety and efficacy analysis for Study 015.

First Dose Date of 015 Study

Day 1: was considered the starting point for determining treatment compliance. Treatment start date was taken from the Study 015 Day 1 visit date when an IP kit was dispensed. For some subjects IP kits were dispensed later (Unscheduled visit or Week 6) and that visit date was considered as first dose date.

Last Dose Date

Last dose available in the Week 46/End of Study form in the eCRF. For "lost to follow-up" or "withdrawal of consent" cases, the last dose date was taken from drug accountability (kit dispensed date) in the eCRF in case it was not available in the Week 46/End of Study form in the eCRF.

Week 46/Early Termination visit

All Week 46 evaluations were to be performed when a subject discontinued from the study prematurely before completing the 46-week treatment period.

Note that data collected beyond Week 46 is not included in any listings or analysis for this report, except for the safety follow-up assessments performed 7 and 30 days after the last dose for patients who completed 46 weeks, but did not continue the study. Those data which were not linked with the visit folder (i.e., AE and concomitant medication [ConMed]) were excluded, as follows:

- AE/ConMed start date after the Week 46 visit date or applicable last contact date (safety follow-up).

- AE/ConMed stop date was an actual value from the database, but it falls beyond the last contact date, as study is still ongoing in the further extension period.

The SAP describes the statistical methods used during the analysis and reporting of data collected under Newron Pharmaceuticals S.p.A. clinical study protocol NW-3509/015/II/2019 (Version 5, Amendment 4, dated 18th June 2021). Complete details of the statistical methods were outlined separately in the SAP presented in Appendix 16.1.9 of this clinical study report (CSR).

All statistical analyses and data presentations were generated in this report using the SAS® Version 9.4 (or later) Software (SAS Institute, Cary, North Carolina, USA).

Study Completion and Discontinuation

The study completion date of any patient from Study 015 was the Week 46 date, irrespective of whether the subject attends the Safety Follow-up (SFUP) visits or not.

Date of discontinuation was the date captured in the Week 46/End of Study form, documented by the Investigator and documented in source documents, regardless of the date on which the last dose of study medication was taken.

Unscheduled Visits

All unscheduled visit data was listed regardless of whether it is collected pre-dose or post-dose. For subjects who had an interruption in their dosing due to running out of medication, before resuming dosing with evenamide, efficacy parameters were taken at an unscheduled visit, as per medical judgement.

For the efficacy analysis, scheduled visits were considered. In case a scheduled visit is not available, unscheduled assessment data were utilized. Unscheduled visit data were displayed as ‘Unscheduled Visit followed by Unsch X.01,.02’ and sorted by date (X denotes the prior visit number).

Analysis time-points

Post-baseline analysis time-points included Weeks 6, 12, 24, 36, and 46 as per the Study 015 visit schedule, i.e., relative to the first dose of the extension study (i.e., Day 1 of 015), as applicable. These analysis timepoints interpreted as Weeks 12, 18, 30, 42 and 52, after including 6 weeks of prior exposure in core Study 014.

9.7.1.1 Analysis approach

Analysis Populations

The Intent-to-Treat (ITT) approach was followed for determining the analysis population, i.e., each subject was in the same dose arm in the extension study to which he/she was randomized in the core Study 014.

Rolled Over Population

The “Rolled Over” Population consisted of those subjects randomized in Study 014 who have completed core study Day 43 and signed the ICF for the extension study (Study 015).

Safety Population

The Safety population consisted of all subjects who had taken at least one dose of study medication in this extension study (Study 015).

Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population comprises patients with a valid Study 014 baseline, who rolled over into Study 015 and received at least one dose of the study medication in this extension study (015) and had at least one post-baseline assessment for the primary efficacy measure, the PANSS total score in Study 015.

Modified Intent-to-Treat Population - Completers (mITT-C)

The mITT Completers population includes subjects in the mITT population who have completed treatment through the Week 46 visit.

Ad-hoc Analysis

The following ad-hoc analyses were performed:

1. Overall combined (all doses of evenamide) safety analysis for safety population (for all safety measures).
2. Overall combined efficacy analysis for mITT population (PANSS, CGI-S/C and LOF).
3. Repeat efficacy analysis dose-wise and overall combined for mITT-C population (PANSS, CGI-S/C and LOF).

Ad-hoc tables are shown with suffix ‘d’ and combined ones with suffix ‘c.’

9.7.1.2 General Considerations

9.7.1.2.1 Data Processing

Data were extracted from the Clinical study database [single Medidata RAVE database for Studies 014 (Core study) and 015 (Extension study)], once all subjects randomized to treatment in Study 014 had either completed the ‘end of study’ visit under Study 015 or had discontinued from the study prior to this visit (Week 46/Early Termination visit), and the database was cleaned and locked. This extraction was performed even if the patients were continuing further in the extension treatment period beyond Week 46 in Study 015.

9.7.1.2.2 Missing Safety Data Dates

A medication with a completely missing end date was considered as continuing during the trial as a concomitant medication.

If an AE has a completely missing onset date, then the AE was considered a treatment-emergent adverse event (TEAE).

If an AE or a medication has a partial missing start or end date (Day or Month missing), or part of the schizophrenia diagnosis date used to calculate the duration of current episode/ duration of illness is missing, the following rules were used to impute the date. The imputed date was used to determine whether a medication is a prior or concomitant medication.

For missing dates (Day and/or month) in diagnosis of schizophrenia and first episode's, first Day and/or Jan was applied except that the year was not imputed. Policies used for imputation of missing dates are summarized in the table below:

Missing Safety Data Dates

Partial/Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, but the year is present	January 1st of that year or date of the first dose if the year is the same as the year of first day of doing.	December 31 of that year
Missing day, but year and month are present	First dose date if the year and month are the same as the year and month of first dose date. First day of that month if the year and month are different from the year and month of first dose date.	Last day of that month
Missing month, but year and day are present	Missing month imputed as January or the month of the first dose date	Missing month imputed as December

9.7.1.2.3 Missing Data Imputation

Other than missing dates, no imputation were performed on safety data.

For the efficacy endpoints (PANSS and CGI-S) sensitivity analyses, missing post first dose data were imputed using SAS PROC MI multiple imputation Monotone Regression Method by each dose group. A total of 10 complete datasets were imputed using the SAS MI procedure described in Appendix 5 of SAP presented in Appendix 16.1.9.

Further sensitivity analyses were performed using the LOCF (Last-observation-carried forward) method for PANSS and CGI-S.

9.7.1.3 Background Characteristics and Demographics

The background and demographic characteristics (age, race, ethnicity, weight, height, BMI, substance use, education, marital status, employment, housing status, past and current medical conditions, etc.) and disease characteristics (severity of illness, duration of illness, concomitant psychotropic medication, etc.) collected at screening in Study 014 were used to describe the patients enrolled in this extension study. Continuous variables were summarized by minimum, maximum, mean, median, and standard deviation, and discrete variables were summarized using frequencies and percentages.

9.7.1.3.1 Subject Disposition

A subject enrollment listing with enrollment details and protocol version was provided. The number and percentage of subjects included in each analysis population (Safety population, Modified Intent-to-Treat Population, Modified Intent-to-Treat Population-Completers and Rolled Over Population), subjects who completed Week 46, discontinued or withdrew early, with a breakdown of the reasons for early discontinuation (e.g., adverse events, lost to follow up withdrawal of consent), were summarized by each evenamide dose group and total.

Subject listings were presented for disposition, including details of randomization (Randomization number and date) and reason for discontinuation, for all randomized subjects who participated in Study 015. Details are included in Table 10-1: Subject Disposition.

9.7.1.3.2 Protocol Deviations

Protocol deviations were collected by the CliniRx clinical team and provided to CliniRx Biostatistics prior to database lock. Protocol deviations were reviewed on a case-by-case basis and classified as minor, major, or critical by the project team prior to database lock. Critical and major protocol deviations were summarized and listed.

9.7.1.3.3 Baseline Characteristics

Study 014 baseline values, as defined in the Study 014 Statistical Analysis Plan, were used for safety and efficacy evaluations for this extension study.

9.7.1.3.4 Disease Characteristics

The disease characteristics, including duration of illness, duration of current episode, number of psychiatric hospitalizations, family history of schizophrenia, and baseline depressive symptoms assessed by CDSS, of the Safety population were summarized. Family history of schizophrenia was also summarized as first-degree and second-degree relatives, by considering subject's parents, siblings, or children as first-degree relatives and others as second-degree relatives.

The duration of current episode was calculated as:

Duration of Current Episode (months) = (Date of Randomization – Start Date of Current Episode+1) /30.4167

The duration of illness for schizophrenia was calculated as:

Duration of Illness (Years) = (Date of randomization – Date of First diagnosis + 1) /365.

9.7.1.3.5 Inclusion/Exclusion Criteria

A listing of all inclusion/exclusion criteria not fulfilled was provided for all subjects screened. This listing was based on data as recorded on the inclusion/exclusion page of the eCRF.

9.7.1.3.6 Study Drug Accountability

Study drug accountability data were presented as an individual data listing (Listing 16.2.5.1).

9.7.1.4 Safety and Tolerability Analyses

Exposure and Treatment Compliance

The duration of exposure and treatment compliance, by evenamide dose group, for the safety population for extension Study 015 are summarized in Table 11-4 and Table 11-5, respectively.

Duration of exposure is the number of days from the treatment start date (from 015 Day 1) to treatment end date (015 Week 46).

Overall dosing compliance (% compliance) was assessed by calculating the #Capsules consumed starting from 015 Study Day 1 till Week 46 and comparing that to the #Capsules expected to be consumed, as follows:

- % Compliance = 100*[#Capsules consumed / #Capsules expected to be consumed],

where #Capsules consumed = Sum of (#Capsules consumed per kit).

- #Capsules consumed per kit calculated as #dispensed Capsules in the kit - #returned/lost Capsules in the kit.
- #Capsules expected to be consumed = 2 * (Last dose date – First dose date + 1).

The Investigator's judgement was considered in cases where a kit was not returned, if applicable. If the Investigator's judgement stated "Complied? YES", despite the kit not being returned, all capsules expected to be consumed over the period from IP bottle dispensing to the returning visit were counted in the calculation.

Intermittent gaps due to IP non-availability (out of medication) were subtracted in the denominator for capsules expected to be consumed.

There were some exceptional cases where manual coding was performed for compliance calculation as per eCRF text data and protocol deviation (PD) list.

Some of out of medication details (due to IP non-availability) and lost capsules were not easily available in the eCRF, and these was provided through a file note.

Compliance was summarized overall at Week 46.

Study exposure data are presented in this report as individual data listings.

To characterize the dosing patterns during the study, summary statistics on the number of subjects with unscheduled dose adjustments, including dose adjustment reasons, are provided. Note that more than one reason per subject may be provided for dose adjustment, kit replacement and other dosing issues, due to multiple modifications.

Reasons for unscheduled dose adjustment are listed below, if applicable:

- Start of adverse event
- End of adverse event
- Other

A subject listing of dose adjustments over the course of the study was provided for the Safety population.

9.7.1.4.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse events were coded according to MedDRA v23.0.

Treatment-emergent AEs (TEAEs) are AEs that are newly occurring or worsened in severity, compared to pre-existing conditions, after the first administration of the study medication in Study 015. The following criteria were used to define treatment emergence for AEs with missing start or stop dates:

- If both the start and stop dates for a particular event are missing, then that event is considered treatment-emergent.
- If the start date for a particular event is missing and the stop date falls after the first dose date, then that event is considered treatment-emergent.
- If the start date is the same as the first dose date, that event is considered treatment-emergent.

For events with a partial start date, the year/month of the event date was compared to the date of the first dose to determine whether the event is treatment-emergent.

The frequency and percentage of subjects experiencing a TEAE for the Safety population was summarized using the MedDRA system organ class (SOC) and preferred term (PT), by evenamide dose group, and total of all dose groups.

AE summary tables include the following, as applicable:

- Overall incidence of SAEs, AEs leading to withdrawal / study drug discontinuation), and AEs leading to death for all TEAEs.
- Summary of TEAEs by SOC by PT
- Summary of TESAEs (Treatment-emergent serious AEs) by SOC by PT
- Summary of Treatment-related TEAEs by SOC by PT
- Summary of AEs leading to study drug discontinuation, by SOC by PT
- Summary of TEAEs by maximum Severity.

Treatment-related adverse events are defined as the TEAEs which are considered possibly or probably related to study drug, or the relationship is unknown (not reported).

A subject with multiple occurrences of the same AE or an ongoing AE that changes in severity was counted only once under the highest reported severity or relationship.

All AEs, TEAEs, and SAEs were presented in individual subject data listings.

Deaths were also listed separately, with autopsy details, if available.

9.7.1.4.2 Vital Signs

Vital signs assessments were performed at all scheduled evaluations. Vital signs include body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. In addition, waist circumference was measured at Week 46. Height, measured at the screening visit in Study 014, was used to calculate BMI. For all vital signs assessments, pulse and blood pressure were measured after the subject was in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing.

Tables presenting descriptive statistics for all the observed vital signs were provided. Changes from baseline at each visit and at endpoint (Week 46 or early discontinuation) were presented by evenamide dose group for temperature, respiratory rate, pulse, weight, BMI, waist circumference, systolic blood pressure and diastolic blood pressure.

Based on the Appendix 2 of the study protocol described in Appendix 16.1.1 counts and percentages of subjects meeting the clinically notable abnormalities criteria for each vital sign variable were provided for each evenamide dose group.

Vital signs listings were presented in three parts: Individual subjects listing with change from Baseline, Time profile, and Treatment-Emergent Clinically Notable Abnormalities. Long text of the reason an assessment was not done was not displayed, due to limitations of page record.

The analysis of vital signs data was done on the Safety population.

9.7.1.4.3 Laboratory Evaluations

The number and percentage of subjects meeting criteria for newly emergent clinically notable abnormalities (see Appendix 2 of the study protocol) for hematology and biochemistry parameters was presented for each evenamide dose group in the Safety population.

Urinalysis data were listed only, along with clinically significant values, as determined by the Investigator. Clinical notable value determinations for urine parameters were selected for Specific Gravity, RBC and WBC casts only.

The summary of change from baseline to each visit was also provided for hematology and biochemistry parameters mentioned in Appendix 3 of the SAP by evenamide dose groups.

The individual values of hematology and biochemistry parameters collected at different central and local (only sites in Italy) laboratories were standardized in SI units and then normalized using either of the normalization formulas presented below for each of the parameters mentioned in Appendix 4 of the SAP.

Metropolis Healthcare Ltd, the central laboratory for all sites in India, was considered as the standard laboratory for normalization for Sri Lanka central laboratory and Italy local laboratories, as the majority of subjects were evaluated using Metropolis central laboratory. Normalization was performed as follows.

Whenever both the lower and upper reference limits of a lab test are available, the location-scale formula was used.

1) Location-scale normalization formula

$$s = L_S + (x - L_X)\frac{U_S - L_S}{U_X - L_X}.$$

Here, it was assumed that the distribution of standard values and the original values belong to the same location-scale family of distributions.

There is a possibility that a derived value becomes negative when there is only a one-sided reference limit (i.e., Fasting Glucose, HDL); in that case, the following scale normalization was used:

2) Scale normalization formula

$$s = x\frac{U_S}{U_X}.$$

where,

s = The transformed individual laboratory value to a common standard laboratory reference range.

X = The original value in SI unit. This value was used for determining clinically notable values as specified in the protocol.

LX = Lower limit of normal range for an individual parameter test.

UX = Upper limit of normal range for an individual parameter test.

LS = Lower limit for the selected common standard laboratory.

US = Upper limit for the selected common standard laboratory.

If lower and upper limits were available for a parameter, the location-scale formula was used. For other cases like Fasting Glucose and HDL, the scale normalization formula was used.

Listings were provided for the following Special Diagnostic Tests (Baseline of Study 014):

- Urine drug screen (Baseline [Baseline of Study 014] and final visit)
- Serum prolactin (Baseline and final visit)
- Serum pregnancy tests (Baseline, Week 24 and final visit)

A listing of laboratory measurements recorded throughout the treatment period was presented along with reference ranges and normalized values, as applicable.

Date and time of sample collection and visit mismatch with external data were used from the eCRF, if applicable.

Indian sites' Subjects #303013, 303015, 304002, 304012, 304015, 304016, 304019, 308001, 311003, and 311006 had repeat laboratory tests performed using local laboratories for certain parameters (e.g., AST, ALT, ALP, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium and Total Bilirubin) at unscheduled visits.

Note that Subjects #309025 and 311017 had Biochemistry Metropolis Lab test values (Total Bilirubin/AST/ALT) that have been reported with <X (below X) and >X (higher X) values. These values were treated as X±0.1 for statistical analysis purposes. In case of <=X or >=X, the values were treated as simply X.

9.7.1.4.4 Electrocardiogram (ECG)

All subjects had a standard 12-lead ECG performed at each scheduled clinic visit, as specified in the Schedule of Evaluations Table 9-4. To ensure consistency in the data analysis across subjects, all ECGs were sent to a central ECG monitoring service (ERT) for review and interpretation; however, the 'real-time' review and interpretation of the 12-lead ECGs that was used for determination of a subject's eligibility for enrolment in the trial, as well as post-dose safety monitoring, was performed by a physician at the investigational site. The parameters include numerical values for heart rate and RR, PR, QRS, QT, QTcB, and QTcF intervals, as provided by the central ECG service.

If the ECG was abnormal at screening, the evaluation was repeated, and if no clinically significant abnormalities were noted, the patient could be considered eligible for the study. At the baseline (014 Baseline) visit, at least 1 hour prior to the first dose, the 12-lead ECG was repeated 3 times, at least 10 minutes apart, and the values for the different parameters were averaged to obtain the baseline values. The mean values were used in determining eligibility for the study.

In case a baseline value was missing, the screening value was considered for the change from baseline analysis.

Post baseline

A summary was provided for the following parameters by each dose group at each scheduled time point for the Safety population:

1) Change from baseline at each visit and at endpoint (Week 46 or early discontinuation) for ECG parameters (Mean Heart Rate, RR Interval, PR Interval, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval).
2) Treatment-emergent abnormalities as assessed by the Central Reader and Principal Investigator.
3) The number (%) of patients meeting the following categorical criteria was summarized by treatment group:
    a. Change from baseline in QTc interval: > 30 msec and </= 60 msec, > 60 msec.
    b. Absolute QTc interval: >450 msec and </=480 msec, >480 msec and </= 500 msec, and >500 msec
    c. Absolute value of PR interval >200 msec and QRS Duration > 110 msec.
    d. More than 25% change from baseline in PR interval and QRS duration.

ECG listings consist of individual subject data with findings from the Principal Investigator and Central Reader, and Treatment-Emergent Abnormalities as Assessed by Central Reader and change from Baseline.

Date and time of ECG assessment and visit mismatch with external data were used from the eCRF, if applicable.

9.7.1.4.5 Physical Examinations

A physical examination was performed at Baseline (014 Baseline), Week 24 and at the final visit (Week 46 or at early discontinuation).

Treatment-emergent post-baseline abnormal findings on any body system in the physical examination (general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system) are summarized and listed by evenamide dose group for the Safety population.

9.7.1.4.6 Neurological Examinations

A neurological examination was performed at Baseline (014 Baseline), Week 24 and at the final visit (Weeks 46 or at early discontinuation).

Treatment-emergent post-baseline abnormal findings on any body system in the neurological examination (mental status, cranial nerves, muscle strength and tone, reflexes, sensory system, coordination and gait) are summarized and listed by evenamide dose group for the Safety population.

9.7.1.4.7 Standard Eye Examination

A standard eye examination was performed at Baseline (014 Baseline), Week 24 and the final visit (Week 46 or at early discontinuation).

Treatment-emergent post-baseline abnormal findings on the eye examination, comprising assessments of visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and the front part of the eyes (eyelids, cornea, conjunctiva, sclera and iris) are summarized and listed by evenamide dose group for the Safety population.

9.7.1.4.8 Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)

The ESRS is a 33-item scale designed to examine changes in motor function associated with pharmacologic treatment (Chouinard G et al, 1980; Chouinard G et al, 2005). It has a 'subjective' part (12 items, 0 - 4 rating) and a part scored 'objectively' on the basis of observation and examination (parkinsonism: eight items, dystonia: two items, dyskinesia: seven items; all scored on a 0 - 6 scale described for each item separately in terms of frequency and severity, some subdivided for body-parts). There are three global scales assessing dyskinesia, parkinsonism and dystonia, and a Hoehn and Yahr stage estimation of parkinsonism. It has been validated in a large number of studies including add-on therapy and drug withdrawal studies for atypical antipsychotics. An abbreviated version of the ESRS, the ESRS-A, was used in this study and was performed every 12 weeks and at the final visit (Week 46 or at early discontinuation).

Ratings of the ESRS-A are summarized for the Safety population by total and global subdomain scores by visit and presented by dose group. The mean change from baseline score and observed score for the total score and sub-scale scores on the ESRS-A for the Safety population are presented by evenamide dose group.

9.7.1.4.9 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a nine-item, observer-rated, semi-structured, goal-directed interview, validated for diagnosing depression in patients with schizophrenia. Each item is scored between 0 and 3 based on operational criteria. A total score of 6 or above is considered predictive of a major depressive episode. Internal reliability as well as inter-rater reliability is high (Addington et al, 1993). In the current study, the CDSS was performed at Week 24 and at the final visit (Week 46 or at early discontinuation) to assess depressive symptoms.

The change from baseline to the final assessment in the CDSS total score for the Safety population is presented by the evenamide dose group.

CDSS scores at baseline (Baseline of Study 014) and final assessment in the Safety population were listed.

9.7.1.5 Analysis of Efficacy Parameters

9.7.1.5.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al, 1987) is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The 30 symptoms are each rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provides a balanced representation of positive and negative symptoms, and gauges their relationship to one another and to global psychopathology. In addition to a total score, this assessment yields separate sub-scores on a Positive Syndrome Scale, a Negative Syndrome Scale, and a General Psychopathology Index. The PANSS interview process typically takes between 30 and 40 minutes to complete. The PANSS was conducted at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation) and was used as the primary efficacy measure in the trial.

The effect of each dose on the PANSS total scores measured at each visit was analyzed descriptively for each randomized group. Group mean changes from baseline to endpoint on the observed PANSS total score, and total scores on the PANSS – Positive Symptoms sub-scale, PANSS – Negative Symptoms sub-scale, and PANSS – General Psychopathology sub-scale were summarized, and results for change from baseline presented by mean, median, and range (min, max) and analyzed using a paired t-test, at each post dose timepoint (Weeks 12, 24, 36 and 46).

Demonstration of a clinically relevant improvement from baseline to endpoint (Week 46 or early discontinuation) on the PANSS total score for any dose of evenamide, was considered as preliminary evidence of benefit as adjunctive therapy in patients with TRS showing inadequate response to their current antipsychotic.

A ‘Responder’ analysis was performed by summarizing the proportion of patients in each of the evenamide groups with improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale (i.e., PANSS total score change > = 20% improvement and > = 4 points improvement on PANSS Positive Symptoms sub-scale score).

To date, no prospective trial evaluating the benefit of a new chemical entity as an add-on to an antipsychotic in patients with TRS has been published. Currently, available data suggests that the benefits of an intervention as an add-on in TRS patients were of low magnitude, i.e., 10% to 20% improvement. An exploratory analysis was performed to describe the magnitude of reduction in PANSS total score over the entire 1-year treatment period (Studies 014/015 combined).

A line graph, including standard deviation (SD) bars, of mean change from baseline of Total Score, Total Positive Score, Total Negative Score, and Total General Psychopathology Score for each of the dose groups was presented by visit.

Dose-wise and combined efficacy analyses of PANSS (Paired t-test p-value along with 95% CI of change from baseline) was performed at Week 46 and preceding visits on the mITT population and mITT-C population, as applicable.

9.7.1.5.2 Clinical Global Impression (CGI)

The CGI (Guy W (Ed)) is the general name for 2 scales: the CGI-Severity (CGI-S) measures global severity of illness at a given point in time, and the CGI-Change (CGI-C) measures change from the baseline state at each post-baseline visit.

The CGI rating scale permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S is performed, in which the investigator rates the severity of a subject's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). At subsequent visits, the investigator assesses the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at baseline (Study 014) using the CGI-C, a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating "no change". The CGI-S and CGI-C assessments were conducted at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation).

Change from baseline to endpoint on the CGI-S was summarized, and a graph, including mean change from baseline of the CGI-S for each treatment group was presented by visit. Paired t-test was also performed at post-dose visits to analyze CGI-S change from baseline within each dose group, at each post-dose time point (i.e., Weeks 12, 24, 36 and 46).

In addition, the mean rating of the CGI-C at each post-dose visit was summarized.

'Responder' analyses were performed by summarizing the proportion of patients in each of the evenamide dose groups with improvement from baseline to endpoint on the CGI-S and CGI-C. For improvement categorization for CGI-S "at least 2-category improvement" and "at least 1-category improvement" were used. For improvement categorization for CGI-C "any improvement", defined as a CGI-C score of 3, 2, or 1; and "at least much improved", defined as a CGI-C score of 2 or 1, were used.

A line graph of mean change from baseline of the CGI-S by visit for each treatment group was presented.

A bar chart of the responder analyses on the CGI-C (any improvement and at least much improved) was presented.

Dose-wise and combined (all doses) efficacy analyses were performed on the mITT population and mITT-C population, as applicable.

9.7.1.5.3 Strauss-Carpenter Level of Functioning (LOF) scale

Changes from baseline to endpoint on the total scores and sub-scale scores on the LOF were summarized and analyzed within each dose group by using a paired t-test, at each post-dose time point (i.e., Weeks 12, 24, 36 and 46). A graph depicting mean (SD) change from baseline by visit was presented for each dose group.

Dose-wise and combined efficacy analyses were performed on the mITT population and mITT-C population, as applicable.

9.7.1.5.4 Efficacy Estimands

Efficacy estimands were considered for the primary efficacy endpoint (PANSS total score change from baseline at Week 46 only).

Estimand: Effect of continuing on the randomized dose of evenamide in the extension study, as it was administered in the core study, regardless of withdrawal from treatment.

Estimator: Estimate of the change from baseline in PANSS total score at Week 46.

Intercurrent Events: Randomized treatment discontinuation due to intake of rescue medication or dose up-titration. Dose up-titration was only applicable to patients randomized to 7.5 mg *bid* whose dose was increased to 15 mg *bid*, as per a protocol amendment. There are many cases in which patients were not dosed due to non-availability of IP, that have not been considered as intercurrent events.

The ‘Treatment Policy’ strategy was considered as a primary efficacy estimand where actual values of the variable were used, regardless of whether the intercurrent events have occurred (OC). In other words, all observations, including those made for patients withdrawn from treatment and returning at Week 46, regardless of other medication taken, were utilized.

For long-term add-on therapy, the efficacy assessment ‘treatment policy’ estimand may be of interest, as it evaluates randomized policy.

The Hypothetical estimand was considered as a supportive efficacy estimand, where base analysis was based on data observed (OC) prior to the randomized treatment withdrawal or discontinuation. Those discontinued subjects who have provided post withdrawal data for Week 46 follow-up were removed from the analysis, as applicable.

For those randomized subjects in the 7.5 mg *bid* arm who were switched to 15 mg *bid* after the protocol Amendment 4.1, their post-switch PANSS measurements were also censored programmatically.

The Hypothetical estimand evaluates the pure effect of dose efficacy, especially for 7.5 mg BID, where up-titration response or post withdrawal data was removed.

Further, a sensitivity analysis was performed using LOCF to account for missing withdrawal data, as per local regulation requirement. Multiple imputation was also performed for

robustness. In case of death, the subject was excluded in the sensitivity analysis, as the analysis is pertaining to Week 46.

Dose-wise and combined efficacy analyses were performed on the mITT population and mITT-C population, as applicable.

Table 9-6 below describes the estimand panel.

Table 9-6: The Estimand Panel

Estimand	Estimand Attributes				Analysis
	Population(s)	Variable	Intercurrent events	Summary	
Primary efficacy estimand	mITT and mITT-C	Change from baseline to Week 46 in PANSS total score	Treatment policy estimand: What is the effect if patients continue treatment until completion as observed cases (OC).	Mean change at Week 46	Paired t-test
Supportive efficacy estimand	mITT and mITT-C	Change from baseline to Week 46 in PANSS total score	Hypothetical estimand: What is the effect if patients on randomized treatment are withdrawn and started on rescue medication, or are up-titrated.	Mean change at Week 46	Paired t-test
Sensitivity: LOCF	mITT	Change from baseline to Week 46 in PANSS total score	Robustness analysis (Treatment Policy): Use of LOCF for imputation of post randomized dose withdrawal data.	Mean change at Week 46	Paired t-test
Sensitivity: Multiple Imputation	mITT	Change from baseline to Week 46 in PANSS total score	Robustness analysis (Treatment Policy): Use of Multiple Imputation for imputation of post randomized dose withdrawal data.	Mean change at Week 46	Paired t-test

9.7.1.5.5 Adjustment for Multiplicity

Estimates and confidence intervals of within dose comparisons were exploratory in nature and are to be used for the planning of future studies. In this case, an adjustment of the type I error was not necessary.

9.7.1.6 Interim analysis

The following interim analyses were performed using the Study 015 data:

- Studies 014/015 (requested by ISMB): 6-month efficacy of first 100 patients randomized, up to and including 30 weeks (6-week duration of core study + 24-week duration of extension): Jan 2023
- Studies 014/015: 1-year efficacy of first 100 patients randomized, up to and including 52 weeks (6-week duration of core study + 46-week duration of extension): Mar 2023
- Studies 014/015: 6-month efficacy of 132 completed patients randomized, up to and including 30 weeks (6-week duration of core study + 24-week duration of extension): July 2023.

9.7.2 Determination of Sample Size

"A priori" assumptions estimated that approximately 100 (67%) of the 150 patients with TRS randomized to treatment in Study 014 would continue the treatment with evenamide in this extension study.

A total of 153 subjects completed Study 014. Of these subjects, 144 consented to enter and rolled over into Study 015.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

9.8.1.1 Amendment 1, dated 13 February 2020 implemented the following changes:

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015) was to increase the number of centers and countries participating in the study to facilitate enrolment and expedite completion of the trial. The study included up to 25 centers, with sites in Sri Lanka and Italy being added to the study. Additionally, revisions were made to the guidelines for use of concomitant psychotropic medication to better reflect current medical practice.

- Specifically, based on recent literature (Anderson and Vande Griend, 2014) and feedback from treating physicians that higher doses of quetiapine were used for sleep and not for antipsychotic effect, the maximum dose of quetiapine that was used as a soporific had been increased from 50 mg to 150 mg *hs*. Patients were allowed to enter the study on this dose of quetiapine, if they were receiving it as a stable dose in the antecedent study (Study NW-3509/014/II/2019 [Study 014]), or could receive this dose as rescue medication to treat insomnia during the treatment period of the study.
- For patients receiving lorazepam, or an equivalent short half-life benzodiazepine, at a stable dose in Study 014, a stipulation that the drug was not to be discontinued, nor reduced, during the current study was added. For patients not receiving a benzodiazepine upon entry into the trial, administration of 0.5 mg lorazepam (or equivalent dose of another benzodiazepine) was allowed as rescue medication during the study on a prn basis, with a maximum daily dose of 2 mg. The protocol was modified to allow daily doses greater than 2 mg (or equivalent) to be administered, if clinically necessary. This change was made based on feedback from investigators.

Other minor changes to the protocol made in this amendment include the following:

- The street address for the Sponsor, Newron Pharmaceuticals SpA, was changed, reflecting a recent move of the company offices.
- The EudraCT Number was added to the cover page, as the study was being conducted in Europe (Italy).
- Contact information for the Contract Research Organization in Sri Lanka was added.
- Tricyclic antidepressants were removed from the list of analytes to be tested in the urine drug screen, as these drugs are rarely abused by patients with schizophrenia.
- The language regarding reporting of overdoses was modified to include the procedures to be followed in Malaysia, Sri Lanka and Italy.

9.8.1.2 Amendment 2, dated 05 July 2020 implemented the following changes:

The purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015) was to update information related to the study and correct some errors and inconsistencies in the protocol. The changes implemented in this amendment include the following:

- Change the local CRO that was managing the study in Malaysia. The contact information for the previous CRO, Klinsel Sdn Bhd, was deleted and replaced with the information for the new CRO, Jigsaw Clinical Research Solutions SDN Bhd.
- Added the local CRO for Italy.
- Modified the estimated Planned Trial Period in the Synopsis, to better reflect the current status of the study, and the expectations for enrolment in light of the global COVID-19 pandemic.
- Modified the number of sites expected to participate in the study.
- Added a description of the results of a recently completed study (Study NW-3509/011/I/2019 [Study 011]) evaluating the safety and tolerability of a single 60-mg dose of evenamide in healthy volunteers, and incorporated this information into the sections on rationale for dose and overdosage.
- Modified the language regarding the use of a central laboratory to indicate that laboratories within in each country were to be used.
- Corrected clinically notable values for several laboratory hematology parameters.

9.8.1.3 Amendment 3, dated 22 September 2020 implemented the following changes:

The purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015) was to make modifications to the protocol in response to the following requests made by the Agenzia Italiana del Farmaco (AIFA) to allow opening of investigational centers in Italy:

- *The study protocol contains a section regarding subject completion and discontinuation (Section 14). However, in this section only discontinuation criteria from the trial are reported. Acceptable discontinuation criteria both from treatment and from the trial and procedures for collection of data relating to withdrawn subjects should be included in the protocol. Applicant is requested to modify the Protocol accordingly.*

Changes to the Protocol: Criteria were added regarding discontinuation of a subject from treatment, in addition to the reasons for discontinuing the subject from the study. Additionally, procedures were described for collecting data from subjects who discontinued treatment but remained in the study and returned for scheduled visits.

- *Even if no adverse findings were reported for any of the reproductive organs in repeated dose toxicity studies of up to 26-weeks (rats) or 39-weeks (dogs) with evenamide, birth control methods to be used during the trial must be clearly listed in the Clinical Study Protocol. As "the effects of evenamide on the nursing infant, or unborn child are not known and may be hazardous" (IB of evenamide, Edition 8, dated 04 June 2020) birth control methods used during the trial should be highly effective, as per CTFG recommendations (Recommendations related to contraception and pregnancy testing in clinical trials, final version 15 Sept 2014). Furthermore, enrolled patients will take standard therapy, and this might put patients at risk. Applicant is requested to modify the Protocol accordingly.* Changes to the Protocol: The inclusion criteria were revised to require use of "highly effective" contraception by women of childbearing potential in order for them to participate in the study. In addition, an appendix was added in which highly effective contraception for women was further defined.
- *The proposed protocol does not contain a section regarding benefit/risk assessment related to the current trial. Applicant is requested to modify the protocol accordingly.* Changes to the Protocol: A benefit/risk assessment for evenamide, based on preclinical and clinical data collected to date, was added in an appendix to the protocol. In addition, the sections of the protocol describing toxicology data, including NOAELs for the rat and dog and calculation of safety ratios for human doses, were updated to reflect the current data.
- *Even if "restrictions on concomitant medications being taken during the treatment period of the study followed those specified in the Exclusion criteria in the study protocol for Study 014" (Section 11.5 - Concomitant Medications), for the sake of clarity a list of permitted and prohibited medications should be reported also in the protocol of the extension study. Applicant is requested to modify the protocol accordingly.* Changes to the Protocol: An appendix was added to the protocol summarizing the guidelines for prior and concomitant medication that were permitted or prohibited in Study 015, as specified in the protocol for the antecedent study, Study 014. The summary was presented by drug class.

  Additional modifications were made to the 015 protocol to correct minor errors and omissions.

9.8.1.4 Amendment 4, dated 18 June 2021, implemented the following changes.

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015) was to discontinue the evenamide 7.5 mg *bid* dose from the study. This change was made in parallel to an amendment to the protocol for the antecedent study, Study NW-3509/014/II/2019 (Study 014) that removed the 7.5 mg *bid* dose group from that study and

changed the paradigm for randomizing patients to the remaining 15 mg *bid* and 30 mg *bid* doses.

- As specified in the protocol for Study 014, an interim safety assessment had been performed by the Independent Safety Monitoring Board (ISMB) after 50 patients were randomized to the 7.5 mg *bid* (n=26) and 15 mg *bid* (n=24) doses and completed their participation in this study. The safety data from these patients, along with data from other completed clinical studies, were reviewed by the ISMB, which determined that it was safe to proceed with the 30 mg *bid* dose. Based on this decision, the 30 mg *bid* dose group was initiated in Study 014, with the originally planned randomization ratio of 1:1:2 to the 7.5, 15 and 30 mg *bid* dose groups, respectively. Based on this decision, the 30 mg *bid* dose was now available for patients enrolled in Study 015 who were randomized to this dose in Study 014 and completed 6 weeks of treatment. With the initiation of the 30 mg *bid* dose, the following statement relating to Study 014 was deleted throughout the Study 015 protocol, as it was no longer applicable:

  If the 30 mg bid group is not added, the 150 patients will be randomly assigned (1:1) to the 7.5 and 15 mg bid treated groups (approximately 75 in each group).

- Additional safety studies evaluating doses of evenamide up to 60 mg had been completed prior to amending the protocol. These include Study NW-3509/011/I/2019 (Study 011), which evaluated single doses of 60 mg in healthy volunteers; Study NW-3509/010/I/2019 (Study 010), which evaluated the effects of single doses of 30 mg and 60 mg on ECG parameters, including QTc; and a 4-week safety study in patients with schizophrenia (NW-3509/008/II/2019 [Study 008]), which evaluated multiple fixed doses of 7.5 and 15 mg *bid*. The safety data from these studies indicate that doses up to 60 mg (single dose) were safe and well tolerated, and support dosing of patients at 30 mg *bid* (60 mg/day).

- Study 008 also assessed the efficacy of doses of 7.5 and 15 mg *bid* and found no evidence of efficacy for either dose in treating patients with schizophrenia not responding adequately to a single atypical antipsychotic. These results indicated that higher doses were needed to achieve efficacious plasma levels of evenamide. A decision to discontinue the 7.5 mg *bid* dose group in the antecedent study (Study 014) had been made based on the results of this efficacy analysis in Study 008. Since more than 25 patients had already been enrolled in Study 014 in the 15 mg *bid* group, the randomization ratio had been changed from 1:2 to 1:3 for the 15 mg *bid* and 30 mg *bid* groups, respectively, so that the number of patients randomized to each of these treatment groups were approximately equal at the end of the study.

- As a result of the 7.5 mg *bid* dose group being discontinued from Study 014, patients were no longer continued on this dose in this optional open-label extension study (Study 015). Therefore, patients randomized to doses of 15 mg *bid* or 30 mg *bid* in Study 014 were continued in Study 015 on the same dose of evenamide they were receiving on the last day (Week 46) of the prior study, while patients randomized to the 7.5 mg *bid* dose in Study 014 had their dose increased to 15 mg *bid* upon entry into Study 015.

Additionally, patients already enrolled in Study 015 at the 7.5 mg *bid* dose had their dose increased to 15 mg *bid* at their next scheduled clinic visit. This allowed all patients to have a minimum dose of 15 mg *bid*, which would have a greater likelihood of achieving efficacious plasma levels of evenamide. The sections of the protocol describing the study medication and dosing were modified to reflect these changes.

The following additional modifications were made to the Study 015 protocol in this amendment to correct minor errors and omissions:

- The planned trial period dates were modified to more accurately reflect the current status of the study.
- The Background Information (Section 7.1 of protocol) was updated to include summaries of the recently completed Study 008 and Study 010 described above.
- The information on Overdosage (Section 10.6 of protocol) was updated to include data on the 60-mg single dose from the recently complete Study 010.
- The section on informed consent (Section 11.1 of protocol) was revised to indicate that the Informed Consent Form was updated to include information on the discontinuation of the 7.5 mg *bid* dose, and to specify that patients were to be reconsented.
- Corrections were made to the definition of women requiring pregnancy tests to indicate that woman must be confirmed to be post-menopausal or surgically sterilized to be exempted from pregnancy testing, and to ensure that the language was consistent throughout the protocol.
- The timing of the safety follow-up visits and the SAE follow-up after discontinuing treatment was clarified.
- The definition of "subject completion" was revised to indicate that returning for the safety follow-up assessment 7 (±2) days after the last dose of study medication was not required for a subject to be considered a completer.
- The requirements for financial disclosure were clarified in Section 17.12. The Benefit/Risk Assessment for Evenamide (Appendix 7 of the study protocol) was updated to incorporate results from recently completed studies and make it more specific to Studies 014 and 015.

9.8.1.5 Amendment 4.1 (India), dated 30 November 2021, implemented the following changes:

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015), which was specific for India, was to discontinue the evenamide 7.5 mg *bid* dose from the study. This change was made in parallel to an amendment to the protocol for the antecedent study, Study NW-3509/014/II/2019 (Study 014) that removed the 7.5 mg *bid* dose group from that study and changed the paradigm for randomizing patients to the remaining 15 mg *bid* and 30 mg *bid* doses. Discontinuation of the 7.5 mg *bid* dose had already been implemented in Amendment 4 to the protocol and v.5.0 of the amended protocol (dated 18 June 2021), which had been submitted to all countries outside India, and to some Ethics Committees within India.

- Additionally, this amendment extended open-label treatment with evenamide in Study 015 for an additional 24 weeks at sites in India. This change was included in this amendment, as the first patient enrolled in India was completing the study in late December 2021. This allowed patients who were doing well on evenamide and completed the full 46 weeks of treatment, as specified in the current protocol, the option of continuing treatment for another 24 weeks, for a total treatment period of 70 weeks. Office visits during this additional treatment period took place at 12-week intervals. The schedule of evaluations had been modified to add an office visit at Week 58 and telephone contacts with the patients at Weeks 52 and 64. All evaluations currently scheduled for the Week 46 visit were repeated at the final visit at Week 70 (or at early discontinuation).

- As specified in the protocol for Study 014, an interim safety assessment had been performed by the Independent Safety Monitoring Board (ISMB) after 50 patients were randomized to the 7.5 mg *bid* (n=26) and 15 mg *bid* (n=24) doses and completed their participation in this study. The safety data from these patients, along with data from other completed clinical studies, were reviewed by the ISMB, which determined that it was safe to proceed with the 30 mg *bid* dose. Based on this decision, the 30 mg *bid* dose group had been initiated in Study 014, with the originally planned randomization ratio of 1:1:2 to the 7.5, 15 and 30 mg *bid* dose groups, respectively. Based on this decision, the 30 mg *bid* dose was available for patients enrolled in Study 015 who were randomized to this dose in Study 014 and completed 6 weeks of treatment. With the initiation of the 30 mg *bid* dose, the following statement relating to Study 014 was deleted throughout the Study 015 protocol, as it was no longer applicable:

  "If the 30 mg bid group is not added, the 150 patients will be randomly assigned (1:1) to the 7.5 and 15 mg bid treated groups (approximately 75 in each group)".

- Additional safety studies evaluating doses of evenamide up to 60 mg had been completed prior to amending the protocol. These include Study NW-3509/011/I/2019 (Study 011), which evaluated single doses of 60 mg in healthy volunteers; Study NW-3509/010/I/2019 (Study 010), which evaluated the effects of single doses of 30 mg and 60 mg on ECG parameters, including QTc; and a 4-week safety study in patients with schizophrenia (NW-3509/008/II/2019 [Study 008]), which evaluated multiple fixed doses of 7.5 and 15 mg *bid*. The safety data from these studies indicate that doses up to 60 mg (single dose) were safe and well tolerated, and support dosing of patients at 30 mg *bid* (60 mg/day).

- Study 008 also assessed the efficacy of doses of 7.5 and 15 mg *bid* and found no evidence of efficacy for either dose in treating patients with schizophrenia not responding adequately to a single atypical antipsychotic. These results indicate that higher doses were needed to achieve efficacious plasma levels of evenamide. A decision to discontinue the 7.5 mg *bid* dose group in the antecedent study (Study 014) had been made based on the results of this efficacy analysis in Study 008. Since more than 25 patients had already been enrolled in Study 014 in the 15 mg *bid* group, the randomization ratio had been changed from 1:2 to 1:3 for the 15 mg *bid* and 30 mg *bid*

groups, respectively, so that the number of patients randomized to each of these treatment groups were approximately equal at the end of the study.

- As a result of the 7.5 mg *bid* dose group being discontinued from Study 014, patients were no longer continued on this dose in this optional open-label extension study (Study 015). Therefore, patients randomized to doses of 15 mg *bid* or 30 mg *bid* in Study 014 were continued in Study 015 on the same dose of evenamide they were receiving on the last day (Week 46) of the prior study, while patients randomized to the 7.5 mg *bid* dose in Study 014 had their dose increased to 15 mg *bid* upon entry into Study 015. Additionally, patients already enrolled in Study 015 at the 7.5 mg *bid* dose had their dose increased to 15 mg *bid* at their next scheduled clinic visit. This allowed all patients the opportunity to be treated with a minimum dose of 15 mg *bid*, which had a greater likelihood of achieving efficacious plasma levels of evenamide. The sections of the protocol describing the study medication and dosing had been modified to reflect these changes.
- Based on the findings that patients who were nearing completion of the 46 weeks of extension treatment with evenamide in Study 015 were benefiting from treatment (as demonstrated by the low discontinuation rate), without any evidence of intolerance, both the Investigators and the patients/caregivers had expressed their desire to have the patients continue treatment in this extension study. The ISMB has approved the extension of treatment for an additional 24 weeks for patients who completed 46 weeks. This amendment, which was specific for India, incorporates the termination of the 7.5 mg *bid* dose and the extension of treatment for an additional 24 weeks for patients completing 46 weeks of treatment. The sections of the protocol describing the study medication and dosing were modified to reflect these changes.

The following additional modifications were made to the Study 015 protocol in this amendment related to extension of the treatment period by 24 weeks, and to correct minor errors and omissions:

- The planned trial period dates were modified to more accurately reflect the current status of the study.
- The proportion of patients enrolled in Study 014 that were expected to continue in this extension study was revised based on the enrollment to date.
- The Background Information (Section 7.1) was updated to include summaries of the recently completed Study 008 and Study 010 described above.
- The information on Overdosage (Section 10.6) was updated to include data on the 60-mg single dose from the recently completed Study 010.
- The section on informed consent (Section 11.1) was revised to indicate that the Informed Consent Form was updated to include information on the discontinuation of the 7.5 mg *bid* dose and the additional 24 weeks of treatment, and to specify that patients were to be reconsented.

- Corrections were made to the definition of women requiring pregnancy tests to indicate that woman must be confirmed to be post-menopausal or surgically sterilized to be exempted from pregnancy testing, and to ensure that the language was consistent throughout the protocol.
- The timing of the safety follow-up visit and the SAE follow-up after discontinuing treatment was clarified.
- The definition of "subject completion" was revised to indicate that returning for the safety follow-up assessment 7 (±2) days after the last dose of study medication was not required for a subject to be considered a completer.
- The requirements for financial disclosure were clarified in Section 17.12.
- The Benefit/Risk Assessment for Evenamide (Appendix 7 of the study protocol) was updated to incorporate results from recently completed studies and make it more specific to Studies 014 and 015.

9.8.1.6 Amendment 4.2 (India), dated 08 July 2022, implemented the following changes:

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015), which was specific for India, was to extend open-label treatment with evenamide in Study 015 for an additional 24 weeks at sites in India. This change was made in the protocol, as the first patients enrolled in India were completing the study in August 2022. Based on the findings that patients who were nearing completion of the 70 weeks of extension treatment with evenamide in Study 015 were benefiting from treatment (as demonstrated by the low discontinuation rate), without any evidence of intolerance, both the Investigators and the patients/caregivers had expressed their desire to have the patients continue treatment in this extension study. This amendment allowed patients who were doing well on evenamide and completed a total of 70 weeks of treatment (initial 46-week treatment period + 24-week additional treatment period), as specified in the current protocol, the option of continuing treatment for an additional 24 weeks in a second additional treatment period, for a total treatment duration of 94 weeks.

- Office visits during this additional 24-week treatment period took place at 12-week intervals. The schedule of evaluations had been modified to add an office visit at Week 82 and telephone contacts with the patients at Weeks 76 and 88. All evaluations currently scheduled for the Week 46 and Week 70 visits were repeated at the final visit at Week 94 (or at early discontinuation) for patients who continued in this additional treatment period.
- As specified in the protocol for Study NW-3509/014/II/2019 (Study 014), the antecedent study, an interim safety assessment was performed by the Independent Safety Monitoring Board (ISMB) after 50 patients were randomized to the 7.5 mg *bid* (n=26) and 15 mg *bid* (n=24) doses and completed their participation in this study. The safety data from these patients, along with data from other completed clinical studies, were reviewed by the ISMB, which determined that it was safe to proceed with the 30 mg *bid* dose. Subsequently, a decision was made to discontinue the 7.5 mg *bid* dose

group in Study 014, as it was considered to be an ineffective dose, and patients were no longer continued on this dose in this optional open-label extension study (Study 015). The ISMB conducted a subsequent review of the safety data from the first 100 patients completing their participation in Study 014 and concluded there were no safety issues that precluded continuing the study as designed with doses of 15 and 30 mg *bid*.

- Additionally, an interim analysis of efficacy data from Study 014 was performed in response to a request from the ISMB for evidence of benefit to determine whether a benefit-risk assessment justifies the long-term treatment of patients with evenamide. The analysis was conducted on group-blinded efficacy data (pooled from all 3 evenamide treatment groups) from the first 100 patients who completed their participation in Study 014. This analysis showed trends for increasing improvement over time for each of the key efficacy measures assessing symptoms of schizophrenia (PANSS) and global disease severity and change from baseline (CGI-S and CGI-C), and secondary measures assessing functioning (LOF) and patient's satisfaction with the study medication (MSQ). Based on the results of this interim efficacy analysis, along with their interim safety assessments, the ISMB approved the extension of treatment for an additional 24 weeks for patients who completed 70 weeks in Study 015. This amendment, which is specific for India, made the necessary changes to the protocol to allow the extension of treatment for an additional 24 weeks for patients completing 70 weeks of treatment.
- This amendment also modified recent changes to the contraception requirements for Study 015, that had been approved previously in India, and made these requirements consistent with the changes made in the Study 014 protocol in Amendment 8.1 (dated 29 June 2022). Prior changes to the contraception requirements made in Amendment 3 to the Study 015 protocol (dated 22 September 2020), based on a request from the Italian regulatory authority (AIFA), were no longer considered necessary in light of all reproductive and developmental toxicity studies having been completed without any evidence of maternal or fetal toxicities. These changes introduced new language related to contraception that has made the protocol virtually impossible to recruit patients for, was objected to by Investigators, and was difficult for patients to comply with. Therefore, the revised language in the selection criteria was similar to that in the Study 015 protocol prior to Amendment 3. The new language in Inclusion Criterion #3 of the protocol related to the enrollment of female patients was as follows:

  For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with adequate contraception, as determined by their Health Care Provider (see Appendix 5 of the study protocol).

Similar changes were made in Section 13.1.8, Pregnancy, and in Appendix 5, Contraception Requirements for Women.

Additional modifications were made to the Study 015 protocol in this amendment, including the following:

- Language regarding discontinuation of the 7.5 mg *bid* dose was updated.
- The section on informed consent (Section 11.1) was revised to indicate that the Informed Consent Form was updated to include information on the additional 24 weeks of treatment, and to specify that patients were to be reconsented.

9.8.1.7 Amendment 4.3 (Sri Lanka), dated 15 July 2022, implemented the following changes:

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015), which was specific to Sri Lanka, was to modify recent changes to the contraception requirements for Study 015, that had been approved previously in Sri Lanka, and make these requirements consistent with the changes made in the Study 014 protocol in Amendment 8.2 (dated 15 July 2022). Prior changes to the contraception requirements made in Amendment 3 to the Study 015 protocol (dated 22 September 2020), based on a request from the Italian regulatory authority (AIFA), were no longer considered necessary in light of all reproductive and developmental toxicity studies having been completed without any evidence of maternal or fetal toxicities. These changes introduced new language related to contraception that had made the protocol virtually impossible to recruit patients for, had been objected to by Investigators, and was difficult for patients to comply with. Therefore, the revised language in the selection criteria was similar to that in the Study 015 protocol prior to Amendment 3. The new language in Inclusion Criterion #3 of the protocol related to the enrollment of female patients was as follows:

> *For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with adequate contraception, as determined by their Health Care Provider (see Appendix 5).*

Similar changes were made in Section 13.1.8, Pregnancy, and in Appendix 5, Contraception Requirements for Women. Additionally, language regarding discontinuation of the 7.5 mg *bid* dose was updated in this amendment.

9.8.2 Changes in the Planned Analyses

Changes from the planned analysis described in the protocol that were made in the final SAP are summarized in the table below.

Sl No	New Changes	Protocol Text	Comments
1	Dose-wise analysis and Ad-hoc Combined analysis	Combined analysis	Dose-wise analysis was suggested in protocol clarification document
2	Efficacy estimands		As per ICH E9 R1
3	Baseline and First dose of core Study 014 used as Baseline of Study 015	Day 43 of Study 014	As per protocol clarification document
4	Missing Data Imputation		As per good statistical practices
5	Schedule of Evaluations		Adapted for statistical programming

Sl No	New Changes	Protocol Text	Comments
6	Study Design		Adapted from protocol for statistical analysis
7	Responder Analysis for PANSS and CGI-C/S.		As per protocol clarification document
8	mITT-C Ad-hoc for PANSS, CGI-C/S and LOF.		As per protocol clarification document

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 153 subjects completed Study 014. Of these subjects, 144 consented to enter and rolled over into Study 015. Subject enrollment details are presented in Listing 16.2.1.1.

The subject disposition in Study 015, including details of the number of subjects rolled over into the study and dosed, completed, and discontinued, along with the reason for discontinuation, is provided in Table 10-1: Subject Disposition and summarized in Listing 16.2.1.2.

A total of 144 subjects were rolled over into Study 015, and 121 subjects (84.0%) including 40 (88.9%), 41 (77.4%) and 40 (87.0%) subjects from the 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* evenamide treatment groups, respectively, completed the 46-week treatment period, while 23 (16.0%) subjects prematurely discontinued from the study. The most common reason for premature discontinuation was withdrawal of consent (16 subjects, 11.1%). Only 1 (0.7%) subject discontinued due to an adverse event and 1 (0.7%) patient died (see narratives in Section 11.6.2).

Table 10-1: Subject Disposition

Status	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Safety Population [a]	45 (100.0)	53 (100.0)	46 (100.0)	144 (100.0)
Modified Intent-to-Treat Population [b]	42 (93.3)	53 (100.0)	46 (100.0)	141 (97.9)
Modified Intent-to-Treat Population-C [c]	39 (86.7)	41 (77.4)	40 (87.0)	120 (83.3)
Completed Week 46	40 (88.9)	41 (77.4)	40 (87.0)	121 (84.0)
Discontinuation or Early Withdrawal	5 (11.1)	12 (22.6)	6 (13.0)	23 (16.0)
Rolled Over	45(100.0)	53(100.0)	46(100.0)	144 (100.0)
Rolled but not dosed in 015	0(0.0)	0(0.0)	0(0.0)	0 (0.0)
Rolled over and dosed in 015	45 (100.0)	53 (100.0)	46 (100.0)	144 (100.0)
Discontinued reasons				
Withdrawal Of Consent	4 (8.9)	8 (15.1)	4 (8.7)	16 (11.1)
Lost To Follow-Up	1 (2.2)	3 (5.7)	1 (2.2)	5 (3.5)
Adverse Event	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Death	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Major Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Status	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.1.2 adapted from Table 14.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
[a] Safety Population: The safety Population consisted of all subjects who took at least one dose of study medication in this extension study.
[b] Modified Intent-to-Treat Population: A modified Intent-to-Treat (mITT) population comprises all patients who had a baseline efficacy assessment in study 014 and receive at least one dose of study medication in this extension study and have at least one post-baseline (study 015) assessment for primary efficacy measure, the PANSS total score.
[c] Modified Intent-to-Treat Population-C: Those mITT subjects who have completed week 46 visit.

10.2 Protocol Deviations

Protocol deviations were reviewed on a case-by-case basis and classified as minor, major, or critical by the project team prior to database lock. Critical and major protocol deviations were summarized in Table 10-2 and listed in Listing 16.2.2.

No critical protocol deviation was reported during the study. A total of 126 (87.5%) subjects had a major protocol deviation, of which 41 (91.1%) were from evenamide 7.5 mg bid, 46 (86.8%) were from evenamide 15 mg *bid*, and 37 (80.4%) were from evenamide 30 mg *bid* groups.

All the major protocol deviations were classified as pertaining to study drug, and none to safety, eligibility, or procedural issues. The majority of these protocol deviations are incidents of non-availability of study medication resulting from disruptions in supply logistics during and after the pandemic.

Table 10-2 Major and Critical Protocol Deviations

Category	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Subjects with Major Protocol Deviation	41 (91.1)	46 (86.8)	39 (84.8)	126 (87.5)
Subjects with Critical Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.2 adapted from Table14.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.

11 SAFETY EVALUATION

11.1 Data Sets Analyzed

Overall, 144 subjects rolled over from Study 014 and comprised the Study 015 Population, including 45 subjects in the evenamide 7.5 mg *bid*, 53 in evenamide 15 mg *bid* group and 46 in evenamide 30 mg *bid* groups (Table 10-1). Of these, 144 subjects (100%) received at least one dose of study drug and qualified for inclusion in the Safety Population. Among these 144 rolled-over subjects, 141 (97.91%) subjects were selected for the mITT population and 120

(83.33%) subjects were selected for the mITT-C (completers) population for the 015 study Week 46 analysis Listing 16.2.1.2.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics for the Safety Population are summarized in Table 11-1. Subjects were predominantly male (71.5%), Asian (98.6%), single (49.3%), not employed (79.9%), living with family (100%) and had education of 9-16 years (69.4%).

The mean (SD) age of the subjects was 38.0 (9.94) years, ranging from 20 to 68 years. The mean (SD) weight, height and body mass index were 67.4 (13.70) kg, 164.1 (8.16) cm. and 25.0 (4.81) kg/m^2, respectively. No demographic or baseline characteristics differed notably between the treatment groups.
Demographic and baseline characteristics data for the Safety, and mITT populations are presented in Table 14.1.3.1.1 and Table 14.1.3.1.2, respectively, and by subject details for the Safety Population in Listing 16.2.4.1.

Table 11-1: Demographic and Baseline Characteristics - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Age (years)	N	45	53	46	144
	Mean (SD)	38.5 (10.41)	37.0 (10.13)	38.7 (9.36)	38.0 (9.94)
	Median	37.0	35.0	39.0	37.0
	Min, Max	23, 68	21, 62	20, 64	20, 68
Weight (kg)					
	Mean (SD)	67.2 (15.37)	67.4 (12.65)	67.5 (13.43)	67.4 (13.70)
	Median	66.9	66.2	65.0	65.8
	Min, Max	42.0, 120.0	44.7, 91.0	42.0, 95.7	42.0, 120.0
Height (cm)					
	Mean (SD)	164.5 (9.85)	164.2 (7.92)	163.4 (6.58)	164.1 (8.16)
	Median	164.8	165.9	164.0	164.0
	Min, Max	136.5, 183.0	145.0, 182.6	149.4, 181.0	136.5, 183.0
BMI (kg/m2)					
	Mean (SD)	24.8 (5.01)	25.0 (4.67)	25.3 (4.86)	25.0 (4.81)
	Median	24.3	25.0	24.5	24.5
	Min, Max	15.52, 37.12	17.31, 34.79	15.62, 37.70	15.52, 37.70
Sex					
Male	n (%)	31 (68.9)	38 (71.7)	34 (73.9)	103 (71.5)
Female	n (%)	14 (31.1)	15 (28.3)	12 (26.1)	41 (28.5)
Childbearing Potential [a]					
Yes	n (%)	11 (78.6)	9 (60.0)	9 (75.0)	29 (70.7)
No	n (%)	3 (21.4)	6 (40.0)	3 (25.0)	12 (29.3)
Race					
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	n (%)	44 (97.8)	53 (100.0)	45 (97.8)	142 (98.6)

Characteristics	Statistic	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	n (%)	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Other	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown or Not Reported	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity					
Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	n (%)	45 (100.0)	53 (100.0)	46 (100.0)	144 (100.0)
Education					
1-8 years	n (%)	11 (24.4)	10 (18.9)	9 (19.6)	30 (20.8)
9-16 years	n (%)	32 (71.1)	37 (69.8)	31 (67.4)	100 (69.4)
>16 years	n (%)	2 (4.4)	6 (11.3)	6 (13.0)	14 (9.7)
Marital Status					
Married	n (%)	17 (37.8)	23 (43.4)	20 (43.5)	60 (41.7)
Single	n (%)	25 (55.6)	24 (45.3)	22 (47.8)	71 (49.3)
Stable union	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Widow / Widower	n (%)	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.4)
Divorced	n (%)	3 (6.7)	4 (7.5)	4 (8.7)	11 (7.6)
Employment					
Full-Time Employment	n (%)	3 (6.7)	6 (11.3)	3 (6.5)	12 (8.3)
Not employed	n (%)	38 (84.4)	42 (79.2)	35 (76.1)	115 (79.9)
Part-Time Employment	n (%)	4 (8.9)	5 (9.4)	8 (17.4)	17 (11.8)
Housing Status					
Living alone	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living with family	n (%)	45 (100.0)	53(100.0)	46(100.0)	144(100.0)
Living with companion	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living in residential care	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living in institution	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living alone, with a caregiver	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)

Source: Listing 16.2.4.1 adapted from Table 14.1.3.1.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

11.2.2 Disease Characteristics

The study subjects enrolled in the current study met the DSM-5 criteria for schizophrenia and had an operational diagnosis of treatment-resistant schizophrenia based on the Treatment Response and Resistance in Psychosis (TRRIP) guidelines.

In the Safety Population, mean (SD) duration of schizophrenia was shortest in evenamide 15 mg *bid* treated group [6.2 (3.00) years] compared to evenamide 7.5 mg *bid* and 30 mg *bid* treated groups with 7.1 (2.37) years and 7.2 (3.56) years, respectively, with an overall mean (SD) of 6.8 (3.03) years. The mean (SD) duration of the current episode of schizophrenia was 8.0 (4.87) months. The mean (SD) duration of the current episode in evenamide 30 mg *bid* treated subjects was shorter [6.3 (3.32) months] compared to evenamide 7.5 mg *bid* treated subjects [8.7 (5.61) months] and evenamide 15 mg *bid* treated subjects [8.7 (5.07) months]. The mean (SD) number of psychiatric hospitalizations was 0.3 (0.71) with a range of 0-4. Most of the subjects [108 (75.0%)] did not have a family history of schizophrenia. Among those who

had a family history of schizophrenia, 20 (13.9%) subjects had 1st degree relatives and 5 (3.5%) had 2nd degree relatives with schizophrenia. The number of subjects with other psychiatric disorders was 20 (13.9%). The mean (SD) CDSS total score at baseline (Study 014) was 0.4 (0.94), 0.6 (1.33) and 0.8 (1.58) among subjects in the 7.5 mg bid, 15 mg *bid* and 30 mg *bid* treated groups, respectively. No disease characteristics differed notably between the treatment groups, other than as described above (Table 11-2). Disease characteristics data are presented in Table 14.1.3.2.1 and by subject in Listing 16.2.4.3.1

Table 11-2: Disease Characteristics - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Duration of Illness - Schizophrenia (Years) [a]					
	Mean (SD)	7.1 (2.37)	6.2 (3.00)	7.2 (3.56)	6.8 (3.03)
	Median	7.3	6.2	7.3	6.7
	Min, Max	1, 13	1, 15	1, 15	1, 15
Duration of Current Episode of Schizophrenia (Months) [b]					
	Mean (SD)	8.7 (5.61)	8.7 (5.07)	6.3 (3.32)	8.0 (4.87)
	Median	6.6	8.4	5.7	6.4
	Min, Max	3, 25	2, 23	2, 15	2, 25
Number of Psychiatric Hospitalization					
	Mean (SD)	0.2 (0.49)	0.3 (0.75)	0.4 (0.83)	0.3 (0.71)
	Median	0.0	0.0	0.0	0.0
	Min, Max	0, 2	0, 4	0, 3	0, 4
Family History of Schizophrenia					
None	n (%)	32 (71.1)	40 (75.5)	36 (78.3)	108 (75.0)
1st Degree Relatives [c]	n (%)	7 (15.6)	7 (13.2)	6 (13.0)	20 (13.9)
Father	n (%)	1 (2.2)	2 (3.8)	2 (4.3)	5 (3.5)
Mother	n (%)	2 (4.4)	4 (7.5)	1 (2.2)	7 (4.9)
Brother	n (%)	2 (4.4)	1 (1.9)	2 (4.3)	5 (3.5)
Sister	n (%)	2 (4.4)	0 (0.0)	1 (2.2)	3 (2.1)
2nd Degree Relatives [d]	n (%)	3 (6.7)	2 (3.8)	0 (0.0)	5 (3.5)
Paternal Grandfather	n (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Paternal Grandmother	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal Grandfather	n (%)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Maternal Grandmother	n (%)	2 (4.4)	1 (1.9)	0 (0.0)	3 (2.1)
Other	n (%)	5 (11.1)	5 (9.4)	5 (10.9)	15 (10.4)
Number of subjects with other psychiatric disorders	n (%)	3 (6.7)	6 (11.3)	11 (23.9)	20 (13.9)
Calgary Depression Scale for Schizophrenia (CDSS)					
CDSS Total Score					
	Mean (SD)	0.4 (0.94)	0.6 (1.33)	0.8 (1.58)	0.6 (1.31)
	Median	0.0	0.0	0.0	0.0
	Min, Max	0, 4	0, 6	0, 6	0, 6

Source: Listing 16.2.4.3.1, Listing 16.2.15. adapted from Table 14.1.3.2.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population,
SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of Randomization - Date of First diagnosis + 1) /365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1) /30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother's brother, father's sister's son, son, uncle, brother of father, daughter, paternal side - father's brother.

11.2.3 Medical History and Psychiatric History

The medical history of the subjects in the Safety Population is given in Table 14.1.3.3.1 and presented by subject in Listing 16.2.4.2.

Overall, 29 subjects (20.1%), including 8 (17.8%) subjects in evenamide 7.5 mg *bid* treated group, 12 (22.6%) subjects in evenamide 15 mg *bid* treated group and 9 (19.6%) subjects in evenamide 30 mg *bid* treated group, reported having medical history. Diabetes Mellitus was the most commonly reported medical history by 9 (6.3%) subjects overall, including 4 (8.9%) subjects in evenamide 7.5 mg *bid* treated group, 3 (5.7%) subjects in evenamide 15 mg *bid* treated group and 2 (4.3%) subjects in evenamide 30 mg *bid* treated group.

The psychiatric history (other than schizophrenia) of the subjects in the Safety Population is detailed in Table 14.1.3.3.2 and presented by subject in Listing 16.2.4.3.2.

Overall, 20 (13.9%) subjects, including 3 (6.7%) subjects in evenamide 7.5 mg *bid* treated group, 6 (11.3%) subjects in evenamide 15 mg *bid* treated group and 11 (23.9%) subjects in evenamide 30 mg *bid* treated group, reported any other psychiatric history. The most common finding in the psychiatric records was, by preferred term (PT): mental disorder (verbatim term, psychiatric illness) in 11 (7.6%) subjects overall [1 subject (2.2%) in evenamide 7.5 mg *bid* treated group, 2 subjects (3.8%) in evenamide 15 mg *bid* treated group and 8 subjects (17.4%) in evenamide 30 mg *bid* treated group], followed by depression (PT) in 3 (2.1%) subjects overall [none in evenamide 7.5 mg *bid* treated group, 1 (1.9%) subject in evenamide 15 mg *bid* treated group and 2 (4.3%) subjects in evenamide 30 mg *bid* treated group].

Other psychiatric history includes acute psychosis, anxiety, brief psychotic disorder, with postpartum onset, obsessive-compulsive disorder, and sleep disorder. Each has 1 (0.7%) subject overall.

11.2.4 Prior and Concomitant Medications

Prior and concomitant medications taken by the subjects in the Safety Population are summarized in Table 14.1.4.1.1 and Table 14.1.4.1.2, and by subject details in Listing 16.2.4.4.1.1 and Listing 16.2.4.4.1.2, respectively.

Overall, use of any prior medication was reported in 38 (26.4%) subjects, including 8 (17.8%) subjects in evenamide 7.5 mg *bid* treated group, 14 (26.4%) subjects in evenamide 15 mg *bid* treated group and 16 (34.8%) subjects in evenamide 30 mg *bid* treated group. Tertiary amines were the most commonly used prior medication that was reported for 25 (17.4%) subjects, followed by Benzodiazepines in 16 (11.1%) subjects, and Diazepines, Oxazepines, Thiazepines and Oxepines in 4 (2.8%) subjects, overall.

Overall, 124 (86.1%) subjects, including 39 (86.7%) subjects in evenamide 7.5 mg *bid* treated group, 46 (86.8%) subjects in evenamide 15 mg *bid* treated group and 39 (84.8%) subjects in evenamide 30 mg *bid* treated group, had a record of concomitant medications [i.e., those medications taken at any time during the study irrespective of the start date] other than antipsychotics. The most commonly used concomitant medications were Trihexyphenidyl (ATC class: Tertiary amines) [94 subjects (65.3%) overall] and Lorazepam (ATC class: Benzodiazepine derivatives) [36 subjects (25.0%) overall].

The number of subjects who had a record of concomitant medications slightly differed between the three treatment groups.

Prior antipsychotic medications (PAM) taken by the subjects in the Safety Population are summarized in Table 14.1.4.2.1 and by subject details in Listing 16.2.4.4.3.1. These were generally characteristic of subjects with schizophrenia.

All 144 subjects in the Safety Population (100%), including 45 subjects (100%) in evenamide 7.5 mg *bid* treated group, 53 subjects (100%) in evenamide 15 mg *bid* treated group and 46 subjects (100%) in evenamide 30 mg *bid* treated group, had a record of PAM [i.e., those prior medications that were reported by sites in the PAM form within the eCRF]. The most commonly used PAMs were Risperidone [121 subjects (84.0%) overall] and Olanzapine [103 subjects (71.5%) overall].

Current antipsychotic medications taken by the subjects in the Safety Population are summarized in Table 14.1.4.2.2. As required by the protocol, all subjects were receiving a stable dose of a single antipsychotic, other than clozapine, at the time of enrolment in the study. Out of the 144 subjects who were currently on antipsychotics during the study treatment, 79 (54.9%) subjects were taking Risperidone, and 39 (27.1%) subjects were taking Olanzapine (Table 11-3). Subjects were taking other atypical (second-generation) antipsychotics (e.g., Aripiprazole, Paliperidone, Quetiapine), with only 16 (11.1%) subjects receiving other types of antipsychotics, including first-generation antipsychotics (e.g., Haloperidol and Trifluoperazine).

Details of current antipsychotic medication by subject during the study treatment are presented in Listing 16.2.4.4.3.2. Two subjects in the study population required administration of rescue medication during the study. A 23-year-old female subject (303021) required Risperidone and a 41-year female subject (311010) required Trifluoperazine as rescue medication (Table 14.1.4.3, Listing 16.2.4.4.3.3). Both the subjects were from the 7.5 mg *bid* treated group.

Table 11-3: Summary of Current Antipsychotic Medication - Safety Population

Drug Name	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Risperidone	23 (51.1)	29 (54.7)	27 (58.7)	79 (54.9)
Olanzapine	12 (26.7)	14 (26.4)	13 (28.3)	39 (27.1)
Aripiprazole	3 (6.7)	3 (5.7)	1 (2.2)	7 (4.9)
Paliperidone	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Quetiapine	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Trifluoperazine	3 (6.7)	6 (11.3)	2 (4.3)	11 (7.4)
Haloperidol	2 (4.4)	0 (0.0)	1 (2.2)	3 (2.1)
Amisulpride	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Blonanserin	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.3.2 adapted from Table 14.1.4.2.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

11.2.5 Prior and Concomitant Procedures

No concomitant procedures were reported during the study (Listing 16.2.4.4.2).

11.3 Measurements of Treatment Compliance

The treatment compliance was monitored throughout the study as described in Section 9.4.1 and analyzed as detailed in Section 9.7.1.4.

The mean (SD) overall treatment compliance was 98.5% (5.57), with a median of 99.7% (range: 50 to 112%). The mean (SD) treatment compliance during the study duration for subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups was 98.5% (7.83), 98.7% (3.55) and 98.3% (4.91), respectively. The maximum treatment compliance of 112% was reported for a subject in the evenamide 30 mg *bid* treated group, and the minimum of 50% was reported for a subject in the evenamide 7.5 mg *bid* treated group (Table 11-4).

Details of treatment compliance for the Safety Population are summarized in Table 14.3.0.1 and by subject details are presented in Listing 16.2.5.2.

Table 11-4: Summary of Treatment Compliance – Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Overall Treatment Compliance (%) [b]	n	45	53	46	144
	Mean (SD)	98.5 (7.83)	98.7 (3.55)	98.3 (4.91)	98.5 (5.57)
	Median	99.7	99.6	99.8	99.7
	Min, Max	50,110	81,109	80,112	50,112

Source: Listing 16.2.5.2 adapted from Table 14.3.0.1
N - Total number of subjects in the Safety Population, n = number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of exposure (days) = (Treatment end date - Treatment start date + 1).
[b] Treatment compliance is computed as 100*[#Capsules consumed / #Capsules expected to be consumed].

11.4 Extent of Exposure

The mean (SD) overall study drug exposure was 297.5 (64.41) days, with a median of 322.0 (range: 9 to 367) days. The mean (SD) study drug exposure for subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups was 300.7 (66.22), 290.4 (69.71) and 302.5 (56.46) days, respectively. The maximum study drug exposure of 367 days was reported for a subject in the evenamide 15 mg *bid* treated group, and the minimum of 9 days was reported for a subject in the evenamide 15 mg *bid* treated group. (Table 11-5)

Table 11-5: Study Drug Exposure - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Duration of Exposure (days) [a]	N	45	53	46	144
	Mean (SD)	300.7 (66.22)	290.4 (69.71)	302.5 (56.46)	297.5 (64.41)
	Median	323.0	322.0	322.0	322.0
	Min, Max	36, 358	9, 367	100,338	9,367

Source: Listing 16.2.5.2; Table 14.3.0.1
Abbreviations: N - Total number of subjects in the Safety Population, n = number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of exposure (days) in study 015 = Treatment end date - Treatment start date + 1.

Details of dose adjustments or kit replacement for the Safety Population are summarized in Table-14.3.0.2, and by subject details are presented in Listing 16.2.5.3.

A total of 134 (93.1%) subjects had a kit replacement or dose adjustment, which includes 43 (95.6%), 50 (94.3%), 41 (89.1%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Subject number 406001 was the only subject who had a dose adjustment, as summarized in Table 14.3.0.2.

The maximum number of subjects with kit replacements was seen in the evenamide 15 mg *bid* group (50 subjects (94.3%)).

11.5 Adverse Events

The primary objective of the study was to evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5 mg, 15 mg and 30 mg *bid*) in patients with TRS not responding adequately to a stable, therapeutic dose of their current antipsychotic medication.

All the adverse events were captured up till the data cut off point (18th Dec 2023) in this CSR. Adverse events beyond 46 weeks have been marked as "#" in footnotes in the Adverse Events Safety Population Listing 16.2.7.1.

11.5.1 Brief Summary of Adverse Events

The overview of TEAEs reported during the study is presented in Table 11-6. During the study duration, 40 (27.8%) subjects reported at least one TEAE, which included 14 (31.1%), 15 (28.3%) and 11 (23.9%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At least one Serious TEAE was reported in 2 (1.4%) subjects, which included 1 (2.2%) subject each in the evenamide 7.5 mg *bid* and 30 mg *bid* treated groups.

Overall, the number of subjects with at least one Treatment-Related TEAE was 10 (6.9%), with 4 (8.9%), 4 (7.5%) and 2 (4.3%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. One subject (0.7%) in the evenamide 30 mg *bid* treated group had a Serious and Treatment-Related TEAE resulting in death. Overall, 1 (0.7%) subject in the 15 mg *bid* treated group had a TEAE leading to study drug discontinuation. Of the 40 overall TEAEs reported, 27 (18.8%) were of mild severity, 10 (6.9%) were of moderate severity and 3 (2.1%) TEAEs were of severe intensity. Out of the 10 overall treatment-related TEAEs

reported, 6 (4.2%) were of mild severity, 3 (2.1%) were of moderate severity and 1 (0.7%) was of severe intensity.

Table 11-6: Overall Summary of TEAEs and SAEs - Safety Population

Category	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
No. of Subjects with at least one TEAE	14 (31.1)	15 (28.3)	11 (23.9)	40 (27.8)
No. of Subjects with at least one Treatment-Related TEAE [a]	4 (8.9)	4 (7.5)	2 (4.3)	10 (6.9)
No. of Subjects with at least one Serious TEAE	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
No. of Subjects with Any Serious and Treatment-Related TEAE	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
No. of Subjects with Any TEAE Leading to Study Drug Discontinuation	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
No. of Subjects with Any TEAE Resulting in Death	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
No. of Subjects with Any TEAE by Severity				
Mild	9 (20.0)	10 (18.9)	8 (17.4)	27 (18.8)
Moderate	5 (11.1)	4 (7.5)	1 (2.2)	10 (6.9)
Severe	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Any Treatment-related TEAE by Severity				
Mild	3 (6.7)	2 (3.8)	1 (2.2)	6 (4.2)
Moderate	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Severe	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listings 16.2.7.1, 16.2.7.2, 16.2.7.3,and 16.2.7.4 adapted from Table 14.3.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication.
Subjects are counted only under the maximum severity observed for TEAE's
[a] Treatment related TEAE's are the TEAE's which is possibly or probably related to study drug, or not reported.

11.5.2 Display of Adverse Events

A summary of TEAEs by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.2 and by subject details in Listing 16.2.7.1. Overall, 40 (27.8%) subjects reported at least one TEAE, which included 14 (31.1%), 15 (28.3%) and 11 (23.9%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively.

The most frequently reported TEAEs (those with a ≥5% incidence of events in overall subjects) by SOC were reported in ‘Investigations’ and ‘Psychiatric disorders’, with 10 (6.9%) and 9 (6.3%) subjects, respectively. Other details on the Safety Population are presented in Table 14.3.1.2 and by subject details in Listing 16.2.7.1.

Overall, 2 (1.4%) subjects reported Serious TEAEs, with 1 subject each in the evenamide 7.5 mg and 30 mg *bid* treated groups. None of the subjects in the 15 mg *bid* treated group reported

a Serious TEAE. The details are presented in Table 14.3.1.1 and by subject details in Listing 16.2.7.2.

A summary of Treatment-related TEAEs by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1. A total of 10 (6.9%) subjects reported a treatment-related TEAE, which included 4 (8.9%), 4 (7.5%) and 2 (4.3%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The most frequently reported treatment-related TEAEs (those reported by more than one subject) by SOC were 'Nervous system disorders' with 3 (2.1%) subjects, and 'General disorders and administration site conditions' with 2 (1.4%) subjects overall. (Table 14.3.1.4).

A summary of TEAEs leading to study drug discontinuation by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.5 and by subject details in Listing 16.2.7.3. One subject (0.7%) (Subject number 401003) from the 15 mg *bid* treated group reported a TEAE leading to study drug discontinuation.

11.5.3 Analysis of Adverse events

11.5.3.1 Overall Incidence of Treatment-Emergent Adverse Events

A summary of TEAEs by System Organ Class (SOC) and Preferred Term (PT) in the Safety Population is presented in Table 11-7, and by Subject listing in 16.2.7.1.

The maximum number of subjects with TEAEs was reported in the evenamide 15 mg *bid* treated group, i.e. 15 (28.3%) subjects, followed by 7.5 mg *bid* treated group [14 (31.1%) subjects], and evenamide 30 mg *bid* treated group [11 (23.9%) subjects].

The most frequently reported TEAEs (those with a ≥5% incidence of events in overall subjects) by SOC were found in 'Investigations' and 'Psychiatry disorders', with 10 (6.9%) and 9 (6.3%) subjects, respectively.

Overall, 10 (6.9%) subjects had TEAEs reported under 'Investigations', with 2 (4.4%) subjects in evenamide 7.5 mg *bid*, 5 (9.4%) subjects in 15 mg *bid* evenamide, and 3 (6.5%) subjects in evenamide 30 mg *bid* treated groups. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were 'Blood cholesterol increased' in 3 (2.1%) subjects overall, including 1 (1.9%) subject in evenamide 15 mg *bid* treated group and 2 (4.3%) subjects in evenamide 30 mg *bid* treated group; 'Blood creatine phosphokinase increased' in 3 (2.1%) subjects overall, including 1 (2.2%) subject in evenamide 7.5 mg *bid* and 2 (3.8%) subjects in 15 mg *bid* treated group; 'Blood glucose increased' in 2 (1.4%) subjects, including 1 (2.2%) subject each in evenamide 7.5 mg and 30 mg *bid* treated groups; and 'Low density lipoprotein increased' in 2 (1.4%) subjects overall, including 1 (1.9%) subject in evenamide 15 mg *bid* and 1 (2.2%) subject in evenamide 30 mg *bid* treated groups.

Overall, 9 (6.3%) subjects reported 'Psychiatric disorders, with 5 (11.1%) subjects in evenamide 7.5 mg *bid*, 4 (7.5%) subjects in evenamide 15 mg *bid* and no subjects in evenamide 30 mg bid treated groups. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were 'Insomnia' reported in 3 (2.1%) subjects overall, including a single (2.2%) subject in evenamide 7.5 mg *bid* treated group and 2 (3.8%) subjects in evenamide 15

mg *bid* treated group; 'Schizophrenia' in 3 subjects (2.1%) overall, including 2 (4.4%) subjects in evenamide 7.5 mg *bid*, and 1 (1.9%) subject in 15 mg *bid* treated group; and 'Irritability' in 2 (1.4%) subjects overall, with both subjects (4.4%) in evenamide 7.5 mg *bid* treated group.

Overall, 4 (2.8%) subjects reported 'Metabolism and nutrition disorders', with 2 (4.4%) subjects in evenamide 7.5 mg *bid*, no subjects (0%) in evenamide 15 mg *bid* and 2 (4.3%) subjects in evenamide 30 mg *bid* treated groups. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were 'Hyponatremia' reported in 2 (1.4%) subjects, both in 7.5 mg *bid* treated group, and 'Type 2 diabetes mellitus' reported in 2 (1.4%) subjects, 1 subject each in 7.5 mg *bid* and 30 mg *bid* treated groups.

Overall, 4 (2.8%) subjects reported 'Skin and subcutaneous tissue disorders', with 2 (4.4%) subjects in evenamide 7.5 mg *bid*, 2 (3.8%) subjects in evenamide 15 mg *bid* and no subject in evenamide 30 mg *bid* treated groups. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were 'Hyperhidrosis' reported in 2 (1.4%) subjects, 1 subject each in 7.5 mg *bid* and 15 mg *bid* treated groups.

Overall, 3 (2.1%) subjects reported 'Blood and lymphatic system disorders' with 1 (2.2%) subject in evenamide 7.5 mg *bid*, 1 (1.9%) subject in evenamide 15 mg *bid* and 1 (2.2%) subject in evenamide 30 mg *bid* treated groups. The reported TEAE was 'Anemia', which was reported in 1 subject in each of the three treated groups.

Out of the reported TEAEs under the SOC 'Infections and infestations', the preferred term 'Upper respiratory tract infection' was reported in 3 subjects in the overall evenamide group. Under the SOCs 'Gastrointestinal disorders', 'Nervous system disorders', 'General disorders and administration site conditions', 'Injury, poisoning and procedural complications', 'Musculoskeletal and connective tissue disorders', 'Hepatobiliary disorders', 'Renal and urinary disorders', 'Reproductive system and breast disorders', 'Respiratory, thoracic and mediastinal disorders' and 'Vascular disorders', each of the individual TEAEs were reported in only 1 subject in the overall evenamide group.

The above details are presented in Table 11-7 below.

Table 11-7: Summary of Most frequent (> 1 subject in Total) Treatment-Emergent Adverse Events by System Organ Class (SOC) and Preferred Term (PT) Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Subject with any TEAE	14 (31.1)	15 (28.3)	11 (23.9)	40 (27.8)
Investigations	2 (4.4)	5 (9.4)	3 (6.5)	10 (6.9)
Blood cholesterol increased	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Blood creatine phosphokinase increase	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Blood glucose increased	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Low density lipoprotein increased	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Psychiatric disorders	5 (11.1)	4 (7.5)	0 (0.0)	9 (6.3)

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Insomnia	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Schizophrenia	2 (4.4)	1 (1.9)	0 (0.0)	3 (2.1)
Irritability	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.4)
Gastrointestinal disorders	3 (6.7)	2 (3.8)	2 (4.3)	7 (4.9)
Nervous system disorders	1 (2.2)	4 (7.5)	1 (2.2)	6 (4.2)
Metabolism and nutrition disorders	2 (4.4)	0 (0.0)	2 (4.3)	4 (2.8)
Hyponatremia	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.4)
Type 2 diabetes mellitus	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Skin and subcutaneous tissue disorders	2 (4.4)	2 (3.8)	0 (0.0)	4 (2.8)
Hyperhidrosis	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)
Blood and lymphatic system disorders	1 (2.2)	1 (1.9)	1 (2.2)	3 (2.1)
Anemia	1 (2.2)	1 (1.9)	1 (2.2)	3 (2.1)
Infections and infestations	3 (6.7)	0 (0.0)	0 (0.0)	3 (2.1)
Upper respiratory tract infection	3 (6.7)	0 (0.0)	0 (0.0)	3 (2.1)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	2 (4.3)	2 (1.4)
Injury, poisoning and procedural complications	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)
Musculoskeletal and connective tissue disorders	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)

Source: Listing 16.2.7.1 adapted from Table 14.3.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication.
Adverse events are coded with MedDRA Version 23.0. Subjects are counted only once per SOC and per PT.

11.5.3.2 Incidence of Treatment-Emergent Adverse Events by Relationship to Study Drug

A summary of treatment-related TEAEs is presented by SOC and PT in Table 11-8, and by Subject listing is included in Listing 16.2.7.1.

A total of 10 subjects (6.9%) reported at least one treatment-related TEAE, which included 4 (8.9%), 4 (7.5%) and 2 (4.3%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The incidence of treatment-related TEAEs was found to be lowest in the evenamide 30 mg *bid* treated group.

The most frequently reported treatment-related TEAEs (those reported by more than one subject) by SOC were ‘Nervous system disorders’, with 3 (2.1%) subjects, and ‘Gastrointestinal disorders’ with 2 (1.4%) subjects, in the overall evenamide group. The treatment-related TEAEs within ‘Nervous system disorders’ were ‘Disturbance in attention’, ‘Extrapyramidal disorder’, ‘Sedation’ and ‘Somnolence’, each reported in only 1 subject, and all of these reported in the evenamide 15 mg bid treated group. The treatment-related TEAEs within ‘Psychiatric disorders’ were ‘Anxiety’, ‘Frustration tolerance decreased’, ‘Insomnia’ and “Irritability”, each reported in only 1 subject, and all of these reported in the evenamide

7.5 mg *bid* treated group. The treatment-related TEAEs within 'Gastrointestinal disorders' were 'Abdominal discomfort' reported in one subject (2.2%) in the evenamide 7.5 mg *bid* treated group, and 'Abdominal distension' reported in one subject (1.9%) in the evenamide 15 mg *bid* treated group.

Overall, 1 subject (0.7%) reported a treatment-related TEAE under 'Blood and lymphatic system disorders', 'General disorders and administration site conditions', 'Metabolism and nutrition disorders', 'Reproductive system and breast disorders', and 'Skin and subcutaneous tissue disorders'.

No individual treatment-related TEAE (by PT) was reported by more than one subject in any SOC.

Table 11-8: Summary of Treatment-Related Treatment-Emergent Adverse Events by SOC and Preferred Term - Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Any Treatment-Related TEAE	4 (8.9)	4 (7.5)	2 (4.3)	10 (6.9)
Nervous system disorders	0 (0.0)	3 (5.7)	0 (0.0)	3 (2.1)
Disturbance in attention	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Extrapyramidal disorder	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Sedation	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Somnolence	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)
Abdominal discomfort	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Abdominal distension	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Psychiatric disorders	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.4)
Anxiety	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Frustration tolerance decreased	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Insomnia	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Irritability	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Blood and lymphatic system disorders	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Anemia	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Death	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Increased appetite	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Reproductive system and breast disorders	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Erectile dysfunction	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total (N=144)
Hyperhidrosis	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.7.1 adapted from Table 14.3.1.4
N- Total number of subjects in the Safety Population, n- number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication.
Treatment related TEAEs are the TEAEs which are possibly or probably related to study drug, or not reported.
Adverse events are coded with MedDRA Version 23.0.
Subjects are counted only once per system organ class and per preferred term.

11.5.3.3 Incidence of Treatment-Emergent Adverse Events by Severity

All TEAEs by maximum severity are presented by SOC and PT in Table 14.3.1.6, and a by subject listing is included in Listing 16.2.7.1. The overall incidence of TEAEs by severity is summarized in Table 11-9.

A total of 40 TEAEs were reported and all the reported TEAEs were assessed as mild, moderate or severe in intensity. Out of the 40 TEAEs, 27 (18.8%) were of mild severity [reported by 9 (20.0%) subjects in evenamide 7.5 mg *bid*, 10 (18.9%) subjects in evenamide 15 mg *bid* and 8 (17.4%) in evenamide 30 mg *bid* treated groups], 10 (6.9%) were of moderate severity [reported by 5 (11.1%) subjects in evenamide 7.5 mg *bid*, 4 (7.5%) subjects in evenamide 15 mg *bid* and 1 (2.2%) in evenamide 30 mg *bid* treated groups], and 3 (2.1%) were of severe intensity [reported by no subject in evenamide 7.5 mg *bid*, 1 (1.9%) subject in evenamide 15 mg *bid* and 2 (4.3%) in evenamide 30 mg *bid* treated group].

Severe TEAEs reported were ‘Death’, ‘Elevated blood glucose level’ and ‘Detected glucose in urine’. Presence of glucose in the urine was reported by one subject (1.9%) in the evenamide 15 mg *bid* treated group, while death of a subject (2.2%) and increased blood glucose in 1 (2.2%) subject were reported in the evenamide 30 mg *bid* treated group.

Table 11-9: Summary of Severity of TEAEs – Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Any TEAE	Mild	9 (20.0)	10 (18.9)	8 (17.4)	27 (18.8)
	Moderate	5 (11.1)	4 (7.5)	1 (2.2)	10 (6.9)
	Severe	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)

Source: Listing 16.2.7.1 adapted from Table 14.3.1.6
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication. Adverse events are coded with MedDRA Version 23.0.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.

11.5.4 Listing of Adverse Events by Subject

All AEs for each subject are presented in Listing 16.2.7.1, in Appendix 16.2 of the CSR. Adverse events occurring beyond 46 weeks have been marked as “#” in footnotes in this Listing.

11.6 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.6.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A death reported in this study is presented in Table 11-10, Listing 16.2.7.4 in Appendix 16.2.7 of the CSR.

Other serious adverse events reported in this study are presented in Table 11-11, Listing 16.2.7.2 in Appendix 16.2.7 of the CSR.

Other significant adverse events leading to study drug discontinuation are presented in Table 11-12, Listing 16.2.7.3 in Appendix 16.2.7 of the CSR.

There were no overdose/ medication errors reported in this study.

The brief narratives of all the serious adverse events, including the death case, other significant adverse events leading to study discontinuation, and one case of pregnancy are described below in Section 11.6.2.

11.6.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Two cases of serious adverse event (including one death) have been reported (Subject Numbers: 401013 and 311006). One subject experienced non-serious adverse events leading to study medication discontinuation (Subject Number: 401003). Additionally, one case of pregnancy (Subject Number: 310003) was reported.

Brief narratives of these cases are presented in this section. Detailed summaries (Expanded Narratives) are provided in Section 14.4.

11.6.2.1 Narratives of two Serious Adverse Events, including Death

Subject Number: 401013 (Death)

This 31-year-old Asian male subject with a 2-year history of treatment-resistant schizophrenia treated with olanzapine and trihexyphenidyl received evenamide 30 mg *bid* up to 01 Mar 2023 (185 days), at which time the subject's family member informed the site that the subject fell on the ground in his house and was taken to the hospital, where they were informed that the subject had died.

The last study visit, performed two weeks before the event, did not detect any significant findings in ECG and vital signs. No symptoms, discomfort or negative effects were reported. During the study the subject showed improvement in symptoms, based on a PANSS total score of 62 (-26% compared to a baseline of 84), a CGI-S of 4 (moderately ill) with a 1-point improvement from baseline, and a CGI-C of 3 (minimally improved).

Based on the post-mortem report indicating the absence of any identifiable cause of death, the investigator considered the event of death as ‘possibly related’ to the study medication.

The autopsy report detected some signs of cardiovascular changes (atherosclerotic plaques in the aorta and in the coronary arteries), but did not clearly establish the cause of death. The final autopsy report stated that sudden cardiac events, such as cardiac arrhythmia, as a cause of death

are impossible to determine at the autopsy examination, therefore a possible role of evenamide cannot be ruled out.

Subject Number: 311006 (Dilutional hyponatremia and acute symptomatic seizure)

A 35-year-old Asian male subject, with a history of chronic schizophrenia, treated with haloperidol since Feb 2018 completed the planned 46 weeks of the study and entered a further extension period of 24 weeks. Due to unavailability of the investigational product at the study site, the subject received the last dose of evenamide 15 mg *bid* on 2 May 2022 for a total of 385 days on evenamide (321 days at 7.5 mg *bid* and 65 days at 15 mg *bid*).

On 28 May 2022 (26 days after the last dose of evenamide), the subject had an episode of tonic-clonic convulsions, associated with a fall, vomiting and bed wetting. The subject was hospitalized in a confused state (post ictal confusion) and was treated with the antiepileptic brivaracetam, pantoprazole, ondansetron, and ceftriaxone/sulbactam.

Serum sodium upon admission was 103.6 mmol/l (normal range 135-155 mEq/L) indicating severe hyponatremia that was treated with one 100 ml bolus of NaCl 3%. There was no prior history of seizure or hyponatremia in the subject.

In the days preceding the event, the subject consumed copious amounts of water for two days and was sleep deprived. A neurologist examined the subject and concluded that the seizure was due to dilutional hyponatremia caused by excessive water intake.

Four days after his hospitalization, the subject was stable, oriented, and conscious, and sodium was 134.9 mEq/l (normal range 135-155 mEq/L) indicating that hyponatremia was almost normalized. The events of acute symptomatic seizure and dilutional hyponatremia were considered resolved and the subject was discharged from the hospital.

Both the neurologist and investigator considered the events of acute symptomatic seizure and dilutional hyponatremia as not related to evenamide that was last administered 26 days before the onset of the events. The seizure had been due to dilutional hyponatremia due to the subject's excessive water intake.

11.6.2.2 Narrative of one TEAE leading to Study Drug Discontinuation

Subject Number: 401003 (Hyperhidrosis, disturbance in attention and somnolence)

This 36-year-old male subject, with a 10-year history of schizophrenia, treated with olanzapine since 2014, after 194 days on evenamide 15 mg *bid* experienced somnolence of moderate intensity and on the same day the study medication was discontinued. Two days before the subject experienced hyperhidrosis and disturbance in attention (increased sweating, and reduced concentration), both considered mild in intensity. All three adverse events were not serious and resolved without any sequalae. Approximately 1-month later the subject was withdrawn from the study. The Investigator considered all three adverse events (hyperhidrosis, disturbance in attention, and somnolence) not serious and as possibly related to evenamide 15 mg *bid*.

11.6.2.3 Narrative of Pregnancy

Subject Number: 310003 (Pregnancy)

A 32-year-old Asian female subject with a 6-year history of treatment-resistant schizophrenia on trifluoperazine, from Dec 2020, received evenamide 7.5 mg *bid* as adjunctive therapy and completed uneventfully Study 015 (1-year on evenamide 7.5 mg *bid*). Laboratory tests performed at the EOS visit (20 days after last menstrual period) indicated that the Beta-human chorionic gonadotropin (Beta-hCG) level was positive for pregnancy. A positive urine pregnancy test, performed approximately 10 days later, confirmed the pregnancy. The subject showed a significant improvement in symptoms based on PANSS total score of 55 (-34% compared to a baseline of 83), a CGI-S of 3 (mildly ill) with 2 point improvement from baseline, and a CGI-C of 2 (much improved). Follow-up information reported that the subject electively terminated the pregnancy (Termination of the pregnancy was not recommended by the physician).

The Investigator considered the event of pregnancy as not related to evenamide.

11.6.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.6.3.1 Deaths

A 30-year-old male subject (number 401013) was found to have fallen and died of an unknown cause. (Table 11-10). A brief narrative of this serious adverse event is presented in Section 11.6.2.1.

Table 11-10: Serious Adverse event – Death

Subject Number	Age/ Sex	Date of First Dose and Time /Last Dose (Day)	Reported Term	Preferred Term/ System Organ Class	Date of Death (Day)	Autopsy performed	Date of Autopsy (Day)	Brief Description of Event
401013	30/M	29AUG2022:10: 05/01MAR2023 (185)	DEATH	Death/General disorders and administration site conditions	01MAR 2023 (141)	Y	01MAR 2023 (141)	Subject's family member contacted the site on 1st Mar 2023 and informed that subject had been found fallen inside the house; and when they brought him to the hospital, they were informed that the subject was dead.

Source: Listing 16.2.7.4 F = Female, M = Male, Age = Age at Screening Y = Yes, N = No, AE = Adverse Event, TEAE = Treatment Emergent Adverse Event, SAE = Serious Adverse Event, Day = Date of last dose of investigational product - Date of first dose of investigational product + 1 if last dose is on or after the date of the first dose of investigational product. Day of AE Start/End = AE start/end date - Date of first dose of investigational product + 1 if the AE start/end date is on or after the date of the first dose of investigational product. Else AE start/end date - Date of first dose of investigational product, Adverse events are coded with MedDRA Version 23.0.

11.6.3.2 Other Serious Adverse Events

A summary of Treatment-Emergent SAEs by SOC and PT in the Safety Population is presented in Table 11-11, and by subject details are presented in Listing 16.2.7.2.

Overall, at least one serious TEAE was reported in 2 (1.4%) subjects. It included a single (2.2%) subject each from 7.5 mg *bid* and 30 mg *bid* treated groups.

One subject (30 mg *bid*) died, and another subject (7.5 mg *bid*) experienced two SAEs of hyponatremia and seizure.

The brief narratives of these serious adverse events are presented in Section 11.6.2.1.

Table 11-11: Treatment-Emergent SAEs by SOC and Preferred Term – Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Any Serious TEAE	1(2.2)	0(0.0)	1(2.2)	2(1.4)
General disorders and administration site conditions	0(0.0)	0(0.0)	1(2.2)	1(0.7)
Death	0(0.0)	0(0.0)	1(2.2)	1(0.7)
Metabolism and nutrition disorders	1(2.2)	0(0.0)	0(0.0)	1(0.7)
Hyponatremia	1(2.2)	0(0.0)	0(0.0)	1(0.7)
Nervous system disorders	1(2.2)	0(0.0)	0(0.0)	1(0.7)
Seizure	1(2.2)	0(0.0)	0(0.0)	1(0.7)

Source: Listing 16.2.7.2 adapted from Table 14.3.1.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication.
Adverse events are coded with MedDRA Version 23.0. Subjects are counted only once per SOC and per PT.

11.6.3.3 Other Significant Adverse Events

TEAEs leading to Study Drug Discontinuation

A summary of TEAEs leading to study drug discontinuation by SOC and PT for the Safety Population is presented in Table 11-12, and by subject details in Listing 16.2.7.3.

Overall, 1 (0.7%) subject reported TEAEs leading to study drug discontinuation. The TEAEs leading to study drug discontinuation, reported by a single subject in the evenamide 15 mg *bid* treated group, by SOC, were ‘Nervous system disorders’ (PT: Disturbance in attention, Somnolence), and ‘Skin and subcutaneous tissue disorders’ (Hyperhidrosis). None of the subjects in evenamide 7.5 mg *bid* and 30 mg *bid* treated groups reported TEAEs leading to study drug discontinuation.

Table 11-12: Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation - Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)	Total (N=144) n (%)
Any TEAE Leading to Study Drug Discontinuation	0(0.0)	1(1.9)	0(0.0)	1(0.7)
Nervous system disorders	0(0.0)	1(1.9)	0(0.0)	1(0.7)
Disturbance in attention	0(0.0)	1(1.9)	0(0.0)	1(0.7)
Somnolence	0(0.0)	1(1.9)	0(0.0)	1(0.7)
Skin and subcutaneous tissue disorders	0(0.0)	1(1.9)	0(0.0)	1(0.7)
Hyperhidrosis	0(0.0)	1(1.9)	0(0.0)	1(0.7)

Source: Listing 16.2.7.3 adapted from Table 14.3.1.5
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication. Adverse events are coded with MedDRA Version 23.0.
Subjects are counted only once per system organ class and per preferred term.

11.7 Clinical Laboratory Evaluation

11.7.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Laboratory measurements are presented by subject in Listing 16.2.8.1 (hematology), Listing 16.2.8.2 (blood chemistry), and Listing 16.2.8.3 (urinalysis) for the Safety Population. Normal laboratory ranges are provided in each individual listing. The criteria for clinically notable laboratory parameters are displayed in Appendix 2 of the Study Protocol presented in Appendix 16.1.1.

Clinical laboratory continuous (serum prolactin) and categorical (serum pregnancy test and urine drug screen results) special diagnostic tests for the Safety Population are presented in Listing 16.2.8.4 and Listing 16.2.8.5, respectively.

11.7.1.1 Hematology: Laboratory Values over Time

Summary statistics of change from baseline by visit were presented for hematology parameters in Table 14.3.2.1 (Observed values and change from baseline). There were no clinically meaningful changes from baseline to Week 46 in mean values for hematology parameters in any of the three treatment groups.

11.7.1.2 Individual Subject Changes

A summary of newly emergent clinically notable abnormal findings in laboratory hematology parameters at any post-baseline in the Safety Population is presented in Table 14.3.2.3. There were no clinically meaningful trends observed in the newly emergent clinically notable abnormalities observed in any of the three treatment groups. The number of newly emergent clinically notable abnormalities was low across all the treatment groups, with no meaningful differences.

The hematology parameters with the maximum number of newly emergent clinically notable abnormal findings were low hemoglobin level (≤ 0.85 x lower limit of normal (LLN) g/L) after 46 weeks, seen in 4 (8.9%)), 1 (1.9%) and 1 (2.2%) subject in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 11-13).

Table 11-13: Laboratory Hematology; Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline - Safety Population

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Eosinophils (10/L)	Week 12	>= 1.5	1 (2.2)	0 (0.0)	1 (2.2)
	Week 36	>= 1.5	0 (0.0)	0 (0.0)	1 (2.2)
Hematocrit (fraction of 1)	Week 12	<=0.85 x LLN	1 (2.2)	1 (1.9)	2 (4.3)
	Week 24	<=0.85 x LLN	2 (4.4)	2 (3.8)	1 (2.2)
	Week 36	<=0.85 x LLN	1 (2.2)	1 (1.9)	1 (2.2)
	Week 46	<=0.85 x LLN	1 (2.2)	2 (3.8)	2 (4.3)
Hemoglobin (g/L)	Week 12	<=0.85 x LLN	1 (2.2)	2 (3.8)	0 (0.0)
	Week 24	<=0.85 x LLN	2 (4.4)	2 (3.8)	1 (2.2)
	Week 36	<=0.85 x LLN	5 (11.1)	1 (1.9)	0 (0.0)
	Week 46	<=0.85 x LLN	4 (8.9)	1 (1.9)	1 (2.2)
Leukocytes (10/L)	Week 24	<= 3.0	1 (2.2)	0 (0.0)	0 (0.0)
	Week 36	<= 3.0	0 (0.0)	0 (0.0)	2 (4.3)
Neutrophils (10/L)	Week 24	=< 1.0	1 (2.2)	1 (1.9)	0 (0.0)
	Week 36	=< 1.0	0 (0.0)	0 (0.0)	1 (2.2)

Source: Listing 16.2.8.1 adapted from Table 14.3.2.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are calculated by considering Male/Female count in each treatment group (Evenamide 7.5 mg BID: 31/14, Evenamide 15 mg BID: 38/15 and Evenamide 30 mg BID: 34/12) whenever the criterion is specific for Male/Female.Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

11.7.2 Blood Chemistry

11.7.2.1 Laboratory Values over Time

Summary statistics of change from baseline by visit are presented for blood chemistry parameters in Table 14.3.2.2 (observed values and change from baseline). There were no clinically meaningful changes from baseline in mean values for blood chemistry parameters in any of the three treatment groups.

11.7.2.2 Individual Subject Changes

A summary of newly emergent clinically notable abnormal findings in laboratory blood chemistry parameters at any post-baseline in the Safety Population is presented in Table 14.3.2.4. There were no clinically meaningful trends observed in the newly emergent clinically notable abnormalities in any of the three treatment groups. The number of newly emergent clinically notable abnormalities was low across all the treatment groups, with no meaningful differences.

At Week 46, the blood chemistry parameters with the maximum number of newly emergent clinically notable abnormal findings were observed in low density lipoprotein level (>= 4.1 mmol/L), seen in 1(2.2%) and 5(10.9%) subjects in evenamide 7.5 mg and 30 mg *bid* treated groups, respectively, and no subjects were observed in 15 mg *bid* treated group (Table 11-14).

Table 11-14: Laboratory Blood Chemistry; Newly Emergent Clinically Notable Abnormal Findings - Safety Population

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Bicarbonate (mmol/L)	Week 12	<= 18	5(11.1)	5(9.4)	2(4.3)
	Week 24	<= 18	2(4.4)	2(3.8)	3(6.5)
	Week 36	<= 18	6(13.3)	4(7.5)	1(2.2)
	Week 46	<= 18	4(8.9)	2(3.8)	1(2.2)
	Week 12	>=33	1(2.2)	0(0.0)	0(0.0)
	Week 36	>=33	1(2.2)	0(0.0)	0(0.0)
Bilirubin (umol/L)	Week 12	>= 34	0(0.0)	0(0.0)	1(2.2)
	Week 36	>= 34	0(0.0)	0(0.0)	1(2.2)
	Week 46	>= 34	0(0.0)	0(0.0)	1(2.2)
Calcium (mmol/L)	Week 24	<= 1.9	1(2.2)	0(0.0)	1(2.2)
	Week 46	<= 1.9	2(4.4)	2(3.8)	0(0.0)
Chloride (mmol/L)	Week 46	<= 90	1(2.2)	0(0.0)	0(0.0)
Chloride (mmol/L)	Week 12	>= 113	0(0.0)	1(1.9)	0(0.0)
	Week 24	>= 113	0(0.0)	1(1.9)	0(0.0)
Cholesterol (mmol/L)	Week 12	>= 7.25	0(0.0)	1(1.9)	1(2.2)
Creatinine (umol/L)	Week 24	>= 177	1(2.2)	0(0.0)	1(2.2)
	Week 36	>= 177	0(0.0)	0(0.0)	1(2.2)

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Week 46	>= 177	0(0.0)	1(1.9)	0(0.0)
Glucose (mmol/L)	Week 24	>= 11.1	1(2.2)	0(0.0)	1(2.2)
	Week 46	>= 11.1	1(2.2)	1(1.9)	1(2.2)
LDL Cholesterol (mmol/L)	Week 12	>= 4.1	1(2.2)	0(0.0)	7(15.2)
	Week 24	>= 4.1	2(4.4)	1(1.9)	2(4.3)
	Week 36	>= 4.1	1(2.2)	1(1.9)	1(2.2)
	Week 46	>= 4.1	1(2.2)	0(0.0)	5(10.9)
Lactate Dehydrogenase (U/L)	Week 24	>= 500	0(0.0)	1(1.9)	0(0.0)
Sodium (mmol/L)	Week 12	<= 127	0(0.0)	0(0.0)	1(2.2)
	Week 24	<= 127	1(2.2)	0(0.0)	0(0.0)
	Week 46	<= 127	1(2.2)	0(0.0)	0(0.0)
	Week 12	>= 152	0(0.0)	1(1.9)	0(0.0)
Triglycerides (mmol/L)	Week 12	>= 4.5	1(2.2)	1(1.9)	0(0.0)
	Week 24	>= 4.5	1(2.2)	0(0.0)	0(0.0)
	Week 36	>= 4.5	0(0.0)	1(1.9)	3(6.5)
	Week 46	>= 4.5	1(2.2)	0(0.0)	2(4.3)

Source: Listing 16.2.8.2 adapted from Table 14.3.2.4
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are calculated by considering Male/Female count in each treatment group (Evenamide 7.5 mg BID: 31/14, Evenamide 15 mg BID: 38/15 and Evenamide 30 mg BID: 34/12) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

11.7.3 Urinalysis

Urinalysis data was listed Listing 16.2.8.3 along with clinically significant values as evaluated by the Investigator. Clinically notable value determinations for urine parameters were performed for Specific Gravity, RBC and WBC casts only.

No summary table or shift table was generated for urinalysis parameters.

11.8 Vital Signs, Physical Findings and Other Observations Related to Safety

11.8.1 Vital Signs

Vital sign measurements are listed by subject in Listing 16.2.9 and at each of the scheduled timepoints in Listing 16.2.9a.

11.8.1.1 Vital Signs over Time

Summary statistics of change from baseline by visit are presented for vital signs in Table

14.3.3.1 (observed values and changes from baseline). There were no clinically meaningful changes from baseline in mean values of vital signs parameters in any of the three treatment groups.

11.8.1.2 Individual Subject Changes

No summary tables for shifts from baseline by visit based on normal ranges for vital signs were generated.

11.8.1.3 Individual Clinically Significant Abnormalities – Vital Signs

A summary of incidence of clinically notable abnormalities is presented for vital signs parameters in Table 14.3.3.2, and by subject details are presented in Listing 16.2.9b. The criteria for clinically notable vital signs abnormalities are displayed in Appendix 2 of the Study Protocol presented in Appendix 16.1.1. No clinically meaningful trends were observed in the clinically notable abnormalities in the vital sign parameters in any of the three treatment groups. The numbers of clinically notable abnormalities were low across all the treatment groups, with no meaningful differences (Table 11-15).

Table 11-15: Incidence of Clinically Notable Abnormalities for Vital Signs - Safety Population

Vital Signs	Visit	Criteria	Evenamide 7.5 mg *BID* (N=45) n(%)	Evenamide 15 mg *BID* (N=53) n(%)	Evenamide 30 mg *BID* (N=46) n(%)
Respiratory Rate (breaths/min)	Week 24	>25	0 (0)	0 (0)	1 (2)
	Week 36	>25	0 (0)	0 (0)	1 (2)
	Week 46	>25	0 (0)	1 (2)	1 (2)
	Safety follow-up-015 - Day 7	>25	0 (0)	1 (2)	1 (2)
Temperature (C)	Week 24	Value >= 38.3 and >= 1.1 increase from baseline	1 (2)	0(0)	0(0)
Weight (kg)	Week 6	>= 7% decrease from Baseline	1 (2)	1 (2)	0 (0)
	Week 6	>=7% increase from Baseline	0 (0)	0 (0)	1 (2)
	Week 12	>= 7% decrease from Baseline	1 (2)	0 (0)	2 (4)
	Week 12	>=7% increase from Baseline	2 (4)	2 (4)	3 (7)
	Week 18	>= 7% decrease from Baseline	1 (2)	1 (2)	2 (4)
	Week 18	>=7% increase from Baseline	2 (4)	1 (2)	3 (7)
	Week 24	>= 7% decrease from Baseline	1 (2)	1 (2)	1 (2)

Vital Signs	Visit	Criteria	Evenamide 7.5 mg *BID* (N=45) n(%)	Evenamide 15 mg *BID* (N=53) n(%)	Evenamide 30 mg *BID* (N=46) n(%)
	Week 24	>=7% increase from Baseline	2 (4)	2 (4)	3 (7)
	Week 36	>= 7% decrease from Baseline	1 (2)	0 (0)	1 (2)
	Week 36	>=7% increase from Baseline	2 (4)	2 (4)	4 (9)
	Week 46	>= 7% decrease from Baseline	1 (2)	1 (2)	1 (2)
	Week 46	>=7% increase from Baseline	2 (4)	4 (8)	5 (11)
	Safety follow-up-015 - Day 7	>= 7% decrease from Baseline	2 (4)	1 (2)	0 (0)
	Safety follow-up-015 - Day 7	>=7% increase from Baseline	0 (0)	5 (9)	2 (4)

Source: Listing 16.2.9b, adapted from Table 14.3.3.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, post-baseline intervals of 015 are of after Day 43 of 014 study dosing.

11.8.2 Electrocardiogram Findings

To ensure consistency in the data analysis across subjects, all ECGs were sent to a central ECG monitoring service (ERT) for review and interpretation; however, the 'real-time' review and interpretation of the 12-lead ECGs that were used for determination of a subject's eligibility for enrollment in the trial, as well as post-dose safety monitoring, was performed by a physician at the investigational site. When an ECG was observed to be abnormal at screening, the evaluation was to be repeated, and if no clinically significant abnormalities were noted, the patient could be considered eligible for the study. At the baseline (014 Baseline) visit, at least 1 hour prior to the first dose, the 12-lead ECG was repeated 3 times, at least 10 minutes apart, and the values for the different parameters were averaged to obtain the baseline values. These mean values were used in determining eligibility for the study, as well as evaluating change from baseline. The parameters included numerical values for heart rate and RR, PR, QRS, QT, QTcB, and QTcF intervals, as provided by the central ECG service.

11.8.2.1 Individual Subject Changes

The change from baseline at each visit and at endpoint (Week 46 or early discontinuation) for ECG parameters (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval) is presented in Table 14.3.5.1, and by subject details in Listing 16.2.11.1. There were no clinically meaningful changes from baseline in mean values for any ECG parameters in any of the three treatment groups.

11.8.2.2 Individual Clinically Significant Abnormalities – Electrocardiogram

Summary of Treatment-Emergent Abnormalities in ECG as assessed by Central Reader is presented in Table 14.3.5.2, and by subject details in Listing 16.2.11.2. Summary of Treatment-Emergent Abnormalities in ECG as Assessed by Investigator in the Safety Population is presented in Table 14.3.5.3, and by subject details in Listing 16.2.11.1. The number of post-baseline ECGs that were assessed as abnormal was low and similar across the treatment groups. The Central Reviewer assessed that 8 (17.8%) subjects in the evenamide 7.5 mg, 6 (11.3%) subjects in 15 mg and 10 (21.7%) subjects in 30 mg *bid* treated groups had treatment-emergent abnormalities in the ECG recordings. The Investigators assessed that 8 (17.8%) subjects in the evenamide 7.5 mg *bid* treated group, 12 (22.6%) in the 15 mg *bid* treated group (15.0%), and 11 (23.9%) subjects in the 30 mg *bid* treated group had treatment-emergent abnormalities in the ECG recordings. None of these abnormalities were considered as clinically significant by the Investigators in any of the three treatment groups.

The ECG Parameters Categorical Analysis for the Safety Population is presented in Table 14.3.5.4, and by subject details in Listing 16.2.11.3. The number (%) of subjects meeting the following categorical criteria were summarized by treatment group:

a) Change from baseline in QTc interval: > 30 msec and </= 60 msec, > 60 msec.
b) Absolute QTc interval: > 450 msec and </= 480 msec, > 480 msec and </= 500 msec, and > 500 msec
c) Absolute value of PR interval > 200 msec and QRS Duration > 110 msec.
d) More than 25% change from baseline in PR interval and QRS duration.

A PR Interval, Aggregate (ms) absolute value >200 msec was present at Week 46 in 1 (2.2%) subject in both the 7.5 mg and 30 mg *bid* evenamide treatment groups, but none in the 15 mg *bid* treated group. More than 25% change from baseline observed in the PR interval at Week 46 was observed in 1 (1.9%) subject in 15 mg *bid* and 1 (2.2%) subject in 30 mg *bid* evenamide treated group.

For the QTcB Interval, Aggregate (ms), at Week 46. a change from Baseline value of > 30 msec AND <= 60 msec was observed in 4 (8.9%), 4 (7.5%), 1 (2.2%) subject treated with 7.5 mg, 15 mg and 30 mg *bid* evenamide, respectively. QTcB Interval, Aggregate (ms) Absolute Values of > 450 msec AND <= 480 msec were observed in 2 (4.4%) and 1 (2.2%) subject in 7.5 mg and 30 mg *bid* evenamide treated groups, respectively. No subjects in the 15 mg *bid* evenamide treated group had QTcB Interval, Aggregate (ms) Absolute Value of > 450 msec AND <= 480 msec, and no subject had a value greater than 480 msec at any timepoint.

For the QTcF Interval, Aggregate (ms) at Week 46, change from Baseline values of > 30 msec AND <= 60 msec were observed in 1 (2.2%) subject in 7.5 mg and 1 (1.9%) subject in 15 mg *bid* evenamide treated groups, however, none were observed in the 30 mg *bid* evenamide treated group.

QTcF Interval, Aggregate (ms) Absolute Values of > 450 msec AND <= 480 msec at Week 46 were observed in 1 (2.2%) subject each in 7.5 mg and 30 mg *bid* treated groups. None were observed in 15 mg *bid* evenamide treated group and no subject had a value greater than 480 msec at any timepoint. (Table 11-16)

Table 11-16: ECG Parameters Categorical Analysis - Safety Population

Parameter	Visit	Criteria	Category	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)
PR Interval, Aggregate (ms)	Week 6	Absolute Value	> 200 msec	0 (0)	0 (0)	2 (4.3)
		Change From Baseline value	More than 25% change from baseline	0 (0)	1 (1.9)	2 (4.3)
	Week 12	Absolute Value	> 200 msec	0 (0)	1 (1.9)	1 (2.2)
		Change From Baseline value	More than 25% change from baseline	0 (0)	2 (3.8)	3 (6.5)
	Week 18	Absolute Value	> 200 msec	1 (2.2)	0 (0)	1 (2.2)
		Change From Baseline value	More than 25% change from baseline	1 (2.2)	2 (3.8)	1 (2.2)
	Week 24	Absolute Value	> 200 msec	1 (2.2)	0 (0)	1 (2.2)
		Change From Baseline value	More than 25% change from baseline	0 (0)	0 (0)	2 (4.3)
	Week 36	Absolute Value	> 200 msec	1 (2.2)	0 (0)	1 (2.2)
		Change From Baseline value	More than 25% change from baseline	0 (0)	0 (0)	1 (2.2)
	Week 46/Early Withdrawal	Absolute Value	> 200 msec	1 (2.2)	0 (0)	1 (2.2)
		Change From Baseline value	More than 25% change from baseline	0 (0)	1 (1.9)	1 (2.2)
QRS Duration, Aggregate (ms)	Week 18	Absolute Value	> 110 msec	0 (0)	0 (0)	1 (2.2)
	Week 36	Change From Baseline value	More than 25% change from baseline	0 (0)	0 (0)	1 (2.2)
QTcB Interval, Aggregate(ms)	Week 6	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	2 (3.8)	1 (2.2)
		Absolute Value	> 450 msec AND <= 480 msec	2 (4.4)	0 (0)	1 (2.2)
	Week 12	Change From Baseline value	> 30 msec AND <= 60 msec	1 (2.2)	5 (9.4)	3 (6.5)

Parameter	Visit	Criteria	Category	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	0 (0)	1 (2.2)
	Week 18	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	5 (9.4)	1 (2.2)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	2 (3.8)	0 (0)
		Change From Baseline value	> 60 msec	1 (2.2)	0 (0)	0 (0)
	Week 24	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	7 (13.2)	0 (0)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	2 (3.8)	0 (0)
		Absolute Value	> 480 msec AND <= 500 msec	0 (0)	1 (1.9)	0 (0)
	Week 36	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	3 (5.7)	3 (6.5)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	0 (0)	0 (0)
	Week 46/Early Withdrawal	Change From Baseline value	> 30 msec AND <= 60 msec	4 (8.9)	4 (7.5)	1 (2.2)
		Absolute Value	> 450 msec AND <= 480 msec	2 (4.4)	0 (0)	1 (2.2)
QTcF Interval, Aggregate (ms)	Week 6	Change From Baseline value	> 30 msec AND <= 60 msec	0 (0)	1 (1.9)	0 (0)
		Absolute Value	> 450 msec AND <= 480 msec	0 (0)	1 (1.9)	0 (0)
	Week 12	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	1 (1.9)	2 (4.3)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	0 (0)	0 (0)

Parameter	Visit	Criteria	Category	Evenamide 7.5 mg *BID* (N=45) n (%)	Evenamide 15 mg *BID* (N=53) n (%)	Evenamide 30 mg *BID* (N=46) n (%)
	Week 18	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	2 (3.8)	0 (0)
		Absolute Value	> 450 msec AND <= 480 msec	0 (0)	1 (1.9)	0 (0)
	Week 24	Change From Baseline value	> 30 msec AND <= 60 msec	2 (4.4)	5 (9.4)	0 (0)
	Week 36	Change From Baseline value	> 30 msec AND <= 60 msec	1 (2.2)	2 (3.8)	0 (0)
	Week 46/Early Withdrawal	Change From Baseline value	> 30 msec AND <= 60 msec	1 (2.2)	1 (1.9)	0 (0)
		Absolute Value	> 450 msec AND <= 480 msec	1 (2.2)	0 (0)	1 (2.2)

Source: Listing 16.2.11.3 adapted from Table 14.3.5.4
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

11.8.3 Physical and Neurological Findings

The treatment-emergent abnormalities from physical and neurological examinations are presented by subject in Listing 16.2.10 and Listing 16.2.12, respectively.

11.8.3.1 Physical Examination Individual Subject Changes

None of the subjects were found to have any treatment-emergent abnormalities on the physical examination in any of the three treatment groups. (Table 14.3.4)

11.8.3.2 Neurological Examination Individual Subject Changes

One subject from evenamide 30 mg *bid* treated group was found to have a clinically non-significant treatment-emergent abnormality (delusions and hallucinations) on the neurological examination conducted at Week 46, while no treatment-emergent abnormalities were reported in either of the other treatment groups. (Table 14.3.6)

11.8.4 Extrapyramidal Symptom Rating Scale

A summary of results for the Extrapyramidal Symptoms Rating Scale - Abbreviated Version (ESRS-A) for the Safety Population for each parameter at Baseline and Weeks 12, 24, 36 and 46 is presented in Table 14.3.8.1. The mean change from baseline score and observed score for the four subscales (parkinsonism, dystonia, dyskinesia, and akathisia) and Total Score of the ESRS-A for the Safety Population are presented in Table 14.3.8.2. The clinical global impression of movement severity (CGI-S) ratings for each of the four subscales, summarized

by visit for the Safety Population, are presented in Table 14.3.8.3. ESRS-A results are presented by subject in Listing 16.2.14.

The incidence of extrapyramidal symptoms reported was very low (minimal or absent), and there were no meaningful differences between the treatment groups. None of the symptoms worsened at Week 46 compared to Baseline.

11.8.5 Calgary Depression Scale (CDSS) for Schizophrenia

The change from baseline in CDSS item scores and total score for the Safety Population is presented in Table 14.3.9, and by subject details in Listing 16.2.15.

The mean (SD) values of CDSS total score recorded at Week 46 were 0.2 (0.78), 0.5 (1.21) and 0.5 (1.10) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The mean (SD) changes from baseline observed at Week 46 were -0.2 (1.11), -0.1 (0.67) and -0.3 (1.13) in depressive symptoms in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, indicating no overall worsening of depression. (Table 11-17)

Table 11-17: Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Total Scores - Safety Population

			Evenamide 7.5 mg *BID* (N=45)		**Evenamide 15 mg *BID* (N=53)**		**Evenamide 30 mg *BID* (N=46)**	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Total Score	Screening	n	45		53		46	
		Mean (SD)	0.5 (1.08)		0.7 (1.39)		0.8 (1.59)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Baseline	n	45		53		46	
		Mean (SD)	0.4 (0.94)		0.6 (1.33)		0.8 (1.58)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.2 (0.59)	-0.2 (0.90)	0.4 (0.96)	-0.1 (0.75)	0.4 (1.07)	-0.2 (1.06)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 3	-3, 2	0, 4	-2, 3	0, 4	-5, 2
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.2 (0.78)	-0.2 (1.11)	0.5 (1.21)	-0.1 (0.67)	0.5 (1.10)	-0.3 (1.13)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 4	-4, 4	0, 6	-2, 2	0, 4	-5, 2

Source: Listing 16.2.15 adapted from Table 14.3.9.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, post-baseline intervals of 015 are of after Day 43 of 014 study dosing.

11.8.6 Standard Eye Examination

Treatment-emergent post-baseline abnormal findings on the eye examination, comprising assessments of visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and the front part of the eyes (eyelids, cornea, conjunctiva, sclera, and iris) are summarized in Table 14.3.7 and listed by evenamide dose group for the Safety Population in Listing 16.2.13.

Treatment-emergent post-baseline abnormal findings (visual field, visual acuity, Cornea, and conjunctival defects) on the eye examination, that were considered non-clinically significant, were noted in 5 (3.5%) subjects. A total of 2 (4.4%) subjects, 2 (3.8%) subjects, and 1 (2.2%) subjects from evenamide 7.5 mg *bid*, 15 mg *bid*, and 30 mg *bid* treated groups, respectively, showed treatment-emergent abnormalities in the standard eye examination.

11.9 Safety Conclusions

The primary objective of the study was to evaluate the long-term safety and tolerability of evenamide given orally in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic dose of their current antipsychotic medication.

A total of 40 (27.8%) subjects reported at least one TEAE, which included 14 (31.1%), 15 (28.3%), and 11 (23.9%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The most frequently reported TEAEs (those with a ≥5% incidence of events in overall subjects) by SOC were reported in 'Investigations' and 'Psychiatric disorders', by 10 (6.9%) and 9 (6.3%) subjects, respectively. Out of the reported TEAEs under the SOC "Investigations", the reported preferred term 'Blood cholesterol increased' was reported in 3 subjects, 'Blood creatine phosphokinase increased' was reported in 3 subjects, 'Blood glucose increased' was reported in 2 subjects, and 'Low density lipoprotein increased' was reported in 2 subjects. All other TEAEs under the SOC "Investigations" were reported in not more than 1 subject in the overall evenamide group. Out of the reported TEAEs under the SOC "Psychiatric disorders", the reported preferred term 'Insomnia' was reported in 3 subjects, 'Schizophrenia' was reported in 3 subjects, and 'Irritability' was reported in 2 subjects. All other TEAE under the SOC "Psychiatric disorders" were reported in not more than 1 subject in the overall evenamide group.

Out of the reported TEAEs under the SOC 'Metabolism and nutrition disorders ', the preferred term 'Hyponatremia' and 'Type 2 diabetes mellitus' was reported in 2 subjects each. Other TEAE (Increased appetite) under the SOC "Metabolism and nutrition disorders" was reported in 1 subject in the overall evenamide group. Out of the reported TEAEs under the SOC 'Skin and subcutaneous tissue disorders' the preferred term 'Hyperhidrosis' was reported in 2 subjects. All other TEAEs under the SOC 'Skin and subcutaneous tissue disorders' were reported in not more than 1 subject in the overall evenamide group.

Out of the reported TEAEs under the SOC 'Blood and lymphatic system disorders' the preferred term 'Anaemia' was reported in 1 subject each in all three treated groups. Out of the reported TEAEs under the SOC 'Infections and infestations' the preferred term 'Upper respiratory tract infection' was reported in 3 subjects in the overall evenamide group.

Under the SOC 'Gastrointestinal disorders', 'Nervous system disorders', 'General disorders and administration site conditions', 'Injury, poisoning and procedural complications', 'Musculoskeletal and connective tissue disorders', 'Hepatobiliary disorders', 'Renal and urinary disorders', 'Reproductive system and breast disorders', 'Respiratory, thoracic and mediastinal disorders' and 'Vascular disorders' each of the individual TEAEs were reported in only 1 subject in the overall evenamide group.

The most-frequently reported treatment-related TEAEs (those reported by more than one subject) by SOC were 'Nervous system disorders' with 3 (2.1%) subjects, and 'Gastrointestinal disorders' and 'Psychiatric disorders' with 2 (1.4%) subjects each, in the overall evenamide group. The treatment-related TEAEs within 'Nervous system disorders' were 'Disturbance in attention', 'Extrapyramidal disorder', 'Sedation' and 'Somnolence', each in one subject, and all of these were reported in the evenamide 15 mg *bid* treated group. The treatment-related TEAEs within 'Psychiatric disorders' were 'Anxiety', 'Frustration tolerance decreased', and 'Insomnia', each in one subject, and all of these were reported in the evenamide 7.5 mg *bid* treated group. The treatment-related TEAEs within 'Gastrointestinal disorders' were 'Abdominal discomfort' reported in one (2.2%) subject in the evenamide 7.5 mg *bid* treated group, and 'Abdominal distension' reported in one (1.9%) subject in the evenamide 15 mg *bid* treated group.

TEAEs were assessed as mild, moderate or severe in intensity. Out of 40 reported TEAEs, 27 (18.8%) were of mild intensity, 10 (6.9%) were of moderate intensity, and 3 (2.1%) were of severe intensity.

Two (1.4%) subjects experienced at least one Serious TEAE. One subject receiving 30 mg *bid* had fallen and died of an unknown cause, while a second subject experienced dilutional hyponatremia leading to a seizure 26 days after receiving his last dose of evenamide (15 mg *bid*).

A total of 10 (6.9%) subjects reported at least one treatment-related TEAE, which included 4 (8.9%), 4 (7.5%) and 2 (4.3%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Overall, 1 (0.7%) subject in the evenamide 15 mg *bid* treated group reported a TEAE leading to study drug discontinuation. Reported TEAEs in this subject were reduced concentration, increased sweating and somnolence.

Overall, 1 (0.7%) TEAE resulting in death was reported during the study in the evenamide 30 mg *bid* treated group. The cause of death could not be discerned.

Very few results for clinical laboratory parameters (hematology and clinical chemistry) were deemed clinically significant by the Principal Investigator. There were no clinically meaningful trends observed in the newly emergent clinically notable abnormalities in laboratory parameters in any of the three treatment groups.

The number of newly emergent clinically notable laboratory abnormalities was low across all the treatment groups, with no meaningful differences. Low hemoglobin level (≤ 0.85 x lower limit of normal (LLN) g/L), was seen in 4 (8.9%), 1 (1.9%) and 1 (2.2%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Vital signs data did not indicate any pattern of clinically notable effects of any of the three doses of evenamide on blood pressure (supine and orthostatic changes), pulse rate, respiratory rate, body temperature, or body weight.

ECG findings indicated no clinically significant effects of any of the three doses of evenamide on cardiac function, including QTc interval. None of the treatment-emergent ECG abnormalities were considered as clinically significant by the Investigators.

No clinically notable effects or trends were observed at the end of treatment compared to baseline for any of the three doses of evenamide on physical examinations, neurological examinations, extrapyramidal symptoms (assessed by the ESRS-A), changes in depressive symptoms (assessed by the CDSS), and standard eye examinations.

Overall, the results for the safety parameters assessed in the study indicated that evenamide given orally at three fixed doses (7.5 mg, 15 mg and 30 mg *bid*) in patients with treatment-resistant schizophrenia was well tolerated, without any major safety concern. No dose-dependent safety concern was observed.

12 EFFICACY EVALUATION

12.1 Analysis of Efficacy

All efficacy assessments were performed by the same blinded rater(s) at the site. To ensure consistency of ratings for key efficacy measures, these assessments were performed approximately at the same time relative to the morning dose of study medication during the scheduled clinic visits at 12, 24 and 36 weeks, and at the final visit at 46 weeks. Patients/caregivers were instructed to withhold the morning dose of study medication on the day of each scheduled visit, as it was administered in the clinic, and the key efficacy assessments, e.g. PANSS and CGI-C/S, were conducted approximately 1-2 hours post-dose. Patients were instructed to take their concomitant antipsychotic and other medications at their residence according to their usual schedule.

12.1.1 Positive and Negative Syndrome Scale Results

The PANSS was conducted at baseline, and at 12, 24 and 36 weeks, and at the final visit at 46 weeks (or at early discontinuation), and used as the primary efficacy measure in the trial.

12.1.1.1 PANSS Total Scores

Primary Efficacy Estimand Analysis

The mean change from baseline to Week 46 in PANSS total score using within group comparisons (*Primary Estimand: Effect of being randomized to an evenamide dose, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline in PANSS total score at Week 46*) was analyzed by using a paired *t-test* for the mITT Population. Results are presented in Table 14.2.1.1, with by subject details in Listing 16.2.6.1.2. The estimand panel is presented in The Hypothetical estimand evaluates the pure effect of dose efficacy, especially for 7.5 mg BID, where up-titration response or post withdrawal data was removed.

Further, a sensitivity analysis was performed using LOCF to account for missing withdrawal data, as per local regulation requirement. Multiple imputation was also performed for robustness. In case of death, the subject was excluded in the sensitivity analysis, as the analysis is pertaining to Week 46.

Dose-wise and combined efficacy analyses were performed on the mITT population and mITT-C population, as applicable.

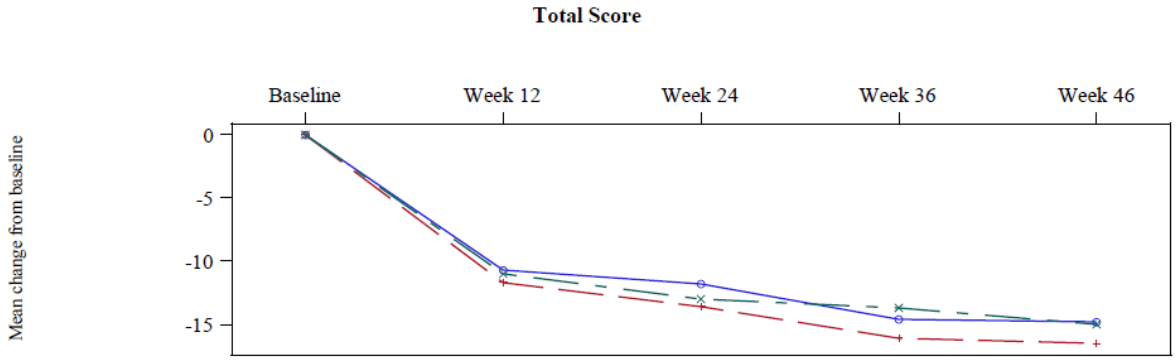
Table 9-6 below describes the estimand panel.

Table 9-6A steady improvement in the PANSS total score (lowering of score) was observed over time across study visits (at 12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline, reflecting a continuation of improvement in the symptoms of schizophrenia in all the three treatment groups.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.28), 79.3 (5.31) and 79.2 (4.54) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a reduction of PANSS total score, with a mean (SD) of 65.2 (11.06), 62.9 (10.22) and 63.8 (11.05), was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -14.8 (9.12) (95% CI: -17.67, -11.83; p<0.001), -16.5 (10.47) (95% CI: -19.57, -13.35; p<0.001) and -15.0 (10.97) (95% CI: -18.51, -11.59; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-1, Figure 12-1).

Figure 12-1: Mean Change from Baseline by Visit in PANSS (Total score) - mITT Population.



	n, Mean (SD)				
Evenamide 7.5 mg BID	42, 0(0)	42, -10.7(7.62)	41, -11.8(7.01)	39, -14.6(7.59)	40, -14.8(9.12)
Evenamide 15 mg BID	53, 0(0)	51, -11.7(7.60)	48, -13.6(8.50)	42, -16.1(9.32)	46, -16.5(10.47)
Evenamide 30 mg BID	46, 0(0)	46, -11.0(6.48)	42, -13.0(7.27)	42, -13.7(8.72)	41, -15.0(10.97)

Source: Listing 16.2.6.1.2, Table 14.2.1.1; Table 14.3.1.3 Figure 14.2.1.1

Table 12-1: Summary of Mean Value and Change from Baseline in PANSS Total Score by Visit Using Within Group Comparisons (Primary Estimand) - mITT Population.

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	N	42		53		46	
	Mean (SD)	80.1 (5.28)		79.3 (5.31)		79.2 (4.54)	

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Median	82.0		80.0		79.0	
	Min, Max	72, 89		70, 89		71, 88	
Week 12	N	42	42	51	51	46	46
	Mean (SD)	69.4 (9.87)	-10.7 (7.62)	67.6 (7.74)	-11.7 (7.60)	68.2 (6.92)	-11.0 (6.48)
	Median	69.0	-11.5	67.0	-11.0	68.0	-10.0
	Min, Max	51, 89	-28, 2	53, 87	-33, 3	52, 84	-33, -1
	95% CI		(-13.06, -8.32)		(-13.86, -9.59)		(-12.95, -9.10)
	p-value		<.001		<.001		<.001
Week 24	n	41	41	48	48	42	42
	Mean (SD)	68.2 (9.65)	-11.8 (7.01)	65.3 (7.89)	-13.6 (8.50)	66.0 (7.45)	-13.0 (7.27)
	Median	69.0	-13.0	64.0	-13.0	64.0	-12.5
	Min, Max	51, 89	-28, 0	46, 86	-40, 0	43, 82	-35, 0
	95% CI		(-13.97, -9.54)		(-16.05, -11.12)		(-15.22, -10.69)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	42	42	42	42
	Mean (SD)	65.2 (9.43)	-14.6 (7.59)	62.9 (8.46)	-16.1 (9.32)	65.2 (8.64)	-13.7 (8.72)
	Median	63.0	-15.0	63.0	-16.0	64.0	-13.5
	Min, Max	51, 88	-32, -1	43, 85	-43, -2	47, 87	-34, 6
	95% CI		(-17.05, -12.13)		(-18.98, -13.17)		(-16.43, -11.00)
	p-value		<.001		<.001		<.001
Week 46	n	40	40	46	46	41	41
	Mean (SD)	65.2 (11.06)	-14.8 (9.12)	62.9 (10.22)	-16.5 (10.47)	63.8 (11.05)	-15.0 (10.97)
	Median	63.0	-15.0	62.0	-14.0	63.0	-14.0
	Min, Max	51, 95	-36, 6	39, 84	-47, 2	35, 85	-44, 4
	95% CI		(-17.67, -11.83)		(-19.57, -13.35)		(-18.51, -11.59)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.1

N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after day 43 of 014 study dosing.

12.1.1.2 PANSS Subscales

PANSS Positive Syndrome subscale scores

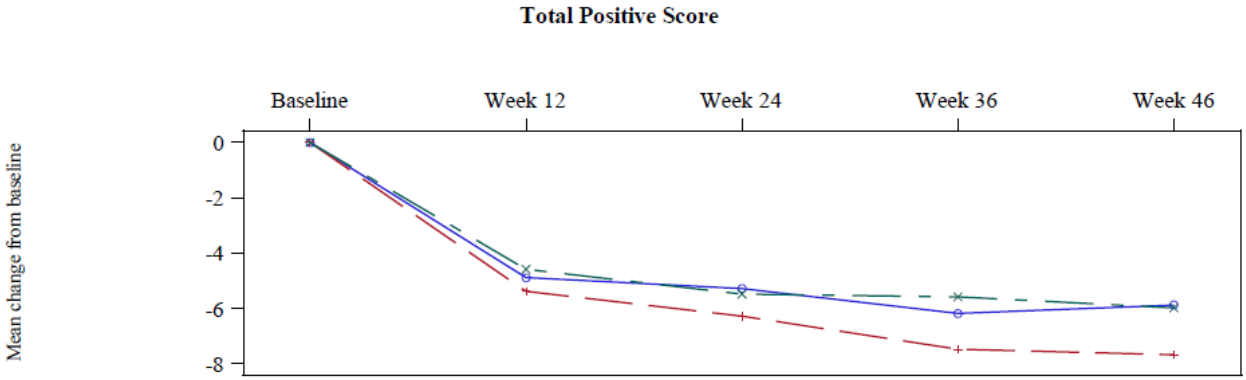
The mean change from baseline at Week 46 in PANSS Positive Syndrome subscale scores using within group comparisons was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3, with by subject details in Listing 16.2.6.1.2.

A significant improvement in the PANSS Positive Syndrome subscale scores (lowering of score) was observed at all study visits (12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS Positive Syndrome subscale scores recorded was 24.1 (3.76), 23.8 (3.42) and 23.3 (2.95) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant mean (SD) change (improvement) from baseline in the PANSS Positive Syndrome subscale scores of -5.9 (4.17) (95% CI: -7.26, -4.59; p<0.001), -7.7 (4.68) (95% CI: -9.06, -6.29; p<0.001) and -6.0 (3.90) (95% CI: -7.23, -4.77); p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. (Table 12-2, Figure -12-2)

Figure 12-2: Mean Change from Baseline by Visit in PANSS Positive Syndrome Subscale Score - mITT Population



n, Mean (SD)

Evenamide 7.5 mg BID	42, 0(0)	42, -4.9(3.90)	41, -5.3(3.65)	39, -6.2(3.31)	40, -5.9(4.17)
Evenamide 15 mg BID	53, 0(0)	51, -5.4(3.98)	48, -6.3(4.29)	42, -7.5(4.32)	46, -7.7(4.68)
Evenamide 30 mg BID	46, 0(0)	46, -4.6(2.86)	42, -5.5(2.98)	42, -5.6(3.42)	41, -6.0(3.90)

Source: Listing 16.2.6.1.2, Table 14.2.1.3, Table 14.2.1.1, Figure 14.2.1.1

Table 12-2: Summary of Change from Baseline in PANSS Positive Syndrome Subscale Score by Visit Using Within Group Comparisons - mITT Population.

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	42		53		46	
	Mean (SD)	24.1 (3.76)		23.8 (3.42)		23.3 (2.95)	
	Median	24.5		24.0		23.0	
	Min, Max	17, 36		17, 30		17, 29	
Week 12	n	42	42	51	51	46	46
	Mean (SD)	19.3 (5.42)	-4.9 (3.90)	18.5 (3.99)	-5.4 (3.98)	18.7 (3.66)	-4.6 (2.86)
	Median	18.0	-4.0	18.0	-4.0	18.0	-4.5
	Min, Max	9, 34	-15, 2	9, 26	-14, 1	10, 27	-11, 0
	95% CI		(-6.07, -3.64)		(-6.47, -4.23)		(-5.46, -3.76)
	p-value		<.001		<.001		<.001

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	41	41	48	48	42	42
	Mean (SD)	18.8 (5.23)	-5.3 (3.65)	17.5 (4.03)	-6.3 (4.29)	17.8 (3.39)	-5.5 (2.98)
	Median	18.0	-4.0	17.0	-5.5	17.5	-6.0
	Min, Max	9, 35	-13, 1	8, 24	-17, 1	10, 25	-11, 0
	95% CI		(-6.44, -4.14)		(-7.52, -5.02)		(-6.41, -4.55)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	42	42	42	42
	Mean (SD)	17.7 (5.07)	-6.2 (3.31)	16.3 (3.96)	-7.5 (4.32)	17.7 (3.61)	-5.6 (3.42)
	Median	16.0	-6.0	16.0	-7.0	17.5	-6.0
	Min, Max	9, 34	-13, 0	8, 24	-17, -1	10, 26	-13, 3
	95% CI		(-7.28, -5.13)		(-8.89, -6.20)		(-6.69, -4.55)
	p-value		<.001		<.001		<.001
Week 46	n	40	40	46	46	41	41
	Mean (SD)	18.0 (5.95)	-5.9 (4.17)	16.1 (4.11)	-7.7 (4.68)	17.2 (4.32)	-6.0 (3.90)
	Median	17.0	-6.0	16.0	-6.0	17.0	-6.0
	Min, Max	9, 40	-14, 4	8, 24	-17, -1	7, 26	-14, 2
	95% CI		(-7.26, -4.59)		(-9.06, -6.29)		(-7.23, -4.77)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2; adapted from Table 14.2.1.3

N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

PANSS Negative Syndrome subscale scores

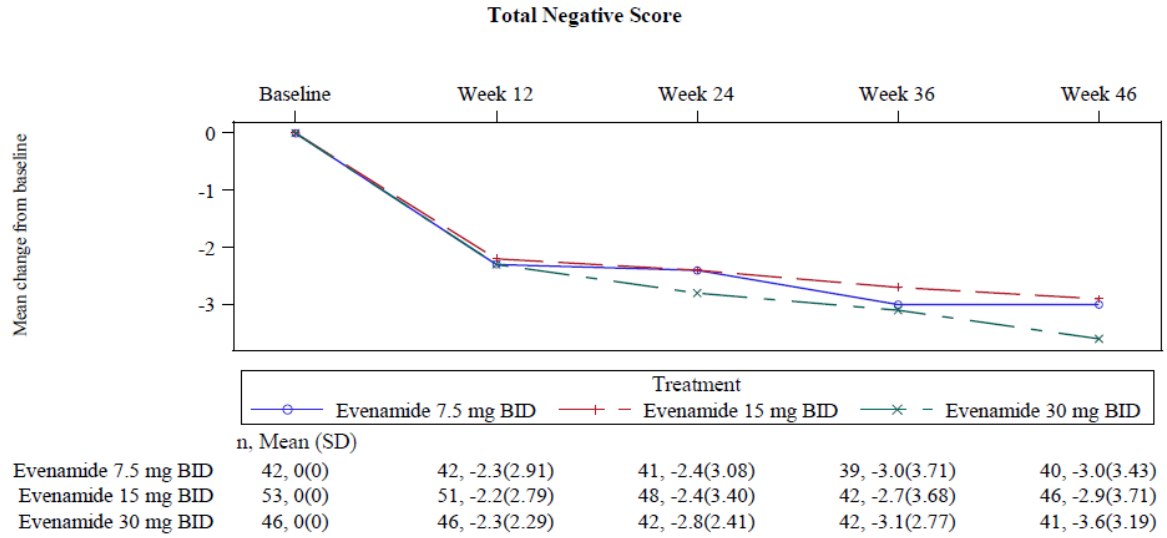
The mean change from Baseline at Week 46 in PANSS Negative Syndrome subscale scores using within group comparisons was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3, with by subject details in Listing 16.2.6.1.2.

A significant improvement in the PANSS Negative Syndrome subscale scores (lowering of score) was observed at all study visits (12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS Negative Syndrome subscale scores recorded was 20.0 (3.32), 19.8 (3.56) and 19.4 (3.08) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant mean (SD) change from baseline in the PANSS Negative Syndrome subscale scores of -3.0 (3.43) (95% CI: -4.12, -1.93; p<0.001), -2.9 (3.71) (95% CI: -3.99, -1.79; p<0.001) and -3.6 (3.19) (95% CI: -4.59, -2.58; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. (Table 12-3, Figure 12-3).

Figure 12-3: Mean Change from Baseline by Visit in PANSS Negative Syndrome Subscale Score - mITT Population



Source: Listing 16.2.6.1.2, Table 14.2.1.3, Table 14.2.1.1; Figure 14.2.1.1

Table 12-3: Summary of Change from Baseline in PANSS Negative Syndrome Subscale Scores by Visit Using Within Group Comparisons - mITT Population.

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	42		53		46	
	Mean (SD)	20.0 (3.32)		19.8 (3.56)		19.4 (3.08)	
	Median	20.0		20.0		20.0	
	Min, Max	12, 31		12, 29		12, 26	
Week 12	n	42	42	51	51	46	46
	Mean (SD)	17.7 (2.64)	-2.3 (2.91)	17.7 (3.60)	-2.2 (2.79)	17.1 (2.96)	-2.3 (2.29)
	Median	18.0	-1.0	18.0	-2.0	17.5	-2.0
	Min, Max	12, 24	-13, 2	11, 26	-11, 4	10, 22	-9, 1
	95% CI		(-3.19, -1.38)		(-2.96, -1.39)		(-3.03, -1.67)
	p-value		<.001		<.001		<.001
Week 24	n	41	41	48	48	42	42
	Mean (SD)	17.6 (2.67)	-2.4 (3.08)	17.4 (3.57)	-2.4 (3.40)	16.5 (2.86)	-2.8 (2.41)
	Median	17.0	-2.0	17.0	-2.0	17.0	-2.5
	Min, Max	11, 24	-14, 2	9, 25	-13, 6	10, 21	-9, 1
	95% CI		(-3.39, -1.44)		(-3.42, -1.45)		(-3.51, -2.01)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	42	42	42	42

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Mean (SD)	17.0 (2.73)	-3.0 (3.71)	17.4 (3.81)	-2.7 (3.68)	16.1 (3.13)	-3.1 (2.77)
	Median	17.0	-2.0	17.5	-2.0	16.5	-3.0
	Min, Max	11, 23	-16, 5	8, 25	-14, 6	9, 23	-9, 3
	95% CI		(-4.20, -1.80)		(-3.81, -1.52)		(-3.96, -2.23)
	p-value		<.001		<.001		<.001
	n	40	40	46	46	41	41
Week 46							
	Mean (SD)	17.0 (2.50)	-3.0 (3.43)	17.1 (4.08)	-2.9 (3.71)	15.7 (3.39)	-3.6 (3.19)
	Median	17.0	-2.5	17.0	-2.0	16.0	-3.0
	Min, Max	11, 23	-17, 2	8, 28	-14, 6	9, 23	-11, 3
	95% CI		(-4.12, -1.93)		(-3.99, -1.79)		(-4.59, -2.58)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.3
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline
p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

PANSS General Psychopathology subscale scores

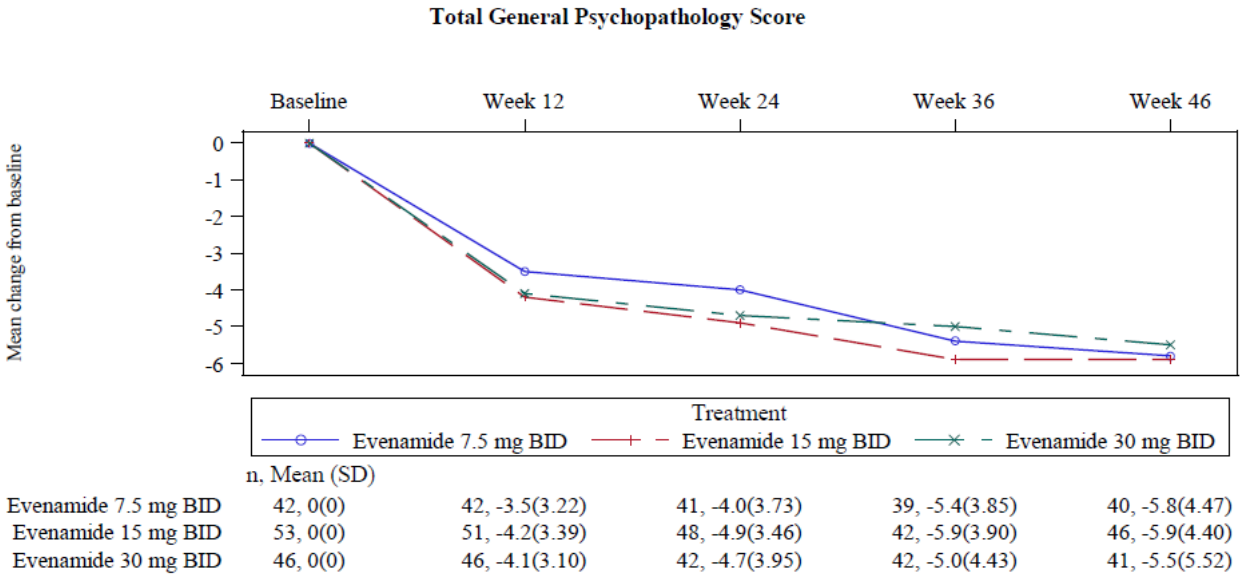
The mean change from Baseline at Week 46 in PANSS General Psychopathology subscale scores using within group comparisons was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3, with by subject details in Listing 16.2.6.1.2.

A significant improvement in the PANSS General Psychopathology subscale scores (lowering of score) was observed at all study visits (12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS General Psychopathology subscale scores recorded was 36.0 (3.83), 35.6 (3.44) and 36.5 (3.64) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant mean (SD) change from baseline in the PANSS General Psychopathology subscale scores of -5.8 (4.47) (95% CI: -7.23, -4.37; p<0.001), -5.9 (4.40) (95% CI: -7.20, -4.59; p<0.001) and -5.5 (5.52) (95% CI: -7.21, -3.72; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. (Table 12-4, Figure 12-4).

Figure 12-4: Mean Change from Baseline by Visit in PANSS General Psychopathology Subscale Score - mITT Population



Source: Listing 16.2.6.1.2, Table 14.2.1.3, Table 14.2.1.1; Figure 14.2.1.1

Table 12-4: Summary of Change from Baseline in PANSS General Psychopathology Subscale Score by Visit Using Within Group Comparisons - mITT Population

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	42		53		46	
	Mean (SD)	36.0 (3.83)		35.6 (3.44)		36.5 (3.64)	
	Median	36.0		35.0		36.5	
	Min, Max	30, 49		29, 46		30, 43	
Week 12	n	42	42	51	51	46	46
	Mean (SD)	32.4 (4.98)	-3.5 (3.22)	31.4 (3.78)	-4.2 (3.39)	32.4 (3.89)	-4.1 (3.10)
	Median	31.5	-4.0	31.0	-4.0	32.5	-4.0
	Min, Max	23, 46	-11, 5	25, 39	-14, 4	26, 41	-15, 2
	95% CI		(-4.55, -2.54)		(-5.15, -3.24)		(-4.99, -3.14)
	p-value		<.001		<.001		<.001
Week 24	n	41	41	48	48	42	42
	Mean (SD)	31.9 (5.35)	-4.0 (3.73)	30.4 (3.97)	-4.9 (3.46)	31.7 (4.55)	-4.7 (3.95)
	Median	31.0	-5.0	29.0	-5.0	32.5	-4.5
	Min, Max	23, 45	-12, 5	24, 39	-16, 2	20, 40	-20, 2
	95% CI		(-5.23, -2.87)		(-5.88, -3.87)		(-5.94, -3.48)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	42	42	42	42
	Mean (SD)	30.5 (5.36)	-5.4 (3.85)	29.2 (3.89)	-5.9 (3.90)	31.4 (5.19)	-5.0 (4.43)

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Median	28.0	-5.0	28.0	-5.5	32.0	-5.0
	Min, Max	23, 45	-13, 2	21, 39	-17, 2	21, 46	-17, 3
	95% CI		(-6.63, -4.14)		(-7.07, -4.64)		(-6.38, -3.62)
	p-value		<.001		<.001		<.001
Week 46	n	40	40	46	46	41	41
	Mean (SD)	30.2 (5.83)	-5.8 (4.47)	29.7 (4.95)	-5.9 (4.40)	30.9 (5.92)	-5.5 (5.52)
	Median	28.0	-5.0	28.0	-6.0	31.0	-5.0
	Min, Max	22, 43	-17, 2	21, 44	-19, 6	18, 47	-22, 4
	95% CI		(-7.23, -4.37)		(-7.20, -4.59)		(-7.21, -3.72)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.3
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Responder Analysis – PANSS Score

'Responder' analyses were performed by summarizing the proportion of patients in each of the evenamide groups with improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Syndromes sub-scale for the mITT Population. The results are presented in Table 14.2.1.7, with by subject details in Listing 16.2.6.1.2.

'Responders' were defined as patients who improved by at least 20% on the PANSS total score from baseline, based on previous studies in TRS patients (Rosenheck et al, 1997; Meltzer 2008) or had a 4-point change (improvement) on the PANSS Positive Syndrome sub-scale score from baseline.

By Week 46, the proportion of responders on the PANSS total score (patients who improved by at least 20% from baseline) increased to 20 of 42 (47.6%), 21 of 53 (39.6%) and 18 of 46 (39.1%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, compared to 10 of 42 (23.8%), 16 of 53 (30.2%), and 9 of 46 (19.6%) responders at Week 12 (Table 12-5). The proportion of patients showing meaningful improvement in positive symptoms alone, based on the responder analysis of PANSS Positive Syndrome sub-scale score, increased with time. By Week 46, the proportion of responders on the PANSS Positive Syndrome total score (patients who improved by at least 4 points from baseline) was 29 of 42 (69.0%), 36 of 53 (67.9%) and 32 of 46 (69.6%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-5).

Table 12-5: Responder Analysis by Visit – PANSS Total and Positive Syndrome Sub-Scale Scores - mITT Population

Visit	PANSS	Improvement Category	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total [a] (N=141)
Week 12	Total Score	Change >=20%	n (%)	10 (23.8)	16 (30.2)	9 (19.6)	35 (24.8)
	Total Positive Score	>=4-Point Improvement	n (%)	24 (57.1)	29 (54.7)	28 (60.9)	81 (57.4)
Week 24	Total Score	Change >=20%	n (%)	12 (28.6)	22 (41.5)	14 (30.4)	48 (34.0)
	Total Positive Score	>=4-Point Improvement	n (%)	25 (59.5)	31 (58.5)	30 (65.2)	86 (61.0)
Week 36	Total Score	Change >=20%	n (%)	21 (50.0)	21 (39.6)	18 (39.1)	60 (42.6)
	Total Positive Score	>=4-Point Improvement	n (%)	31 (73.8)	34 (64.2)	30 (65.2)	95 (67.4)
Week 46	Total Score	Change >=20%	n (%)	20 (47.6)	21 (39.6)	18 (39.1)	59 (41.8)
	Total Positive Score	>=4-Point Improvement	n (%)	29 (69.0)	36 (67.9)	32 (69.6)	97 (68.8)

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.7
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat. Responder analyses performed by summarizing the proportion of patients in each of the evenamide groups with different categories of improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale.
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

Supportive Efficacy Estimand Analysis

A steady improvement in the PANSS total score (lowering of score) was observed over time across study visits (at 12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline reflecting a continuation of improvement in symptoms of schizophrenia in all three treatment groups. Mean (SD) values of the PANSS total score showed a decreasing trend at all the time points during the study in the three treatment groups compared to baseline.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.28), 79.3 (5.31) and 79.2 (4.54) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a reduction of PANSS total score, with a mean (SD) of 62.2 (9.03), 61.8 (9.85) and 63.3 (10.70), was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -16.9 (7.48) (95% CI: -19.89, -13.97; p<0.001), -17.2 (10.73) (95% CI: -20.58, -13.81; p<0.001) and -15.4 (10.87) (95% CI: -18.88, -11.92; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-6).

Table 12-6: Summary of Mean Value and Change from Baseline in PANSS Total Score by Visit Using Within Group Comparisons (Supportive Efficacy Estimand) - mITT Population.

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	42		53		46	
	Mean (SD)	80.1 (5.28)		79.3 (5.31)		79.2 (4.54)	
	Median	82.0		80.0		79.0	
	Min, Max	72, 89		70, 89		71, 88	
Week 12	n	39	39	51	51	46	46
	Mean (SD)	69.6 (9.99)	-10.4 (7.44)	67.6 (7.74)	-11.7 (7.60)	68.2 (6.92)	-11.0 (6.48)
	Median	69.0	-11.0	67.0	-11.0	68.0	-10.0
	Min, Max	51, 89	-28, 2	53, 87	-33, 3	52, 84	-33, -1
	95% CI		(-12.85, -8.03)		(-13.86, -9.59)		(-12.95, -9.10)
	p-value		<.001		<.001		<.001
Week 24	n	35	35	48	48	42	42
	Mean (SD)	68.6 (10.02)	-11.6 (6.68)	65.3 (7.89)	-13.6 (8.50)	66.0 (7.45)	-13.0 (7.27)
	Median	69.0	-13.0	64.0	-13.0	64.0	-12.5
	Min, Max	51, 89	-24, 0	46, 86	-40, 0	43, 82	-35, 0
	95% CI		(-13.89, -9.31)		(-16.05, -11.12)		(-15.22, -10.69)
	p-value		<.001		<.001		<.001
Week 36	n	29	29	42	42	42	42
	Mean (SD)	64.7 (8.68)	-14.8 (6.65)	62.9 (8.46)	-16.1 (9.32)	65.2 (8.64)	-13.7 (8.72)
	Median	63.0	-16.0	63.0	-16.0	64.0	-13.5
	Min, Max	51, 84	-27, -2	43, 85	-43, -2	47, 87	-34, 6
	95% CI		(-17.36, -12.30)		(-18.98, -13.17)		(-16.43, -11.00)
	p-value		<.001		<.001		<.001
Week 46	n	27	27	41	41	40	40
	Mean (SD)	62.2 (9.03)	-16.9 (7.48)	61.8 (9.85)	-17.2 (10.73)	63.3 (10.70)	-15.4 (10.87)
	Median	59.0	-18.0	60.0	-15.0	63.0	-14.0
	Min, Max	52, 83	-29, -3	39, 83	-47, 2	35, 85	-44, 4
	95% CI		(-19.89, -13.97)		(-20.58, -13.81)		(-18.88, -11.92)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.2.
N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.1.1.3 Sensitivity Analysis on Change from Baseline in PANSS Total Score

Paired t-test Using Multiple Imputation

The mean change from Baseline at Week 46 in PANSS total score using within group comparisons (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.4, with by subject details in Listing 16.2.6.1.2. The missing post first dose data were imputed using SAS PROC MI multiple imputation Monotone Regression Method by each dose group.

In this sensitivity analysis (*Multiple Imputation*), an improvement in the PANSS total score (lowering of score) was observed at Week 46 compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.28), 79.3 (5.31) and 79.2 (4.54) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant improvement in PANSS total score (lowering of score), with a mean (SD) of 65.5 (10.89), 63.0 (9.93) and 63.6 (11.19) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -14.6 (8.92) (95% CI: -17.38, -11.82; p<0.001), -16.3 (10.25) (95% CI: -19.15, -13.50; p<0.001) and -15.4 (11.34) (95% CI: -18.85, -12.04; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-7).

Table 12-7: Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Score at Week 46 - Paired t-test Using Multiple Imputation mITT Population

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Baseline	N	42	53	46
	Mean (SD)	80.1 (5.28)	79.3 (5.31)	79.2 (4.54)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 88
Week 46	N	42	53	45
	Mean (SD)	65.5 (10.89)	63.0 (9.93)	63.6 (11.19)
	Median	65.0	62.0	63.0
	Min, Max	51, 95	39, 84	35, 85
Week 46	Mean change from Baseline (SD)	-14.6 (8.92)	-16.3 (10.25)	-15.4 (11.34)
	95% CI	(-17.38, -11.82)	(-19.15, -13.50)	(-18.85, -12.04)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.4
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval, mITT = Modified intent-to-treat, Min=Minimum, Max=Maximum, p-value = Paired t-test.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics.
Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Paired t-test Using LOCF Supportive Estimand

The mean change from Baseline at Week 46 in PANSS total score using within group comparisons (*sensitivity analysis: LOCF Supportive Efficacy Estimand*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.5, with by subject details in Listing 16.2.6.1.2. The sensitivity analysis was performed using the LOCF (Last-observation-carried forward). In case subjects had not taken any rescue medication and not added any further efficacy data LOCF was considered as supportive.

In the sensitivity analysis (*LOCF Supportive Efficacy Estimand*), an improvement in the PANSS total score (lowering of score) was observed at Week 46 compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.28), 79.3 (5.31) and 79.2 (4.54) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant improvement in PANSS total score (lowering of score), with a mean (SD) of 65.6 (11.00), 63.4 (9.95) and 63.9 (10.92) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -14.5 (8.99) (95% CI: -17.26, -11.65; p<0.001), -15.9 (10.24) (95% CI: -18.75, -13.10; p<0.001) and -15.2 (11.00) (95% CI: -18.53, -11.92; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-8).

Table 12-8: Sensitivity Analysis on Change from Baseline in PANSS Total Score at Week 46 - Paired t-test Using LOCF Supportive Estimand - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Baseline	N	42	53	46
	Mean (SD)	80.1 (5.28)	79.3 (5.31)	79.2 (4.54)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 88
Week 46	N	42	53	45
	Mean (SD)	65.6 (11.00)	63.4 (9.95)	63.9 (10.92)
	Median	65.0	62.0	63.0
	Min, Max	51, 95	39, 84	35, 85
Week 46	Mean change from Baseline (SD)	-14.5 (8.99)	-15.9 (10.24)	-15.2 (11.00)
	95% CI	(-17.26, -11.65)	(-18.75, -13.10)	(-18.53, -11.92)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.5
Abbreviations: N - Total number of subjects in the mITT Population, Min = Minimum, Max = Maximum, n = number of patients, LOCF = Last observation-carried forward, SD = Standard Deviation, CI = Confidence Interval, mITT = Modified intent-to-treat. The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data is not carried forward to post baseline visit.
p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Comparison Analysis of Different Models

A comparison of the different models used for the Sensitivity Analysis on change from baseline in PANSS total score at Week 46 for the mITT Population is presented in Table 14.2.1.6, with by subject details in Listing 16.2.6.1.2.

Similar decreasing trends (improvement) were observed in the different models (*Primary estimand*, *Supportive estimand*, *LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in PANSS total score at Week 46 (Table 12-9). A significant mean (SD) change from baseline (*p<0.001*) was observed in all the three treatment groups with all models, across the visits.

Table 12-9: Sensitivity Analysis on Change from Baseline in PANSS Total Score at Week 46 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Primary Estimand	Mean change from Baseline (SD)	-14.8 (9.12)	-16.5 (10.47)	-15.0 (10.97)
	95% CI	(-17.67, -11.83)	(-19.57, -13.35)	(-18.51, -11.59)
	p-value	<.001	<.001	<.001
Supportive Estimand	Mean change from Baseline (SD)	-16.9 (7.48)	-17.2 (10.73)	-15.4 (10.87)
	95% CI	(-19.89, -13.97)	(-20.58, -13.81)	(-18.88, -11.92)
	p-value	<.001	<.001	<.001
MI	Mean change from Baseline (SD)	-14.6 (8.92)	-16.3 (10.25)	-15.4 (11.34)
	95% CI	(-17.38, -11.82)	(-19.15, -13.50)	(-18.85, -12.04)
	p-value	<.001	<.001	<.001
LOCF	Mean change from Baseline (SD)	-14.5 (8.99)	-15.9 (10.24)	-15.2 (11.00)
	95% CI	(-17.26, -11.65)	(-18.75, -13.10)	(-18.53, -11.92)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.6
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test. MI = Multiple Imputation, LOCF = Last observation-carried forward, CI = Confidence Interval. The results obtained in each model are compared in this table.

The PANSS total score in the mITT population, as assessed by the Primary Efficacy Estimand at Week 46, showed a significant mean (SD) change from baseline of -14.8 (9.12) (95% CI: -17.67, -11.83; p<0.001), -16.5 (10.47) (95% CI: -19.57, -13.35; p<0.001) and -15.0 (10.97) (95% CI: -18.51, -11.59; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by the Supportive Efficacy Estimand at Week 46, showed a significant mean (SD) change from baseline of -16.9 (7.48) (95% CI: -19.89, -13.97; p<0.001), -17.2 (10.73) (95% CI: -20.58, -13.81; p<0.001) and -15.4 (10.87) (95% CI: -18.88, -11.92; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by LOCF at Week 46, showed a significant mean (SD) change from baseline of -14.5 (8.99) (95% CI: -17.26, -11.65; p<0.001), -15.9 (10.24) (95% CI: -18.75, -13.10; p<0.001) and -15.2 (11.00) (95% CI: -18.53, -11.92; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by Multiple Imputation at Week 46, showed a significant mean (SD) change from baseline of -14.6 (8.92) (95% CI: -17.38, -11.82; p<0.001), -16.3 (10.25) (95% CI: -19.15, -13.50; p<0.001) and -15.4 (11.34) (95% CI: -18.85, -12.04; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Thus, the significant improvement from baseline (lowering of scores) in the PANSS total score over time up to Week 46 was supported by various models of Efficacy Estimands.

12.1.2 Clinical Global Impression Results

The Clinical Global Impression (CGI) has two components— the CGI-Severity (CGI-S) measures global severity of illness at a given point in time, and the CGI-Change (CGI C) measures change from the baseline state at each post-baseline visit. The CGI rating scale

permits a global evaluation of the subject's improvement over time. In this study, the ratings of the CGI-C and CGI-S were performed by the same blinded clinician who performed the rating of the PANSS. The CGI-S and CGI-C assessment was conducted at Weeks 12, 24 and 36, and at the final visit (Week 46 or at early discontinuation).

12.1.2.1 Clinical Global Impression – Severity of Illness (CGI-S) score

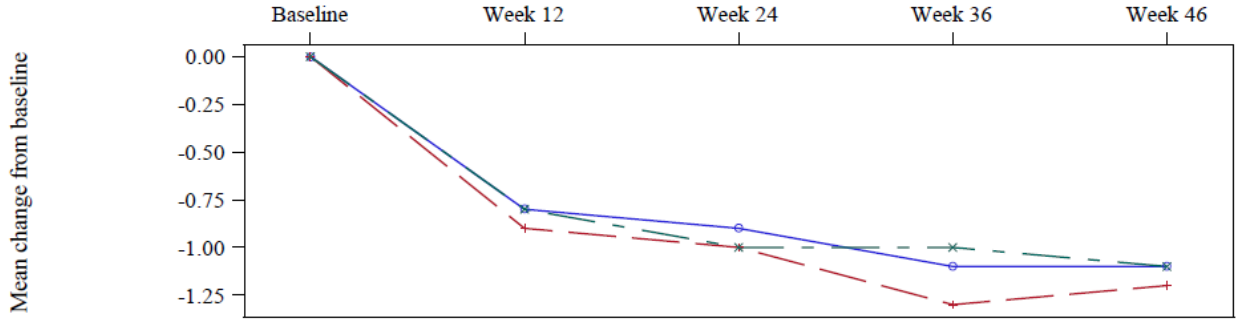
The mean change from Baseline at Week 46 on the CGI-S was summarized by visit and is presented in Table 14.2.2.1, with by subject details in Listing 16.2.6.2. Paired *t-test* was performed at all post-dose visits to analyze CGI-S change from baseline within each dose group.

A significant ($p<0.001$) improvement (lowering of scores) in the CGI-S was observed at all study visits (at 12, 24, 36, and 46 weeks) compared to baseline in all the three treatment groups, indicating improvement in overall severity of illness.

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.66), 4.6 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a reduction of CGI-S scores with a mean (SD) of 3.6 (0.78), 3.5 (0.66) and 3.3 (0.57) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -1.1 (0.68) (95% CI: -1.27, -0.83; p<0.001), -1.2 (0.71) (95% CI: -1.38, -0.96; p<0.001) and -1.1 (0.69) (95% CI: -1.29, -0.86; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-10 and Figure 12-5).

Figure 12-5: Mean Change from Baseline by Visit in Clinical Global Impression - Severity of Illness (CGI-S) - mITT Population.



n, Mean (SD)					
Evenamide 7.5 mg BID	42, 0(0)	42, -0.8(0.62)	41, -0.9(0.60)	39, -1.1(0.58)	40, -1.1(0.68)
Evenamide 15 mg BID	53, 0(0)	51, -0.9(0.63)	48, -1.0(0.62)	42, -1.3(0.67)	46, -1.2(0.71)
Evenamide 30 mg BID	46, 0(0)	46, -0.8(0.58)	42, -1.0(0.64)	42, -1.0(0.66)	41, -1.1(0.69)

Source: Listing 16.2.6.2; Table 14.2.2.1; Figure 14.2.2.1

Table 12-10: Summary of Mean Value and Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Within Group Comparison - mITT Population.

		Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	42		53		46	
	Mean (SD)	4.6 (0.66)		4.6 (0.60)		4.4 (0.50)	
	Median	4.5		5.0		4.0	
	Min, Max	4, 6		4, 6		4, 5	
Week 12	n	42	42	51	51	46	46
	Mean (SD)	3.8 (0.79)	-0.8 (0.62)	3.6 (0.59)	-0.9 (0.63)	3.6 (0.49)	-0.8 (0.58)
	Median	4.0	-1.0	4.0	-1.0	4.0	-1.0
	Min, Max	3, 6	-2, 0	3, 5	-2, 0	3, 4	-2, 0
	95% CI		(-0.95, -0.57)		(-1.10, -0.75)		(-0.98, -0.63)
	p-value		<.001		<.001		<.001
Week 24	n	41	41	48	48	42	42
	Mean (SD)	3.7 (0.74)	-0.9 (0.60)	3.5 (0.55)	-1.0 (0.62)	3.4 (0.55)	-1.0 (0.64)
	Median	4.0	-1.0	3.5	-1.0	3.0	-1.0
	Min, Max	3, 5	-2, 0	3, 5	-2, 0	2, 4	-3, 0
	95% CI		(-1.07, -0.69)		(-1.22, -0.86)		(-1.18, -0.78)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	42	42	42	42
	Mean (SD)	3.5 (0.68)	-1.1 (0.58)	3.4 (0.53)	-1.3 (0.67)	3.4 (0.53)	-1.0 (0.66)
	Median	3.0	-1.0	3.0	-1.0	3.0	-1.0
	Min, Max	3, 5	-2, 0	2, 4	-2, 0	2, 4	-3, 0
	95% CI		(-1.26, -0.89)		(-1.50, -1.08)		(-1.25, -0.84)
	p-value		<.001		<.001		<.001
Week 46	n	40	40	46	46	41	41
	Mean (SD)	3.6 (0.78)	-1.1 (0.68)	3.5 (0.66)	-1.2 (0.71)	3.3 (0.57)	-1.1 (0.69)
	Median	3.0	-1.0	3.0	-1.0	3.0	-1.0
	Min, Max	3, 6	-2, 1	2, 5	-2, 0	2, 5	-3, 0
	95% CI		(-1.27, -0.83)		(-1.38, -0.96)		(-1.29, -0.86)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.1
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval. mITT = Modified intent-to-treat. Change from Baseline = Post Dose – Baseline. p-value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Responder Analysis - CGI-S

The responder analysis for the CGI-S was performed by summarizing the proportion of patients in each of the evenamide dose groups with improvement from baseline to endpoint. The improvement categorizations for the CGI-S of “at least 2-category improvement” and “at least 1- category improvement" were analyzed at 12, 24, 36 and 46 weeks (or at early discontinuation) for the

mITT population. The results are presented in Table 14.2.2.5, and by subject details in Listing 16.2.6.2. The details are given in Table 12-11.

Responders (CGI-S score change from baseline of -2 or below)

The responder analysis was done considering change in the subject's condition from baseline, as indicated by the CGI-S score change of -2 or below, indicating at least a 2-category improvement.

Overall, in all three treatment groups combined, the proportion of "responders" (CGI-S score change of -2 or below) was 11.3% at Week 12, which further improved over time to 14.9%, 23.4% and 24.1% at Week 24, Week 36 and Week 46, respectively. The proportion of responders in the evenamide 7.5 mg *bid* treated group was 9.5% at Week 12, which increased to 21.4 % at Week 46. The proportion of responders in the evenamide 15 mg *bid* treated group was 15.1% at Week 12, which increased to 30.2% at Week 46. The proportion of responders in the evenamide 30 mg *bid* treated group was 8.7% at Week 12, which increased to 19.6% at Week 46.

Responders (CGI-S score change from baseline of -1 or below)

An additional responder analysis was done considering change in the subject's condition from baseline, as indicated by the CGI-S score change of -1 or below, indicating a 1- category improvement.

Overall, in all three treatment groups combined, the proportion of "responders" (CGI-S score change of -1 or below) was greater than 70% at all time points. The proportion of responders in the evenamide 7.5 mg *bid* treated group was 66.7% at Week 12 and 81.0% at Week 46. The proportion of responders in the evenamide 15 mg *bid* treated group was 73.6% at Week 12 and 71.7% at Week 46. The proportion of responders in the evenamide 30 mg *bid* treated group was 71.7% at Week 12 and 73.9% at Week 46.

Table 12-11 Responder Analysis - Clinical Global Impression – Severity of Illness (CGI-S) Score - mITT Population

Visit	Improvement Category	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total [a] (N=141)
Week 12	Improvement of at least 2 categories	n (%)	4 (9.5)	8 (15.1)	4 (8.7)	16 (11.3)
	Improvement of at least 1 category	n (%)	28 (66.7)	39 (73.6)	33 (71.7)	100 (70.9)
Week 24	Improvement of at least 2 categories	n (%)	5 (11.9)	10 (18.9)	6 (13.0)	21 (14.9)
	Improvement of at least 1 category	n (%)	31 (73.8)	40 (75.5)	34 (73.9)	105 (74.5)
Week 36	Improvement of at least 2 categories	n (%)	8 (19.0)	17 (32.1)	8 (17.4)	33 (23.4)
	Improvement of at least 1 category	n (%)	34 (81.0)	37 (69.8)	35 (76.1)	106 (75.2)

Visit	Improvement Category	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total [a] (N=141)
Week 46	Improvement of at least 2 categories	n (%)	9 (21.4)	16 (30.2)	9 (19.6)	34 (24.1)
	Improvement of at least 1 category	n (%)	34 (81.0)	38 (71.7)	34 (73.9)	106 (75.2)

Source: Listing 16.2.6.2 adapted from Table 14.2.2.5
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat.
Improvement at least 2 Categories = Change = (Post Dose - Baseline) CGI-S Score is -2 or below.
Similarly, improvement at least 1 Category = Change is -1 or below. Percentages are calculated by all patient in the respective mITT population in denominator (N).
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

12.1.2.2 Sensitivity Analysis on Change from Baseline in CGI-S Score

Paired t-test Using Multiple Imputation

The mean change from Baseline at Week 46 in the CGI-S score using within group comparisons (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.2.2, with by subject details in Listing 16.2.6.2. The missing post first dose data was imputed using SAS PROC MI multiple imputation Monotone Regression Method by each dose group.

In the sensitivity analysis (*Multiple Imputation*), an improvement in the CGI-S score (lowering of score) was observed at Week 46 compared to baseline in all the three treatment groups. Mean (SD) values of the CGI-S score decreased in all the three treatment groups.

A significant (*p<0.001*) improvement (lowering of scores) in the CGI-S was observed at Week 46 compared to baseline in all the three treatment groups, indicating improvement in severity of illness (Table 12-12).

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.66), 4.6 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant reduction of CGI-S scores with a mean (SD) of 3.6 (0.77), 3.4 (0.63) and 3.3 (0.57) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -1.0 (0.67) (95% CI: -1.24, -0.82; p<0.001), -1.1 (0.70) (95% CI: -1.32, -0.93; p<0.001) and -1.1 (0.70) (95% CI: -1.30, -0.87; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Table 12-12: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Week 46 - Paired t-test Using Multiple Imputation - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Baseline	n	42	53	46
	Mean (SD)	4.6 (0.66)	4.6 (0.60)	4.4 (0.50)
	Median	4.5	5.0	4.0

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
	Min, Max	4, 6	4, 6	4, 5
Week 46	n	42	53	45
	Mean (SD)	3.6 (0.77)	3.4 (0.63)	3.3 (0.57)
	Median	3.0	3.0	3.0
	Min, Max	3, 6	2, 5	2, 5
Week 46	Mean change from Baseline (SD)	-1.0 (0.67)	-1.1 (0.70)	-1.1 (0.70)
	95% CI	(-1.24, -0.82)	(-1.32, -0.93)	(-1.30, -0.87)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.2
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, mITT = Modified Intent-to-treat. CI = Confidence Interval. Min = Minimum, Max = Maximum, p-value = Paired t-test.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics.
Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Paired t-test Using LOCF

The mean change from Baseline at Week 46 in CGI-S score using within group comparisons (sensitivity analysis: LOCF) was analyzed by using a paired t-test for the mITT Population and presented in Table 14.2.2.3, with by subject details in Listing 16.2.6.2. The sensitivity analysis was performed using the LOCF (Last-observation-carried forward). In case subjects had not taken any rescue medication and not added any further efficacy data LOCF was considered as supportive.

In the sensitivity analysis (LOCF), an improvement in the CGI-S score (lowering of score) was observed at Week 46 compared to baseline in all the three treatment groups. Mean (SD) values of the CGI-S score showed a decreasing trend over time during the study, reflecting a continuation of improvement in severity of illness (Table 12-13).

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.66), 4.6 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, a significant reduction of CGI-S scores with a mean (SD) of 3.6 (0.77), 3.5 (0.64) and 3.3 (0.56) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -1.0 (0.68) (95% CI: -1.24, -0.81; p<0.001), -1.1 (0.74) (95% CI: -1.30, -0.89; p<0.001) and -1.1 (0.70) (95% CI: -1.30, -0.88; p<0.001) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Table 12-13: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Week 46 - Paired t-test Using LOCF - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Baseline	N	42	53	46

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
	Mean (SD)	4.6 (0.66)	4.6 (0.60)	4.4 (0.50)
	Median	4.5	5.0	4.0
	Min, Max	4, 6	4, 6	4, 5
Week 46	n	42	53	45
	Mean (SD)	3.6 (0.77)	3.5 (0.64)	3.3 (0.56)
	Median	3.0	3.0	3.0
	Min, Max	3, 6	2, 5	2, 5
Week 46	Mean change from Baseline (SD)	-1.0 (0.68)	-1.1 (0.74)	-1.1 (0.70)
	95% CI	(-1.24, -0.81)	(-1.30, -0.89)	(-1.30, -0.88)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.3
Abbreviations: LOCF = Last observation-carried forward, N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. mITT = Modified Intent-to-treat.
The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data is not carried forward to post baseline visit. p-value = Paired t-test.
Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Comparison Analysis of Different Models

A comparison of the different models used for the Sensitivity Analysis on CGI-S at Week 46 for the mITT Population is presented in Table 14.2.2.4, with by subject details in Listing 16.2.6.2.

Similar decreasing trends (improvement) were observed in each of the models (*LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in CGI-S score at Week 46. A significant mean (SD) change from baseline ($p<0.001$) was observed in all the three treatment groups with all models (Table 12-14).

Table 12-14: Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Week 46 – Comparison of Different Models - mITT Population

Models	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)
Paired t-test	Mean change from Baseline (SD)	-1.1 (0.68)	-1.2 (0.71)	-1.1 (0.69)
	95% CI	(-1.27, -0.83)	(-1.38, -0.96)	(-1.29, -0.86)
	p-value	<.001	<.001	<.001
MI	Mean change from Baseline (SD)	-1.0 (0.67)	-1.1 (0.70)	-1.1 (0.70)
	95% CI	(-1.24, -0.82)	(-1.32, -0.93)	(-1.30, -0.87)
	p-value	<.001	<.001	<.001
LOCF	Mean change from Baseline (SD)	-1.0 (0.68)	-1.1 (0.74)	-1.1 (0.70)
	95% CI	(-1.24, -0.81)	(-1.30, -0.89)	(-1.30, -0.88)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.4
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test. mITT = Modified Intent-to-treat. CI = Confidence Interval, MI = Multiple Imputation, LOCF = Last observation-carried forward, the results obtained in each model are compared in this table.

12.1.2.3 Clinical Global Impression - Change (CGI-C)

The rating of change from baseline (Study 014) in Clinical Global Impression – Change (CGI-C) Score at 12, 24, 36 and 46 weeks (or at early discontinuation) for the mITT Population is presented in Table 14.2.3.1, with by subject details in Listing 16.2.6.3.

At Week 12, the mean (SD) of CGI-C scores recorded were 2.9 (0.79), 2.9 (0.65) and 2.9 (0.58) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 24, the mean (SD) of CGI-C scores recorded were 2.9 (0.78), 2.7 (0.62) and 2.8 (0.66) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 36, the mean (SD) of CGI-C scores recorded were 2.7 (0.77), 2.6 (0.67) and 2.9 (0.93) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 46, the mean (SD) of CGI-C scores recorded were 2.7 (0.92), 2.8 (0.90) and 2.8 (0.93) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-15).

A reduction in the mean CGI-C score was observed between Week 12 and Week 46, from 2.9 to 2.7 in evenamide 7.5 mg, from 2.9 to 2.8 in evenamide 15 mg, and from 2.9 to 2.8 in evenamide 30 mg *bid* treated groups.

Table 12-15: Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population

Visit	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total [a] (N=141)
Week 12	n	42	51	46	139
	Mean (SD)	2.9 (0.79)	2.9 (0.65)	2.9 (0.58)	2.9 (0.67)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1, 4	2, 4	2, 4	1, 4
Week 24	n	41	48	42	131
	Mean (SD)	2.9 (0.78)	2.7 (0.62)	2.8 (0.58)	2.8 (0.66)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1, 4	2, 4	2, 4	1, 4
Week 36	n	39	42	42	123
	Mean (SD)	2.7 (0.77)	2.6 (0.67)	2.9 (0.93)	2.7 (0.80)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1, 4	1, 4	1, 6	1, 6
Week 46	n	40	46	41	127
	Mean (SD)	2.7 (0.92)	2.8 (0.90)	2.8 (0.93)	2.7 (0.91)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1, 5	1, 5	1, 6	1, 6

Source: Listing 16.2.6.3 adapted from Table 14.2.3.1
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, Min = Minimum, Max = Maximum, mITT = Modified intent-to-treat
Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Week 46 of 014 study dosing.
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

12.1.2.4 Responder Analysis - CGI-C

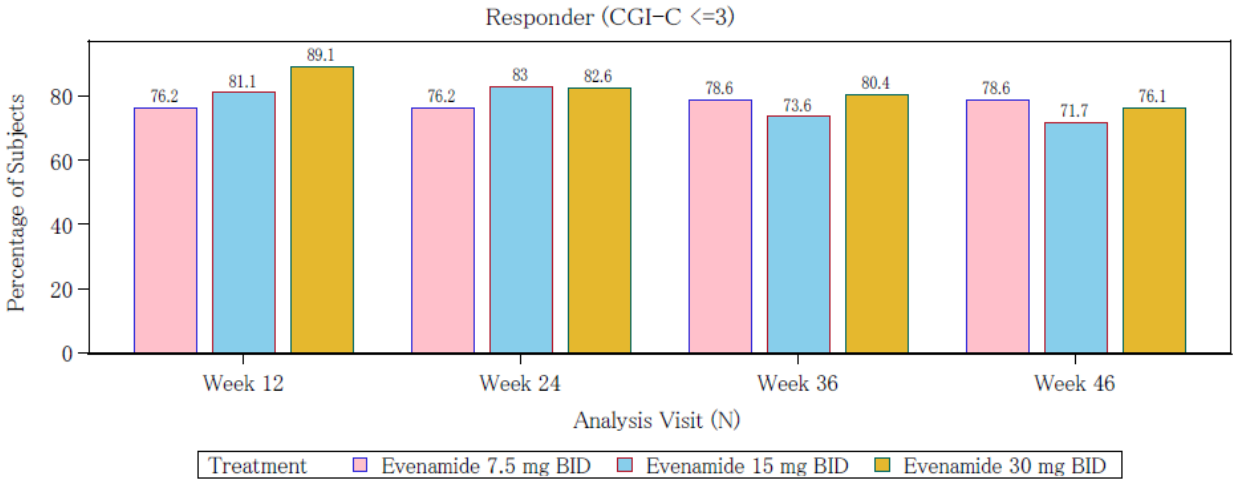
The proportion of subjects rated improved (score of 1, 2 or 3, corresponding to 'very much', 'much' or 'minimally' improved, respectively) on the CGI-C at 12, 24, 36 and 46 weeks (or at early discontinuation) for the mITT population is presented in Table 14.2.3.2, with by subject details in Listing 16.2.6.3.

Responders (CGI-C score ≤ 3)

The responder analysis was done considering change in the subject's condition from baseline, as indicated by the CGI-C score (CGI-C score ≤ 3 [indicating improvement]) and (CGI-C score >3 [indicating no change or worsening]).

At all visits, within each treatment group, the proportion of "responders" (CGI-C score ≤ 3 [indicating improvement]) was greater than 70%. The proportion of responders in the evenamide 7.5 mg *bid* treated group was 76.2% at Week 12 and 78.6% at Week 46. The proportion of responders in the evenamide 15 mg *bid* treated group was 81.1% at Week 12 and 71.7% at Week 46. The proportion of responders in the evenamide 30 mg *bid* treated group was 89.1% at Week 12 and 76.1% at Week 46. (Table 12-16; Figure 12-6).

Figure 12-6: Bar Chart for Clinical Global Impression – Change from Baseline (CGI-C) Responder Analysis (CGI-C<=3) - mITT Population



Source: Listing 16.2.6.3; Table 14.2.3.2; Figure 14.2.3.1

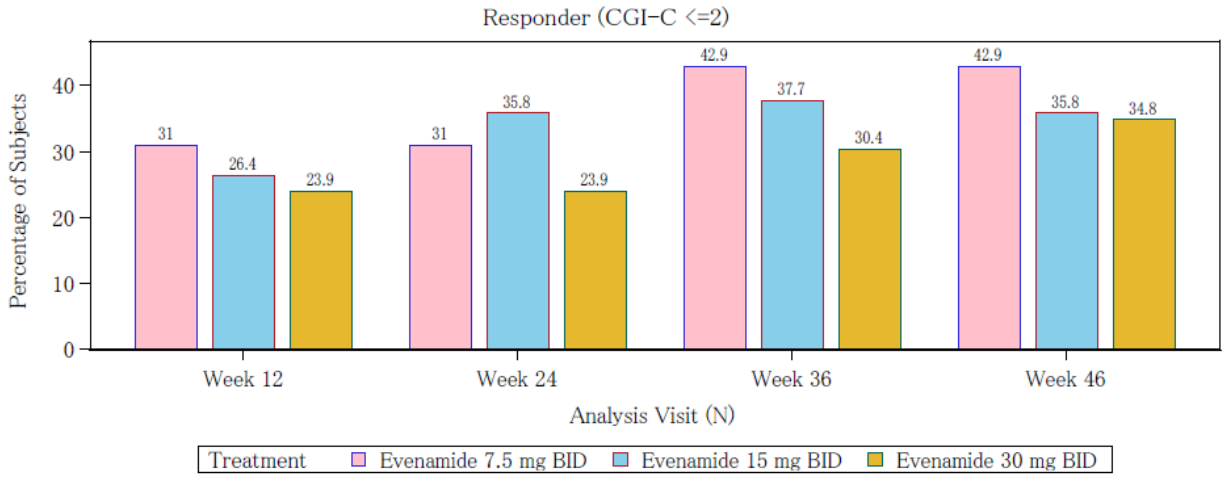
Responders (CGI-C score ≤ 2)

An additional responder analysis was done considering change in the subject's condition from baseline, as indicated by the CGI-C score (CGI-C score change ≤ 2 [indicating 'very much' or 'much' improvement]) and (CGI-C score change >3 [indicating no change or worsening]).

The proportion of responders based on the CGI-C score ≤ 2 (i.e., "much improved" and "very much improved") increased over time in all three treatment groups. The proportion of responders in the evenamide 7.5 mg *bid* treated group was 31% at Week 12 and 42.9% at Week 46. The proportion of responders in the evenamide 15 mg *bid* treated group was 26.4%

at Week 12 and 35.8% at Week 46. The proportion of responders in the evenamide 30 mg *bid* treated group was 23.9% at Week 12 and 34.8% at Week 46 indicating the benefit of long-term use of evenamide in patients (Table 12-16; Figure 12-7).

Figure 12-7: Bar Chart for Clinical Global Impression – Change from Baseline (CGI-C) Responder Analysis (CGI-C<=2) - mITT Population



Source: Listing 16.2.6.3; Table 14.2.3.2; Figure 14.2.3.1

Table 12-16: Responder Analysis - Clinical Global Impression - Change (CGI-C) - mITT Population

Visit	Category	Statistic	Evenamide 7.5 mg *BID* (N=42)	Evenamide 15 mg *BID* (N=53)	Evenamide 30 mg *BID* (N=46)	Total [a] (N=141)
Week 12	CGI-C score <= 3	n (%)	32 (76.2)	43 (81.1)	41 (89.1)	116 (82.3)
	CGI-C score <= 2	n (%)	13 (31.0)	14 (26.4)	11 (23.9)	38 (27.0)
Week 24	CGI-C score <= 3	n (%)	32 (76.2)	44 (83.0)	38 (82.6)	114 (80.9)
	CGI-C score <= 2	n (%)	13 (31.0)	19 (35.8)	11 (23.9)	43 (30.5)
Week 36	CGI-C score <= 3	n (%)	33 (78.6)	39 (73.6)	37 (80.4)	109 (77.3)
	CGI-C score <= 2	n (%)	18 (42.9)	20 (37.7)	14 (30.4)	52 (36.9)
Week 46	CGI-C score <= 3	n (%)	33 (78.6)	38 (71.7)	35 (76.1)	106 (75.2)
	CGI-C score <= 2	n (%)	18 (42.9)	19 (35.8)	16 (34.8)	53 (37.6)

Source: Listing 16.2.6.3 adapted from Table 14.2.3.2
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, mITT = Modified Intent-to-treat.
CGI-C score <=3 Category = patients rated as 1 = Very much improved, or 2 = Much improved, or 3 = Minimally improved.
CGI-C score <=2 Category = patients rated as 1 = Very much improved, or 2 = Much improved.
Percentages are calculated by all patients in the respective mITT population in denominator (N).
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

12.1.3 Strauss-Carpenter Level of Functioning (LOF) Scale Results

Change from baseline to endpoint on the total scores and Sub-scale scores on the LOF was summarized and analyzed within each dose group by using a paired *t-test*.

Total Score and Sub-scale Scores at Week 46 – Within Group Comparisons for the mITT

Population are presented in Table 12-17, Table 12-18, Table 12-19, Table 12-20, Table 12-21 and by Subject details in Listing 16.2.6.4 and 16.2.6.4a.

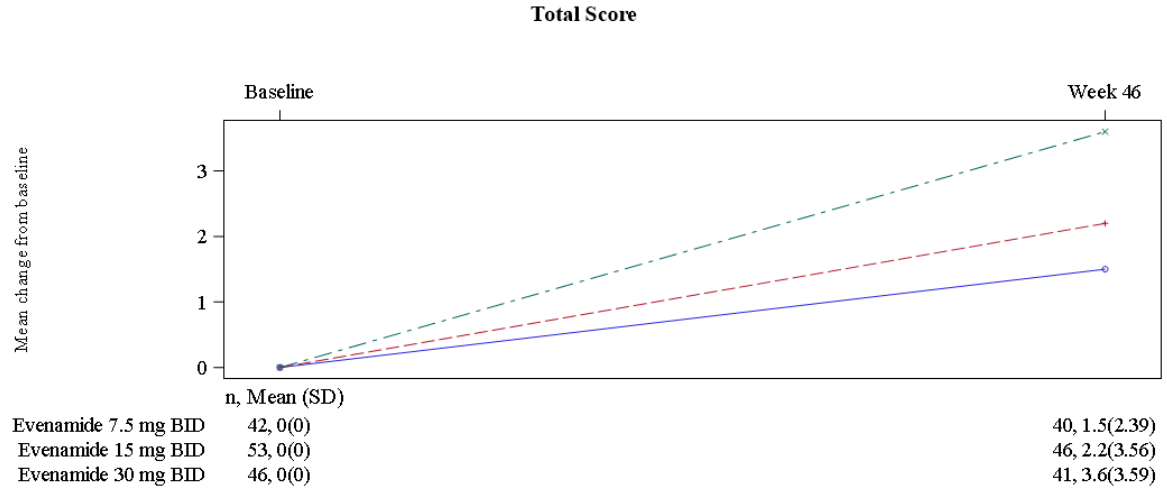
Total Score

Significant increases in mean (SD) values of the LOF total score were observed over time across all study visits (at 12, 24 and 36 weeks, and at the final visit at 46 weeks) compared to baseline in all the three treatment groups indicating improvement in functionality of subjects after treatment (Table 12-17).

At baseline, the mean (SD) of LOF total scores recorded were 18.0 (3.81), 18.1 (4.00) and 18.0 (3.64) in evenamide 7.5 mg, 15 mg and 30 mg bid treated groups, respectively.

At Week 46, an increase in LOF total score, with a mean (SD) of 19.7 (3.07), 20.1 (3.74) and 21.5 (4.51), was recorded in evenamide 7.5 mg, 15 mg and 30 mg bid treated groups, respectively. The mean (SD) change from baseline in the LOF total score was 1.4 (2.03) (95% CI: 0.72, 1.99; p<0.001) at Week 12 and 1.5 (2.39) (95% CI: 0.71, 2.24; p<0.001) at Week 46 in the evenamide 7.5 mg bid treated group. The mean (SD) change from baseline in the LOF total score was 1.5 (2.70) (95% CI: 0.71, 2.23; p<0.001) at Week 12 and 2.2 (3.56) (95% CI: 1.12, 3.23; p<0.001) at Week 46 in the evenamide 15 mg bid treated group. The mean (SD) change from baseline in the LOF total score was 2.5 (3.26) (95% CI: 1.49, 3.43;p<0.001) at Week 12 and 3.6 (3.59) (95% CI: 2.45, 4.72; p<0.001) at Week 46 in the evenamide 30 mg bid treated group.(Table 12-17, Figure 12-8)

Figure 12-8: Mean Change from Baseline by Visit in Strauss-Carpenter - Level of Functioning Scale (LOF) mITT population



Source: Listing 16.2.6.4; Table 14.2.4, Figure 14.2.4.1

Table 12-17: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score at Week 46 – Within Group Comparisons - mITT Population.

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Total Score	Baseline	N	42		53		46	
		Mean (SD)	18.0 (3.81)		18.1 (4.00)		18.0 (3.64)	
		Median	19.0		19.0		19.0	
		Min, Max	9.0, 26.0		9.0, 30.0		12.0, 28.0	
Total Score	Week 46	N	40	40	46	46	41	41
		Mean (SD)	19.7 (3.07)	1.5 (2.39)	20.1 (3.74)	2.2 (3.56)	21.5 (4.51)	3.6 (3.59)
		Median	20.0	1.0	20.0	2.0	22.0	3.0
		Min, Max	12.0, 24.0	-7.0, 7.0	10.0, 29.0	-10.0, 15.0	12.0, 31.0	-3.0, 12.0
		95% CI		(0.71, 2.24)		(1.12, 3.23)		(2.45, 4.72)
		p-value		<.001		<.001		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF. Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Social Contacts

An increase in the LOF Social Contacts Sub-scale scores was observed at Week 46 compared to baseline in all the three treatment groups, indicating improvement in frequency and quality of social contacts in subjects after treatment (Table 12-18).

At baseline, the mean (SD) of LOF Social Contacts Sub-scale scores recorded were 1.3 (0.83), 1.3 (0.98) and 1.5 (1.01) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 46 an increase in LOF Social Contacts Sub-scale scores, with a mean (SD) of 1.7 (0.79), 1.8 (1.05) and 2.0 (1.14) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.5 (0.78), 0.5 (0.75), 0.5 (0.95) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups was observed. These mean changes at Week 46 were found to be statistically significant (P <.001) in all treatment groups.

Table 12-18: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Social Contacts) Scores at Week 46 – Within Group Comparisons - mITT Population

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Social Contacts	Baseline	N	42		53		46	
		Mean (SD)	1.3 (0.83)		1.3 (0.98)		1.5 (1.01)	

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
		Median	1.3		1.5		2.0	
		Min, Max	0.0, 3.0		0.0, 4.0		0.0, 4.0	
Social Contacts	Week 46	N	40	40	46	46	41	41
		Mean (SD)	1.7 (0.79)	0.5 (0.78)	1.8 (1.05)	0.5 (0.75)	2.0 (1.14)	0.5 (0.95)
		Median	2.0	0.0	2.0	0.0	2.0	0.0
		Min, Max	0.5, 3.0	-1.5, 2.5	0.0, 4.0	-0.5, 3.0	0.0, 4.0	-2.0, 2.5
		95% CI		(0.21, 0.71)		(0.27, 0.71)		(0.15, 0.75)
		p-value		<.001		<.001		0.004

Source: Listing 16.2.6.4 adapted from Table 14.2.4
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF. Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Work

At baseline, the mean (SD) of LOF Work Sub-scale scores recorded were 1.3 (0.94), 1.2 (0.99) and 1.1 (1.00) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-19).

At Week 46, LOF Sub-scale (Work) scores with a mean (SD) of 1.4 (0.90), 1.3 (0.97) and 1.6 (1.07) were recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.1 (0.53), 0.2 (0.99) and 0.5 (0.90) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, was observed. This mean change was found to be statistically significant (P <.001) in the 30 mg *bid* treated group only.

Table 12-19: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Work) Scores at Week 46 – Within Group Comparisons - mITT Population

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Work	Baseline	n	42		53		46	
		Mean (SD)	1.3 (0.94)		1.2 (0.99)		1.1 (1.00)	
		Median	2.0		1.0		1.0	
		Min, Max	0.0, 3.0		0.0, 3.0		0.0, 3.0	
	Week 46	n	40	40	46	46	41	41
		Mean (SD)	1.4 (0.90)	0.1 (0.53)	1.3 (0.97)	0.2 (0.99)	1.6 (1.07)	0.5 (0.90)
		Median	2.0	0.0	2.0	0.0	2.0	0.0
		Min, Max	0.0, 3.0	-1.0, 2.0	0.0, 3.0	-2.0, 3.0	0.0, 4.0	-1.0, 2.0
		95% CI		(-0.09, 0.24)		(-0.08, 0.51)		(0.25, 0.82)

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
		p-value		0.372		0.142		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF. Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test. Baseline: Pre-dose of 014, post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Symptomatology

An increase in the LOF Symptomatology Sub-scale scores was observed at Week 46 compared to baseline in all three treatment groups, indicating improvement in symptoms and reduced need for hospitalization in subjects after treatment (Table 12-20).

At baseline, the mean (SD) of LOF Symptomatology Sub-scale scores recorded was 2.8 (0.31), 2.8 (0.39) and 2.8 (0.52) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, an increase of LOF Symptomatology Sub-scale scores with a mean (SD) of 3.1 (0.39), 3.2 (0.33) and 3.1 (0.49) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.3 (0.37), 0.4 (0.45) and 0.4 (0.47) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, was observed. These mean changes at Week 46 were found to be statistically significant (P <.001) in all treatment groups.

Table 12-20: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Symptomatology) Scores at Week 46 – Within Group Comparisons - mITT Population

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Symptomatology	Baseline	n	42		53		46	
		Mean (SD)	2.8 (0.31)		2.8 (0.39)		2.8 (0.52)	
		Median	3.0		3.0		3.0	
		Min, Max	2.5, 4.0		1.0, 4.0		1.0, 3.5	
	Week 46	n	40	40	46	46	41	41
		Mean (SD)	3.1 (0.39)	0.3 (0.37)	3.2 (0.33)	0.4 (0.45)	3.1 (0.49)	0.4 (0.47)
		Median	3.0	0.5	3.5	0.5	3.0	0.5
		Min, Max	2.5, 3.5	-1.0, 1.0	2.5, 3.5	-1.0, 2.0	1.0, 3.5	-0.5, 2.0

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
		95% CI		(0.16, 0.39)		(0.29, 0.56)		(0.24, 0.54)
		p-value		<.001		<.001		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Function

At baseline, the mean (SD) of LOF Function Sub-scale scores recorded was 2.5 (0.45), 2.5 (0.43) and 2.4 (0.44) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Week 46, LOF Function Sub-scale scores with a mean (SD) of 2.4 (0.44), 2.5 (0.38) and 2.7 (0.51) were recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of -0.1 (0.24), -0.0 (0.38) and 0.3 (0.45) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, was observed (Table 12-21). This mean change was found to be statistically significant (P <.001) in the 30 mg *bid* treated group only.

Table 12-21: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Function) Scores at Week 46 – Within Group Comparisons - mITT Population

			Evenamide 7.5 mg *BID* (N=42)		Evenamide 15 mg *BID* (N=53)		Evenamide 30 mg *BID* (N=46)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Function	Baseline	n	42		53		46	
		Mean (SD)	2.5 (0.45)		2.5 (0.43)		2.4 (0.44)	
		Median	2.7		2.7		2.7	
		Min, Max	1.3, 3.3		1.3, 4.0		1.3, 3.3	
	Week 46	n	40	40	46	46	41	41
		Mean (SD)	2.4 (0.44)	-0.1 (0.24)	2.5 (0.38)	-0.0 (0.38)	2.7 (0.51)	0.3 (0.45)
		Median	2.7	0.0	2.7	0.0	2.7	0.0
		Min, Max	1.3, 2.7	-0.7, 0.7	1.3, 3.3	-1.3, 0.7	2.0, 4.0	0.0, 2.0
		95% CI		(-0.13, 0.03)		(-0.14, 0.08)		(0.14, 0.42)
		p-value		0.193		0.587		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2 Additional Analysis

Additional efficacy analyses were conducted using an overall evenamide group, which combines data from all three treatment groups.

12.2.1 Positive and Negative Syndrome Scale Results

The mean change from baseline at Week 46 in PANSS total score using the overall evenamide group (*Primary Estimand*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.1c, with by subject details in Listing 16.2.6.1.2.

A steady improvement in the PANSS total score (lowering of score) was observed at all study visits (Weeks 12, 24, 36, and 46) compared to baseline in the overall evenamide group. Mean (SD) values of the PANSS total score showed a decreasing trend at all the time points during the study, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of the PANSS total score was recorded as 79.5 (5.04). At Week 46, a reduction of PANSS total score with a mean (SD) of 63.9 (10.71) was recorded, with statistically significant mean (SD) change from baseline of -15.5 (10.18) (95% CI: -17.25, -13.68; p<0.001) being observed in the overall evenamide group (Table 12-22).

12.2.1.1 PANSS Total Scores in the overall evenamide group

Primary Efficacy Estimand Analysis

Table 12-22: Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score (Primary Estimand Treatment Policy) mITT Population - Overall

		Evenamide (N=141)		
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	n	141		
	Mean (SD)	79.5 (5.04)		
	Median	80.0		
	Min, Max	70, 89		
Week 12	n	139	139	139
	Mean (SD)	68.3 (8.18)	-11.2 (7.22)	-14.0 (8.83)
	Median	67.0	-11.0	-13.5
	Min, Max	51, 89	-33, 3	-39, 4
	95% CI		(-12.39, -9.97)	
	p-value		<.001	
Week 24	n	131	131	131
	Mean (SD)	66.5 (8.38)	-12.8 (7.65)	-16.1 (9.34)
	Median	66.0	-13.0	-15.3
	Min, Max	43, 89	-40, 0	-47, 0
	95% CI		(-14.15, -11.53)	
	p-value		<.001	
Week 36	n	123	123	123
	Mean (SD)	64.4 (8.84)	-14.8 (8.58)	-18.6 (10.34)
	Median	63.0	-15.0	-19.3
	Min, Max	43, 88	-43, 6	-50, 7
	95% CI		(-16.17, -13.11)	

		Evenamide (N=141)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	
Week 46	n	127	127	127
	Mean (SD)	63.9 (10.71)	-15.5 (10.18)	-19.4 (12.32)
	Median	62.0	-14.0	-18.8
	Min, Max	35, 95	-47, 6	-55, 7
	95% CI		(-17.25, -13.68)	
	p-value		<.001	

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.1c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline) /Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.1.2 Change from baseline in PANSS total score using within group comparison (primary estimand group policy) mITT-C Population

The mean change from baseline at Week 46 in PANSS total score within group comparison (primary estimand group policy) was analyzed for the mITT-C Population, consisting of subjects who completed the 46-week treatment period, and the same is presented in Table 14.2.1.1d, with by subject details in Listing 16.2.6.1.2.

A steady improvement in the PANSS total score (lowering of score) was observed across all study visits (Weeks 12, 24, 36, and 46) compared with baseline, using within group comparisons (primary estimand group policy) for the mITT-C Population. Mean (SD) values of the PANSS total score showed a decreasing trend at all the time points in all three treatment groups during the study, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of the PANSS total score was recorded as 79.8 (5.36), 79.0 (5.55), and 78.7 (4.27) in 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 46, a reduction of PANSS total score with a mean (SD) of 64.7 (10.72), 61.8 (9.85) and 63.3 (10.7) was recorded in 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, with statistically significant mean (SD) changes from baseline of -15.1 (8.91) (95% CI: -18.02, -12.24); p<0.001), -17.2 (10.73) (95% CI: -20.58, -13.81); p<0.001), -15.4 (10.87) (95% CI: -18.88, -11.92; p<0.001) being observed in 7.5 mg, 15 mg and 30 mg *bid* evenamide treated groups, respectively (Table 12-23).

Table 12-23: Change from baseline in PANSS total score use within group comparison (primary estimand group policy) mITT-C Population

		Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	39		41		40	
	Mean (SD)	79.8 (5.36)		79.0 (5.55)		78.7 (4.27)	

		Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Median	81.0		80.0		78.5	
	Min, Max	72, 89		70, 89		71, 87	
Week 12	n	39	39	41	41	40	40
	Mean (SD)	69.1 (9.75)	-10.7 (7.44)	67.7 (7.69)	-11.3 (7.74)	68.2 (6.00)	-10.5 (5.41)
	Median	69.0	-12.0	67.0	-10.0	68.0	-10.0
	Min, Max	51, 89	-28, 2	53, 87	-33, 3	58, 80	-25, -1
	95% CI		(-13.13, -8.30)		(-13.74, -8.85)		(-12.26, -8.79)
	p-value		<.001		<.001		<.001
Week 24	n	39	39	41	41	40	40
	Mean (SD)	67.7 (9.45)	-12.1 (6.91)	64.9 (8.06)	-14.1 (8.71)	65.6 (7.43)	-13.1 (7.30)
	Median	68.0	-13.0	64.0	-16.0	64.0	-12.5
	Min, Max	51, 89	-28, 0	46, 86	-40, -1	43, 82	-35, 0
	95% CI		(-14.37, -9.89)		(-16.82, -11.32)		(-15.44, -10.76)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	41	41	40	40
	Mean (SD)	65.2 (9.43)	-14.6 (7.59)	63.0 (8.53)	-15.9 (9.39)	64.9 (8.63)	-13.9 (8.70)
	Median	63.0	-15.0	63.0	-16.0	63.5	-13.5
	Min, Max	51, 88	-32, -1	43, 85	-43, -2	47, 87	-34, 6
	95% CI		(-17.05, -12.13)		(-18.89, -12.96)		(-16.66, -11.09)
	p-value		<.001		<.001		<.001
Week 46	n	39	39	41	41	40	40
	Mean (SD)	64.7 (10.72)	-15.1 (8.91)	61.8 (9.85)	-17.2 (10.73)	63.3 (10.70)	-15.4 (10.87)
	Median	62.0	-16.0	60.0	-15.0	63.0	-14.0
	Min, Max	51, 95	-36, 6	39, 83	-47, 2	35, 85	-44, 4
	95% CI		(-18.02, -12.24)		(-20.58, -13.81)		(-18.88, -11.92)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.1d
Abbreviations: N - Total number of subjects in the mITT-C Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.1.3 Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score (Supportive Estimand Hypothetical) mITT-C Population - Overall

The mean change from baseline at Week 46 in PANSS total scores (Supportive Estimand Hypothetical) was analyzed for the mITT-C Population – Overall and is presented in Table 14.2.1.1cd, with by subject details in Listing 16.2.6.1.2.

An improvement in the PANSS Positive Syndrome scores (lowering of score) was observed at all study visits (Weeks 12, 24, 36 and 46) compared to baseline in the overall evenamide group. At Week 46, a significant mean (SD) change from baseline in the PANSS total score of -15.9 (10.18) (95% CI: -17.77, -14.08; p<0.001) was observed in the overall evenamide group (Table 12-24). This change at Week 46 was equivalent to a mean (SD) percent reduction from baseline of 20.0 (12.28) %.

Table 12-24: Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score (Primary Estimand Treatment Policy) mITT-C Population - Overall

		Evenamide (N=120)		
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	N	120		
	Mean (SD)	79.2 (5.07)		
	Median	79.0		
	Min, Max	70, 89		
Week 12	N	120	120	120
	Mean (SD)	68.3 (7.90)	-10.9 (6.89)	-13.7 (8.47)
	Median	67.0	-10.0	-13.4
	Min, Max	51, 89	-33, 3	-38, 4
	95% CI		(-12.10, -9.60)	
	p-value		<.001	
Week 24	N	120	120	120
	Mean (SD)	66.0 (8.36)	-13.1 (7.67)	-16.5 (9.34)
	Median	64.0	-13.0	-16.5
	Min, Max	43, 89	-40, 0	-47, 0
	95% CI		(-14.50, -11.73)	
	p-value		<.001	
Week 36	N	120	120	120
	Mean (SD)	64.3 (8.84)	-14.8 (8.58)	-18.6 (10.33)
	Median	63.0	-15.0	-19.1
	Min, Max	43, 88	-43, 6	-50, 7
	95% CI		(-16.36, -13.26)	
	p-value		<.001	
Week 46	N	120	120	120
	Mean (SD)	63.2 (10.40)	-15.9 (10.18)	-20.0 (12.28)
	Median	62.0	-14.5	-19.6
	Min, Max	35, 95	-47, 6	-55, 7
	95% CI		(-17.77, -14.08)	

			Evenamide (N=120)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
	p-value		<.001	

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.1cd
N - Total number of subjects in the mITT-C Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.1.4 PANSS Subscales in the overall evenamide group

PANSS Positive Syndrome subscale scores

The mean change from baseline at Week 46 in PANSS Positive Syndrome subscale scores using the overall evenamide group comparison was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3c, with by subject details in Listing 16.2.6.1.1.

Improvement in the PANSS Positive Syndrome subscale scores (lowering of score) was observed at all study visits (Weeks 12, 24, 36 and 46) compared to baseline in the overall evenamide group. At Week 46, a significant mean (SD) change from baseline in the PANSS Positive Syndrome subscale scores of -6.6 (4.32) (95% CI: (-7.34, -5.82; p*<0.001*) was observed in the overall evenamide group. (Table 12-25). This change at Week 46 was equivalent to a mean (SD) percent reduction from baseline of -27.7 (17.15) %.

Table 12-25: Summary of Change from Baseline in PANSS Subscales (Positive scale) score by Visit Using Overall Comparison - mITT Population

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	n	141		
	Mean (SD)	23.7 (3.38)		
	Median	24.0		
	Min, Max	17, 36		
Week 12	n	139	139	139
	Mean (SD)	18.8 (4.36)	-5.0 (3.61)	-20.8 (14.59)
	Median	18.0	-4.0	-18.2
	Min, Max	9, 34	-15, 2	-56, 8
	95% CI		(-5.56, -4.35)	
	p-value		<.001	
Week 24	n	131	131	131
	Mean (SD)	18.0 (4.27)	-5.7 (3.71)	-23.9 (14.88)
	Median	17.0	-5.0	-22.7
	Min, Max	8, 35	-17, 1	-68, 5
	95% CI		(-6.35, -5.07)	
	p-value		<.001	

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Week 36	n	123	123	123
	Mean (SD)	17.2 (4.26)	-6.5 (3.78)	-27.1 (14.99)
	Median	17.0	-6.0	-25.0
	Min, Max	8, 34	-17, 3	-68, 14
	95% CI		(-7.14, -5.79)	
	p-value		<.001	
Week 46	n	127	127	127
	Mean (SD)	17.1 (4.85)	-6.6 (4.32)	-27.7 (17.15)
	Median	17.0	-6.0	-27.3
	Min, Max	7, 40	-17, 4	-68, 11
	95% CI		(-7.34, -5.82)	
	p-value		<.001	

Source: Listing 16.2.6.1.1 adapted from Table 14.2.1.3c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

PANSS Negative Syndrome subscale scores

The mean change from baseline at Week 46 in PANSS Negative Syndrome subscale scores using the overall evenamide group comparison was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3c, with by subject details in Listing 16.2.6.1.1.

An improvement in the PANSS Negative Syndrome subscale scores (lowering of score) was observed at all study visits (Weeks 12, 24, 36 and 46) compared to baseline in the overall evenamide group. At Week 46, a significant mean (SD) change from baseline in the PANSS Negative Syndrome subscale scores of -3.2 (3.45) (95% CI: -3.76, -2.55; *p<0.001*) was observed in the overall evenamide group. (Table 12-26). This change at Week 46 was equivalent to a mean (SD) percent reduction from baseline of 15.0 (15.97) %.

Table 12-26: Summary of Change from Baseline in PANSS (Negative Syndrome subscale) score by Visit Using Overall Comparison - mITT Population.

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	n	141		
	Mean (SD)	19.8 (3.32)		
	Median	20.0		
	Min, Max	12, 31		
Week 12	n	139	139	139
	Mean (SD)	17.5 (3.12)	-2.3 (2.66)	-10.7 (12.32)
	Median	18.0	-2.0	-9.5
	Min, Max	10, 26	-13, 4	-50, 33
	95% CI		(-2.71, -1.82)	

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
	p-value		<.001	
Week 24	n	131	131	131
	Mean (SD)	17.2 (3.10)	-2.5 (2.99)	-11.9 (13.92)
	Median	17.0	-2.0	-10.0
	Min, Max	9, 25	-14, 6	-59, 35
	95% CI		(-3.05, -2.02)	
	p-value		<.001	
Week 36	n	123	123	123
	Mean (SD)	16.8 (3.28)	-2.9 (3.38)	-13.7 (15.92)
	Median	17.0	-2.0	-13.3
	Min, Max	8, 25	-16, 6	-64, 35
	95% CI		(-3.52, -2.31)	
	p-value		<.001	
Week 46	n	127	127	127
	Mean (SD)	16.6 (3.46)	-3.2 (3.45)	-15.0 (15.97)
	Median	17.0	-3.0	-13.6
	Min, Max	8, 28	-17, 6	-64, 35
	95% CI		(-3.76, -2.55)	
	p-value		<.001	

Source: Listing 16.2.6.1.1 adapted from Table 14.2.1.3c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

PANSS General Psychopathology subscale scores

The mean change from baseline at Week 46 in PANSS General Psychopathology subscale scores in the overall evenamide group comparison was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.3c, with by subject details in Listing 16.2.6.1.1.

A steady improvement in the PANSS General Psychopathology subscale scores (lowering of score) was observed at all study visits (Weeks 12, 24, 36 and 46) compared to baseline in the overall evenamide group. At Week 46, a significant mean (SD) change from baseline in the PANSS general psychopathology subscale scores of -5.7 (4.78) (95% CI: (-6.56, -4.89; p<0.001) was observed in the overall evenamide group (Table 12-27). This change at Week 46 was equivalent to a mean (SD) percent reduction from baseline of 15.9 (12.59) %.

Table 12-27: Summary of Change from Baseline in PANSS (General Psychopathology subscale) score by Visit Overall Comparison - mITT Population.

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	n	141		

			Evenamide (N=141)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
	Mean (SD)	36.0 (3.62)		
	Median	36.0		
	Min, Max	29, 49		
Week 12	n	139	139	139
	Mean (SD)	32.0 (4.21)	-4.0 (3.24)	-10.9 (8.70)
	Median	31.0	-4.0	-11.8
	Min, Max	23, 46	-15, 5	-35, 15
	95% CI		(-4.50, -3.41)	
	p-value		<.001	
Week 24	n	131	131	131
	Mean (SD)	31.3 (4.64)	-4.6 (3.69)	-12.7 (9.89)
	Median	31.0	-5.0	-13.2
	Min, Max	20, 45	-20, 5	-50, 15
	95% CI		(-5.20, -3.93)	
	p-value		<.001	
Week 36	n	123	123	123
	Mean (SD)	30.4 (4.89)	-5.4 (4.06)	-15.1 (10.84)
	Median	29.0	-5.0	-14.7
	Min, Max	21, 46	-17, 3	-45, 7
	95% CI		(-6.14, -4.69)	
	p-value		<.001	
Week 46	n	127	127	127
	Mean (SD)	30.2 (5.54)	-5.7 (4.78)	-15.9 (12.59)
	Median	29.0	-5.0	-15.4
	Min, Max	18, 47	-22, 6	-55, 16
	95% CI		(-6.56, -4.89)	
	p-value		<.001	

Source: Listing 16.2.6.1.1 adapted from Table 14.2.1.3c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, PostBaseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.1.5 Sensitivity Analysis on Change from Baseline in PANSS Total Score

Paired t-test Using Multiple Imputation in the overall evenamide group

The mean change from baseline at Week 46 in the PANSS total score in the overall evenamide group (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.4c, with by subject details in Listing 16.2.6.1.2.

In this sensitivity analysis (*Multiple Imputation*), an improvement in the PANSS total score (lowering of score) was observed at Week 46 compared to baseline in the overall evenamide group.

At baseline, the mean (SD) of PANSS total score recorded was 79.5 (5.04) in the overall evenamide group. At Week 46, a reduction of PANSS total score with a mean (SD) of 63.9 (10.61) was recorded, with a statistically significant mean (SD) change from baseline of -15.5 (10.20) (95% CI: -17.23, -13.82; *p<0.001*) observed in the overall evenamide group (Table 12-28).

Table 12-28: Sensitivity Analysis on Change from Baseline in PANSS Total Score Overall Comparison at Week 46 - Paired t-test Using Multiple Imputation-- mITT Population.

Visit	Statistic	Evenamide (N=141)
Baseline	n	141
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Week 46	n	140
	Mean (SD)	63.9 (10.61)
	Median	63.0
	Min, Max	35, 95
Week 46	Mean change from Baseline (SD)	-15.5 (10.20)
	95% CI	(-17.23, -13.82)
	p-value	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.4c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval, mITT = Modified intent-to-treat, Min=Minimum, Max=Maximum, p-value = Paired t-test.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Paired t-test Using LOCF Supportive Estimand in the overall evenamide group

The mean change from baseline at Week 46 in PANSS Total Score in the overall evenamide group (*sensitivity analysis: LOCF Supportive Efficacy Estimand*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.5c, with by subject details in Listing 16.2.6.1.2. _The sensitivity analysis was performed using the LOCF. In case the subject had not taken any rescue medication and not added any further efficacy data, LOCF was considered as supportive.

In this sensitivity analysis (*LOCF Supportive Efficacy Estimand*), an improvement in the PANSS total score (lowering of score) was observed at Week 46 compared to baseline in the overall evenamide group.

At baseline, the mean (SD) of PANSS total score recorded was 79.5 (5.04) in the overall evenamide group. At Week 46, a reduction of PANSS total score with a mean (SD) of 64.2 (10.55) was recorded, with a statistically significant mean (SD) change from baseline of -15.3 (10.09) (95% CI: -16.94, -13.57; *p<0.001*) observed in the overall evenamide group (Table 12-29)

Table 12-29: Sensitivity Analysis on Change from Baseline in PANSS Total Score Overall Comparison at Week 46 – Paired t-test Using LOCF Supportive Estimand mITT Population.

Visit	Statistic	Evenamide (N=141)
Baseline	n	141
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Week 46	n	140
	Mean (SD)	64.2 (10.55)
	Median	63.0
	Min, Max	35, 95
Week 46	Mean change from Baseline (SD)	-15.3 (10.09)
	95% CI	(-16.94, -13.57)
	p-value	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.5c
Abbreviations: N – Total number of subjects in the mITT Population, Min = Minimum, Max = Maximum, n = number of patients, LOCF = Last observation-carried forward, SD = Standard Deviation, CI = Confidence Interval.
mITT = Modified intent-to-treat. The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data is not carried forward to post baseline visit.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Comparison Analysis of Different Models in the overall evenamide group

A comparison of the different models used for the Sensitivity Analysis of change from baseline in PANSS total score at Week 46 using the overall evenamide group comparison for the mITT Population is presented in Table 14.2.1.6c, with by subject details in Listing 16.2.6.1.2.

Similar decreasing trends (improvement) were observed in all of the models (*Primary estimand, Supportive estimand, LOCF and Multiple Imputation*) for the Sensitivity Analysis of change from baseline in PANSS total score at Week 46 using the overall evenamide group comparison (Table 12-30). A statistically significant mean (SD) change from baseline (*p<0.001*) in all four models was observed in the overall evenamide group analysis.

Table 12-30: Sensitivity Analysis on Change from Baseline in PANSS Total Score at Week 46 – Comparison of Different Models

Models	Statistic	Evenamide (N=141)
Primary Estimand	Mean change from Baseline (SD)	-15.5 (10.18)
	95% CI	(-17.25, -13.68)
	p-value	<.001
Supportive Estimand	Mean change from Baseline (SD)	-16.5 (10.02)
	95% CI	(-18.37, -14.55)
	p-value	<.001
MI	Mean change from Baseline (SD)	-15.5 (10.20)
	95% CI	(-17.23, -13.82)
	p-value	<.001

Models	Statistic	Evenamide (N=141)
LOCF	Mean change from Baseline (SD)	-15.3 (10.09)
	95% CI	(-16.94, -13.57)
	p-value	<.001

Source: Listing 16.2.6.1.2 adapted from Table 14.2.1.6c
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test. MI = Multiple Imputation, LOCF = Last observation-carried forward, CI = Confidence Interval. The results obtained in each model are compared in this table.

12.2.2 Clinical Global Impression – Severity of Illness (CGI-S) score

12.2.2.1 Clinical Global Impression – Severity of Illness (CGI-S) score in the overall evenamide group

The mean change from baseline at Week 46 on the CGI-S using the overall evenamide group was summarized by visit and is presented in Table 14.2.2.1c, and by subject details are presented in Listing 16.2.6.2.

A significant (p<0.001) improvement (lowering of scores) in the CGI-S was observed at all study visits (Weeks 12, 18, 24, 36 and 46) compared to baseline in the overall evenamide group, indicating improvement in severity of illness.

At baseline, the mean (SD) of CGI-S score of 4.5 (0.59) was recorded in the overall evenamide group. At Week 46, a reduction of CGI-S scores with a mean (SD) of 3.5 (0.68) was recorded. A change from baseline in the mean CGI-S score at Week 46, was -1.1 (0.69) (95% CI: -1.22, -0.98; p<0.001), indicating continuing improvement in overall severity of illness (Table 12-31).

Table 12-31: Summary of Mean Value and Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Overall Comparison - mITT Population.

		Evenamide (N=141)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	4.5 (0.59)	
	Median	4.0	
	Min, Max	4, 6	
Week 12	n	139	139
	Mean (SD)	3.7 (0.63)	-0.8 (0.61)
	Median	4.0	-1.0
	Min, Max	3, 6	-2, 0
	95% CI		(-0.94, -0.73)
	p-value		<.001
Week 24	n	131	131
	Mean (SD)	3.6 (0.62)	-1.0 (0.62)
	Median	4.0	-1.0
	Min, Max	2, 5	-3, 0

			Evenamide (N=141)
Visit	**Statistic**	**Observed**	**Change from Baseline**
	95% CI		(-1.08, -0.86)
	p-value		<.001
Week 36	n	123	123
	Mean (SD)	3.4 (0.59)	-1.1 (0.64)
	Median	3.0	-1.0
	Min, Max	2, 5	-3, 0
	95% CI		(-1.25, -1.02)
	p-value		<.001
Week 46	n	127	127
	Mean (SD)	3.5 (0.68)	-1.1 (0.69)
	Median	3.0	-1.0
	Min, Max	2, 6	-3, 1
	95% CI		(-1.22, -0.98)
	p-value		<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.1c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat,
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.2.2 Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) –Within Group Comparisons mITT-C Population

The mean change from baseline at Week 46 on the CGI-S using the completers (mITT-C) population within group comparison was summarized by visit and is presented in Table 14.2.2.1d.

At baseline, the mean (SD) CGI-S scores recorded were 4.6 (0.67), 4.6 (0.62), 4.4 (0.50) in the 7.5 mg,15 mg and 30 mg *bid* evenamide treatment groups. At Week 46, a decrease of CGI-S scores with a mean (SD) of 3.5 (0.76), 3.4 (0.63) and 3.3 (0.57) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The mean (SD) changes from baseline were -1.1 (0.66), -1.2 (0.70) and -1.1 (0.69) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, all of which were statistically significant (p<0.001) (Table 12-32).

Table 12-32: Summary of Change from Baseline in Clinical Global Impression - Severity of Illness (CGI- S) – Within Group Comparisons mITT-C Population

		Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	39		41		40	
	Mean (SD)	4.6 (0.67)		4.6 (0.62)		4.4 (0.50)	
	Median	5.0		5.0		4.0	
	Min, Max	4, 6		4, 6		4, 5	

		Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Week 12	n	39	39	41	41	40	40
	Mean (SD)	3.8 (0.79)	-0.8 (0.61)	3.6 (0.58)	-1.0 (0.63)	3.6 (0.49)	-0.8 (0.58)
	Median	4.0	-1.0	4.0	-1.0	4.0	-1.0
	Min, Max	3, 6	-2, 0	3, 5	-2, 0	3, 4	-2, 0
	95% CI		(-0.99, -0.60)		(-1.20, -0.80)		(-0.96, -0.59)
	p-value		<.001		<.001		<.001
Week 24	n	39	39	41	41	40	40
	Mean (SD)	3.7 (0.72)	-0.9 (0.60)	3.5 (0.55)	-1.1 (0.60)	3.4 (0.55)	-1.0 (0.62)
	Median	4.0	-1.0	3.0	-1.0	3.0	-1.0
	Min, Max	3, 5	-2, 0	3, 5	-2, 0	2, 4	-3, 0
	95% CI		(-1.09, -0.70)		(-1.31, -0.93)		(-1.17, -0.78)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	41	41	40	40
	Mean (SD)	3.5 (0.68)	-1.1 (0.58)	3.4 (0.54)	-1.3 (0.67)	3.4 (0.53)	-1.1 (0.64)
	Median	3.0	-1.0	3.0	-1.0	3.0	-1.0
	Min, Max	3, 5	-2, 0	2, 4	-2, 0	2, 4	-3, 0
	95% CI		(-1.26, -0.89)		(-1.48, -1.06)		(-1.25, -0.85)
	p-value		<.001		<.001		<.001
Week 46	n	39	39	41	41	40	40
	Mean (SD)	3.5 (0.76)	-1.1 (0.66)	3.4 (0.63)	-1.2 (0.70)	3.3 (0.57)	-1.1 (0.69)
	Median	3.0	-1.0	3.0	-1.0	3.0	-1.0
	Min, Max	3, 6	-2, 1	2, 5	-2, 0	2, 5	-3, 0
	95% CI		(-1.29, -0.86)		(-1.46, -1.02)		(-1.30, -0.85)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.1d
Abbreviations: N - Total number of subjects in the mITT-C Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT-C = Modified intent-to-treat-Completers, Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.2.3 Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) mITT-C Population - Overall

A steady improvement in the CGI-S was observed at all study visits (Weeks 12, 24, 36, and 46) compared to baseline in the overall evenamide group for the mITT-C Population. Mean (SD) values of the CGI-S score showed a decreasing trend up to Week 36 during the study (Table 14.2.2.1cd), reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of the CGI-S score was recorded as 4.6 (0.61). At Week 46, a reduction of CGI-S score with a mean (SD) of 3.4 (0.66) was recorded, with a statistically significant mean (SD) change from baseline of -1.1 (0.69) (95% CI: -1.26, -1.01; p<0.001) in the overall evenamide group (Table 12-33).

Table 12-33: Summary of Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) mITT-C Population - Overall

			Evenamide (N=120)
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	N	120	
	Mean (SD)	4.6 (0.61)	
	Median	4.0	
	Min, Max	4, 6	
Week 12	N	120	120
	Mean (SD)	3.7 (0.63)	-0.9 (0.61)
	Median	4.0	-1.0
	Min, Max	3, 6	-2, 0
	95% CI		(-0.97, -0.75)
	p-value		<.001
Week 24	N	120	120
	Mean (SD)	3.6 (0.62)	-1.0 (0.61)
	Median	3.5	-1.0
	Min, Max	2, 5	-3, 0
	95% CI		(-1.11, -0.89)
	p-value		<.001
Week 36	N	120	120
	Mean (SD)	3.4 (0.59)	-1.1 (0.63)
	Median	3.0	-1.0
	Min, Max	2, 5	-3, 0
	95% CI		(-1.25, -1.02)
	p-value		<.001
Week 46	N	120	120
	Mean (SD)	3.4 (0.66)	-1.1 (0.69)
	Median	3.0	-1.0
	Min, Max	2, 6	-3, 1
	95% CI		(-1.26, -1.01)
	p-value		<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.1cd
Abbreviations: N - Total number of subjects in the mITT- C Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT-C = Modified intent-to-treat-Completers.
Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.2.4 Sensitivity Analysis on Change from Baseline in CGI-S Score in the overall evenamide group

Paired t-test using Multiple Imputation in the overall evenamide group

The mean change from baseline at Week 46 in the CGI-S score for the overall evenamide group (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.2.2c, with by subject details in Listing 16.2.6.2.

In the sensitivity analysis (*Multiple Imputation*), an improvement in the CGI-S score (lowering of score) was observed at Week 46 compared to baseline in the overall evenamide group.

At baseline, the mean (SD) of CGI-S score of 4.5 (0.59) was recorded. At Week 46, a reduction of CGI-S score with a mean (SD) of 3.4 (0.66) was recorded, with a statistically significant mean (SD) change from baseline of -1.1 (0.69) (95% CI: (-1.20, -0.97; *p<0.001*) in the overall evenamide group (Table 12-34).

Table 12-34: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) using Overall Evenamide Group Comparison at Week 46 - Paired t-test Using Multiple Imputation mITT Population.

Visit	Statistic	Evenamide (N=141)
Baseline	N	141
	Mean (SD)	4.5 (0.59)
	Median	4.0
	Min, Max	4, 6
Week 46	N	140
	Mean (SD)	3.4 (0.66)
	Median	3.0
	Min, Max	2, 6
Week 46	Mean change from Baseline (SD)	-1.1 (0.69)
	95% CI	(-1.20, -0.97)
	p-value	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.2c
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, mITT = Modified Intent-to-treat. CI = Confidence Interval. Min = Minimum, Max = Maximum, p-value = Paired t-test.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Paired t-test using LOCF in the overall evenamide group

The mean change from baseline at Week 46 in CGI-S score for the overall evenamide group (sensitivity analysis: LOCF) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.2.3c, with by subject details in Listing 16.2.6.2. The sensitivity analysis was performed using the LOCF. In case the subject had not taken any rescue medication and not added any further efficacy data LOCF was considered as supportive.

In the sensitivity analysis (LOCF), an improvement in the CGI-S score (lowering of score) was observed at Week 46 compared to baseline in the overall evenamide group. Mean (SD) values of the CGI-S score showed a decreasing trend reflecting a continuation of reduction in severity of illness.

At baseline, the mean (SD) of CGI-S score of 4.5 (0.59) was recorded. At Week 46, a reduction of CGI-S score with a mean (SD) of 3.5 (0.66) was recorded with a statistically significant mean (SD) change from baseline of -1.1 (0.71) (95% CI: -1.19, -0.95; p<0.001) in the overall evenamide group (Table 12-35).

Table 12-35: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) using Overall evenamide group Comparison at Week 46- Paired t-test Using LOCF - mITT Population.

Visit	Statistic	Evenamide (N=141)
Baseline	N	141
	Mean (SD)	4.5 (0.59)
	Median	4.0
	Min, Max	4, 6
Week 46	N	140
	Mean (SD)	3.5 (0.66)
	Median	3.0
	Min, Max	2, 6
Week 46	Mean change from Baseline (SD)	-1.1 (0.71)
	95% CI	(-1.19, -0.95)
	p-value	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.3c
Abbreviations: LOCF = Last observation-carried forward, N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. mITT = Modified Intent-to-treat.
The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data is not carried forward to post baseline visit. p-value = Paired t-test.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Comparison Analysis of Different Models for CGI-S in the overall evenamide group

A comparison of the different models used for the Sensitivity Analysis of CGI-S at Week 46 for the mITT Population is presented in Table 14.2.2.4c, with by subject details in Listing 16.2.6.2.

Similar decreasing trends (improvement) were observed in all of the models (Paired t-test,

LOCF and Multiple imputations) for the Sensitivity Analysis of change from baseline in CGI-S score at Week 46. A significant mean (SD) change from baseline (p<0.001) was observed in the overall evenamide group with all models. Data for the Paired t-test, MI and LOCF are compared in Table 12-36.

Table 12-36: Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Week 46 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide (N=141)
Paired t-test	Mean change from Baseline (SD)	-1.1 (0.69)
	95% CI	(-1.22, -0.98)
	p-value	<.001
MI	Mean change from Baseline (SD)	-1.1 (0.69)
	95% CI	(-1.20, -0.97)
	p-value	<.001
LOCF	Mean change from Baseline (SD)	-1.1 (0.71)
	95% CI	(-1.19, -0.95)
	p-value	<.001

Source: Listing 16.2.6.2 adapted from Table 14.2.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test. mITT = Modified Intent-to-treat. CI = Confidence Interval, MI = Multiple Imputation,
LOCF = Last observation-carried forward, The results obtained in each model are compared in this table.

12.2.2.5 Clinical Global Impression - Change (CGI-C) in mITT-C Population

The mean rating of change from baseline in Clinical Global Impression – Change (CGI-C) Score at Weeks 12, Week 24, Week 36, Week and 46 (or at early discontinuation) for the comparative evenamide groups, as well as overall evenamide group, for the mITT-C Population is presented in Table 14.2.3.1d and by subject details in Listing 16.2.6.3.

At Week 12, the mean (SD) of the CGI-C score in mITT-C population was 2.9 (0.65), which decreased to 2.7 (0.86) by Week 46, in the overall evenamide group, indicating continuing improvement in overall severity of illness. (Table 12-37).

Mean (SD) CGI-C scores recorded at Week 12 were 2.9 (0.77), 2.9 (0.64), 2.9 (0.65) in a 7.5 mg,15 mg and 30 mg bid evenamide treatment groups, respectively. Mean (SD) scores at Week 46 were 2.6 (0.90), 2.6 (0.77), 2.8 (0.92) in 7.5 mg,15 mg and 30 mg bid evenamide treatment groups, respectively.

Table 12-37: Clinical Global Impression Scale in mITT-C population

Visit	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
Week 12	n	39	41	40	120
	Mean (SD)	2.9 (0.77)	2.9 (0.64)	2.9 (0.53)	2.9 (0.65)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1,4	2,4	2,4	1,4
Week 24	n	39	41	40	120
	Mean (SD)	2.8 (0.78)	2.7 (0.62)	2.8 (0.56)	2.8 (0.66)

Visit	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1,4	2,4	2,4	1,4
Week 36	n	39	41	40	120
	Mean (SD)	2.7 (0.77)	2.6 (0.67)	2.8 (0.88)	2.7 (0.78)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1,4	1,4	1,6	1,6
Week 46	n	39	41	40	120
	Mean (SD)	2.6 (0.90)	2.6 (0.77)	2.8 (0.92)	2.7 (0.86)
	Median	3.0	3.0	3.0	3.0
	Min, Max	1,5	1,4	1,6	1,6

Source: Listing 16.2.6.3 adapted from table 14.2.3.1d
N - Total number of subjects in the mITT-C Population, n = number of patients,SD = Standard Deviation,
Min = Minimum, Max = Maximum, mITT-C = Modified intent-to-treat-
Completers, Change from Baseline = Post Dose - Baseline.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

12.2.3 Strauss-Carpenter Level of Functioning (LOF) Scale Results in the overall evenamide group

The Change from Baseline in LOF Total Score and Sub-scale Scores at Week 46 in the overall evenamide group for the mITT Population are presented in Table 12-38, Table 12-41, Table 12-42, Table 12-44 , with by subject details in Listings 16.2.6.4 and 16.2.6.4a.

Total Score

An increase in the LOF total score was observed at Week 46 compared to baseline for the overall evenamide group, indicating improvement in functionality of subjects after treatment.

At baseline, the mean (SD) of LOF total score recorded was 18.0 (3.80) in the overall evenamide group. At Week 46, an increase in LOF total score with a mean (SD) of 20.4 (3.86) was observed. A significant mean (SD) change from baseline of 2.4 (3.34) (95% CI: 1.82, 3.00; p<0.001) was observed in the overall evenamide group (Table 12-38)

Table 12-38: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score at Week 46 – Overall Comparisons - mITT Population.

			Evenamide (N=141)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Total Score	Baseline	n	141	
		Mean (SD)	18.0 (3.80)	
		Median	19.0	
		Min, Max	9.0, 30.0	
	Week 46	n	127	127
		Mean (SD)	20.4 (3.86)	2.4 (3.34)
		Median	20.0	2.0
		Min, Max	10.0, 31.0	-10.0, 15.0

				Evenamide (N=141)
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
		95% CI		(1.82, 3.00)
		p-value		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.3.1 Change from Baseline in Strauss-Carpenter-Level of Functioning Scale (LOF) Total Score and Sub-scale Scores Within Group Comparisons - mITT-C Population

In Table 14.2.4d, mean (SD) values of the LOF total score showed an increasing trend up to 46 weeks in all the three groups in the mITT-C Population (completers), reflecting a continuation of improvement in subjects' functioning.

At baseline, the mean (SD) of the LOF total score was recorded as 18.3 (3.76), 17.8 (4.00) and 17.9 (3.36) in 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. At Week 46, a total score with a mean (SD) of 19.8 (3.08), 20.0 (3.64) and 21.5 (4.56) was recorded, in 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, with a statistically significant mean (SD) change from baseline of 1.5 (2.42) (95% CI: 0.68, 2.24); p<0.001), 2.2 (3.64) (95% CI: 1.05, 3.34); p<0.001) and 3.7 (3.59) (95% CI: 2.53, 4.82; p<0.001) was observed in 7.5 mg, 15 mg and 30 mg *bid* evenamide treated groups, respectively (Table 12-39).

Table 12-39: Summary change from Baseline in Strauss-Carpenter-Level of Functioning Scale (LOF) Total Score Within Group Comparisons - mITT-C Population

			Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Total Score	Baseline	N	39		41		40	
		Mean (SD)	18.3 (3.76)		17.8 (4.00)		17.9 (3.36)	
		Median	19.0		18.0		19.0	
		Min, Max	9.0, 26.0		9.0, 30.0		12.0, 26.0	
	Week 12	n	39	39	41	41	40	40
		Mean (SD)	19.6 (3.13)	1.3 (2.01)	19.1 (3.76)	1.3 (2.69)	20.6 (4.60)	2.7 (3.41)
		Median	20.0	1.0	20.0	1.0	20.0	1.0
		Min, Max	10.0, 24.0	-4.0, 6.0	9.0, 26.0	-7.0, 8.0	12.0, 35.0	-1.0, 11.0
		95% CI		(0.63, 1.93)		(0.49, 2.19)		(1.63, 3.82)
		p-value		<.001		0.003		<.001
Total Score	Week 24	n	39	39	41	41	40	40
		Mean (SD)	19.5 (3.47)	1.2 (2.47)	19.8 (3.34)	2.0 (2.85)	21.1 (4.69)	3.3 (3.51)
		Median	20.0	1.0	20.0	1.0	20.0	2.5

			Evenamide 7.5 mg *BID* (N=39)		Evenamide 15 mg *BID* (N=41)		Evenamide 30 mg *BID* (N=40)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
		Min, Max	10.0, 24.0	-7.0, 6.0	10.0, 26.0	-8.0, 10.0	12.0, 35.0	-1.0, 11.0
		95% CI		(0.40, 2.01)		(1.10, 2.90)		(2.13, 4.37)
		p-value		0.004		<.001		<.001
	Week 36	n	39	39	41	41	40	40
		Mean (SD)	19.8 (3.14)	1.5 (2.51)	20.0 (3.64)	2.2 (3.71)	21.1 (4.51)	3.2 (3.45)
		Median	20.0	1.0	20.0	1.0	20.5	3.0
		Min, Max	12.0, 24.0	-7.0, 7.0	10.0, 29.0	-11.0, 15.0	12.0, 33.0	-3.0, 11.0
		95% CI		(0.67, 2.30)		(1.00, 3.34)		(2.12, 4.33)
		p-value		<.001		<.001		<.001
Total Score	Week 46	n	39	39	41	41	40	40
		Mean (SD)	19.8 (3.08)	1.5 (2.42)	20.0 (3.64)	2.2 (3.64)	21.5 (4.56)	3.7 (3.59)
		Median	20.0	1.0	20.0	2.0	22.0	3.0
		Min, Max	12.0, 24.0	-7.0, 7.0	10.0, 29.0	-10.0, 15.0	12.0, 31.0	-3.0, 12.0
		95% CI		(0.68, 2.24)		(1.05, 3.34)		(2.53, 4.82)
		p-value		<.001		<.001		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4d
Abbreviations: N - Total number of subjects in the mITT-C Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT-C = Modified intent-to-treat -Completers.
Total score is calculated as the sum of scores of the nine items in LOF. Change from Baseline = Post Dose - Baseline,
P-Value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

12.2.3.2 Change from Baseline in Strauss-Carpenter-Level of Functioning Scale (LOF) Total Score and Sub-scale Scores Within Group Comparisons - mITT-C Population – Overall

The Change from Baseline in LOF Total Score and Sub-scale Scores at Week 46 and within group comparisons for the overall evenamide group for the mITT-C Population are presented in Table 14.2.4cd, with by subject details in Listings 16.2.6.4 and Listings16.2.6.4a.

An increase (improvement) in the LOF total score was observed at Week 46 compared to baseline for the overall evenamide group, indicating improvement in functionality of subjects after treatment.

At baseline, the mean (SD) of LOF total score recorded was 18.0 (3.69) in the overall evenamide group. At Week 46, an increase in LOF total score with a mean (SD) of 20.4 (3.86) was recorded. A significant mean (SD) change from baseline of 2.5 (3.38) (95% CI: 1.84, 3.06); p<0.001) was observed in the overall evenamide group (Table 12-40).

Table 12-40: Summary change from Baseline in Strauss-Carpenter-Level of Functioning Scale (LOF) Total Score and Sub-scale Scores Within Group Comparisons - mITT-C Population – Overall

				Evenamide (N=120)
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Total Score	Baseline	n	120	
		Mean (SD)	18.0 (3.69)	
		Median	19.0	
		Min, Max	9.0, 30.0	
	Week 12	n	120	120
		Mean (SD)	19.8 (3.90)	1.8 (2.83)
		Median	20.0	1.0
		Min, Max	9.0, 35.0	-7.0, 11.0
		95% CI		(1.27, 2.29)
		p-value		<.001
Total Score	Week 24	n	120	120
		Mean (SD)	20.1 (3.91)	2.2 (3.07)
		Median	20.0	1.0
		Min, Max	10.0, 35.0	-8.0, 11.0
		95% CI		(1.60, 2.71)
		p-value		<.001
	Week 36	n	120	120
		Mean (SD)	20.3 (3.82)	2.3 (3.33)
		Median	20.0	1.0
		Min, Max	10.0, 33.0	-11.0, 15.0
		95% CI		(1.70, 2.90)
		p-value		<.001
Total Score	Week 46	n	120	120
		Mean (SD)	20.4 (3.86)	2.5 (3.38)
		Median	20.0	2.0
		Min, Max	10.0, 31.0	-10.0, 15.0
		95% CI		(1.84, 3.06)
		p-value		<.001

Source: Listing 16.2.6.4 adapted from Table14.2.4cd
N - Total number of subjects in the mITT-C Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat-Completers.
Total score is calculated as the sum of scores of the nine items in LOF. Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Social Contacts in the overall evenamide group

An increase in the LOF Social Contacts Sub-scale score was observed at Week 46 compared to baseline in the overall evenamide group, indicating improvement in frequency and quality of social contacts in subjects after treatment (Table 14.2.4c and Table 12-41).

At baseline, the mean (SD) of LOF Social Contacts Sub-scale scores recorded was 1.4 (0.94)

in the overall evenamide group. At Week 46, an increase of LOF Social Contacts Sub-scale scores, with a mean (SD) of 1.8 (1.01) and a mean (SD) change from baseline of 0.5 (0.82), in the overall evenamide group was observed.

Table 12-41: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Social Contacts) Scores at Week 46 – Overall Comparisons - mITT Population

				Evenamide (N=141)
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Social Contacts	Baseline	n	141	
		Mean (SD)	1.4 (0.94)	
		Median	1.5	
		Min, Max	0.0, 4.0	
	Week 46	n	127	127
		Mean (SD)	1.8 (1.01)	0.5 (0.82)
		Median	2.0	0.0
		Min, Max	0.0, 4.0	-2.0, 3.0
		95% CI		(0.32, 0.61)
		p-value		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Work in the overall evenamide group

A small increase in the LOF Work Sub-scale score was observed at Week 46 compared to baseline in the overall evenamide group, indicating improvement in quantity and quality of useful work in subjects after treatment (Table 12-42).

At baseline, the mean (SD) of LOF Work Sub-scale scores recorded was 1.2 (0.98) in the overall evenamide group. At Week 46, an increase of LOF Work Sub-scale scores, with a mean (SD) of 1.5 (0.98) and a mean (SD) change from baseline of 0.3 (0.85), in the overall evenamide group was observed.

Table 12-42: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Work) Scores at Week 46– Overall Comparisons - mITT Population

				Evenamide (N=141)
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Work	Baseline	n	141	
		Mean (SD)	1.2 (0.98)	
		Median	1.0	
		Min, Max	0.0, 3.0	

			Evenamide (N=141)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
	Week 46	n	127	127
		Mean (SD)	1.5 (0.98)	0.3 (0.85)
		Median	2.0	0.0
		Min, Max	0.0, 4.0	-2.0, 3.0
		95% CI		(0.13, 0.43)
		p-value		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Symptomatology in the overall evenamide group

An increase in the LOF Symptomatology Sub-scale score was observed at Week 46 compared to baseline in the overall evenamide group, indicating improvement in symptoms and the need for hospitalization in subjects after treatment (Table 12-43).

At baseline, the mean (SD) of LOF Symptomatology Sub-scale scores recorded was 2.8 (0.42) in the overall evenamide group. At Week 46, an increase of LOF Symptomatology Sub-scale scores, with a mean (SD) of 3.2 (0.41) and a mean (SD) change from baseline of 0.4 (0.43), in the overall evenamide group was observed.

Table 12-43: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Symptomatology) Scores at Week 46 – Overall Comparisons - mITT Population

			Evenamide (N=141)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Symptomatology	Baseline	n	141	
		Mean (SD)	2.8 (0.42)	
		Median	3.0	
		Min, Max	1.0, 4.0	
	Week 46	n	127	127
		Mean (SD)	3.2 (0.41)	0.4 (0.43)
		Median	3.0	0.5
		Min, Max	1.0, 3.5	-1.0, 2.0
		95% CI		(0.29, 0.44)
		p-value		<.001

Source: Listing 16.2.6.4 adapted from Table 14.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-baseline intervals of 015 are after Day 43 of 014 study dosing.

Subscale: Function in the overall evenamide group

A small increase in the LOF Function Sub-scale score was observed at Week 46 compared to baseline in the overall evenamide group, indicating improvement in ability to meet basic needs, fullness of life, and overall level of function in subjects after treatment (Table 12-44).

At baseline, the mean (SD) of LOF Function Sub-scale scores recorded was 2.5 (0.44) in the overall evenamide group. At Week 46, an increase of LOF Function Sub-scale scores, with a mean (SD) of 2.6 (0.45) and a mean (SD) change from baseline of 0.1 (0.40), in the overall evenamide group was observed.

Table 12-44: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Function) Scores at Week 46– Overall Comparisons - mITT Population

			Evenamide (N=141)	
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Function	Baseline	n	141	
		Mean (SD)	2.5 (0.44)	
		Median	2.7	
		Min, Max	1.3, 4.0	
	Week 46	n	127	127
		Mean (SD)	2.6 (0.45)	0.1 (0.40)
		Median	2.7	0.0
		Min, Max	1.3, 4.0	-1.3, 2.0
		95% CI		(-0.01, 0.13)
		p-value		0.071

Source: Listing 16.2.6.4 adapted from Table 14.2.4c
Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum,
CI = Confidence Interval, mITT = Modified intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline, P-Value = Paired t-test.
Baseline: Pre-dose of 014, Post-baseline intervals of 015 are after Day 43 of 014 study dosing.

12.3 Statistical/Analytical Issues

Detailed documentation of statistical methods is presented in Section 9.7.1 and in the Statistical Analysis Plan (Appendix 16.1.9). There were no statistical/analytical issues reported.

12.3.1 Handling of Dropouts or Missing Data

Handling of missing data is described in Section 9.7.1.2.3.

12.3.2 Interim Analyses and Data Monitoring

The following interim analyses were performed during the study to assess efficacy:

- Studies 014/015 (requested by ISMB): 6-month efficacy of first 100 patients randomized, up to and including 30 weeks (6-week duration of core study + 24-week duration of extension): Jan 2023.

- Studies 014/015: 1-year efficacy of first 100 patients randomized, up to and including 52 weeks (6-week duration of core study + 46-week duration of extension): Mar 2023
- Studies 014/015: 6-month efficacy of 132 completed patients randomized, up to and including 30 weeks (6-week duration of core study + 24-week duration of extension): July 2023.

Details are presented in Section 9.7.1.6. Safety $_{data}$ from all patients was examined periodically by an Independent Safety Monitoring Board (ISMB). Details are presented in Section 9.5.1.1.13

12.3.3 Multicenter Studies

This study was conducted in India, Sri Lanka and Italy at multiple sites. Site and country effects were not accounted for in the statistical analysis due to the unbalanced number of subjects across countries and sites.

12.3.4 Multiple Comparisons/Multiplicity

Multiplicity adjustment is detailed in Section 9.7.1.5.5.

12.3.5 Tabulation of Individual Response Data

Individual efficacy response data are provided in Appendix 16.2.6.

12.3.6 Drug Dose, Drug Concentration, and Relationships to Response

Not Applicable for this study

12.3.7 Drug-Drug and Drug-Disease Interactions

Not applicable

12.3.8 By-Subject Displays

Not applicable

12.4 Efficacy Conclusions

The secondary objectives of the study were to evaluate preliminary evidence of long-term efficacy of evenamide, based on symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S). Secondarily, efficacy was determined by the long-term effect of evenamide on daily functioning based on changes in the Strauss-Carpenter Level of Functioning (LOF) scale.

Positive and Negative Syndrome Scale (PANSS)

The PANSS, a standard scale for assessing the individual symptoms of schizophrenia, was used as the primary efficacy measure for the study. The analysis was done using within group comparisons [Primary Estimand: Effect of continuing on the randomized dose of evenamide in the extension study, as it was administered in the core study, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline (Study 014) in PANSS total score at Week 46 using a paired *t-test* for the mITT Population.]

The baseline mean value of the PANSS total score was similar in all three treatment groups. A steady improvement in the PANSS total score (lowering of score) was observed over time across all study visits (Weeks 12, 24, 36 and 46) compared to baseline in all three treatment groups (evenamide 7.5 mg, 15 mg and 30 mg *bid*), reflecting a continuation of improvement in symptoms of schizophrenia. Within group comparisons of changes from baseline in the PANSS total score were analyzed using a paired t-test. In the mITT population, as assessed by the Primary Efficacy Estimand at Week 46, the PANSS total score showed a significant mean (SD) change from baseline of -14.8 (9.12) (95% CI: -17.67, -11.83; p<0.001), -16.5 (10.47) (95% CI: -19.57, -13.35; p<0.001) and -15.0 (10.97) (95% CI: -18.51, -11.59; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by the Supportive Efficacy Estimand at Week 46, showed a significant mean (SD) change from baseline of -16.9 (7.48) (95% CI: -19.89, -13.97; p<0.001), -17.2 (10.73) (95% CI: -20.58, -13.81; p<0.001) and -15.4 (10.87) (95% CI: -18.88, -11.92; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by LOCF at Week 46, showed a significant mean (SD) change from baseline of -14.5 (8.99) (95% CI: -17.26, -11.65; p<0.001), -15.9 (10.24) (95% CI: -18.75, -13.10; p<0.001) and -15.2 (11.00) (95% CI: -18.53, -11.92; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The PANSS total score in the mITT population, as assessed by Multiple Imputation at Week 46, showed a significant mean (SD) change from baseline of -14.6 (8.92) (95% CI: -17.38, -11.82; p<0.001), -16.3 (10.25) (95% CI: -19.15, -13.50; p<0.001) and -15.4 (11.34) (95% CI: -18.85, -12.04; p<0.001) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Thus, the improvement in the PANSS total score from baseline over time up to Week 46 was supported by various models of Efficacy Estimands.

Within group comparisons of changes from baseline in the scores of the PANSS subscales (Positive Syndrome, Negative Syndrome, and General Psychopathology) were analyzed using a paired t-test for the mITT Population. A significant mean (SD) change (improvement) from baseline at Week 46 was observed in all three treatment groups for each of the subscales.

'Responder' analyses were performed by summarizing the proportion of patients in each of the evenamide groups with a specified minimum level of improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Syndrome sub-scale. By Week 46, the proportion of responders on the PANSS total score (patients who improved by at least 20% from baseline) increased to 20 of 42 (47.6%), 21 of 53 (39.6%) and 18 of 46 (39.1%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, compared to 10 of 42 (23.8%), 16 of 53 (30.2%), 9 of 46 (19.6%) responders at Week 12. A greater portion of patients showed meaningful improvement in positive symptoms alone, based on the responder analysis of PANSS Positive Syndrome sub-scale score. By Week 46, the proportion of responders on the PANSS Positive Syndrome total score (patients who improved by at least 4 points from baseline) was 29 of 42 (69.0%), 36 of 53 (67.9%) and 32 of 46 (69.6%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Thus, the proportion of patients with TRS exhibiting a clinically meaningful improvement in symptoms of schizophrenia with evenamide treatment was substantial and increased over time.

Clinical Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S)

The baseline mean value of the CGI-S was similar in all three treatment groups. A significant ($p<0.001$; paired t-test) improvement (lowering of scores) in the CGI-S was observed at all study visits (Weeks 12, 18, 24, 36 and 46) compared to baseline in all three treatment groups, indicating improvement in overall severity of illness.

The results of the paired *t-test* performed at Week 46 to analyze CGI-S change from baseline within each dose group showed a significant reduction, with mean (SD) changes from baseline of -1.1 (0.68) (95% CI: -1.27, -0.83; $p<0.001$), -1.2 (0.71) (95% CI: -1.38, -0.96; $p<0.001$) and -1.1 (0.69) (95% CI: -1.29, -0.86; $p<0.001$) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. These results were confirmed by the trends for decreasing CGI-S score (improvement) and significant ($p<0.001$) reductions observed in different models (LOCF and Multiple Imputations) of the Sensitivity Analysis on change from baseline at Week 46.

A responder analysis was performed for the CGI-S by summarizing the proportion of patients in each of the evenamide dose groups with improvement in CGI-S from baseline to endpoint. Overall, in all three treatment groups combined, the proportion of "responders" for CGI-S score of at least 2-category improvement was 11.3% at Week 12, which further improved over time to 14.9%, 23.4% and 24.1% at Week 24, Week 36 and Week 46. respectively. Overall, in all three treatment groups combined, the proportion of "responders" for CGI-S score of at least 1-category improvement was greater than 70%.

A reduction in the mean (SD) CGI-C score, was observed between Weeks 12 and 46, from 2.9 (0.79) to 2.7 (0.92) in evenamide 7.5 mg, from 2.9 (0.65) to 2.8 (0.90) in evenamide 15 mg, and from 2.9 (0.65) to 2.8 (0.90) in evenamide 30 mg *bid* treated groups, indicating continuing improvement in overall severity of illness. A responder analysis was performed considering change in each subject's condition from baseline, as indicated by the CGI-C score (CGI-C score $\leq$ 2 [indicating "much improved" or "very much improved"]). The proportion of responders based on a CGI-C score ≤ 2 increased over time, from 31% at Week 12 to 42.9% at Week 46 in the evenamide 7.5 mg *bid* treated group, from 26.4% at Week 12 to 35.8% at Week 46 in the evenamide 15 mg *bid* treated group, and from 23.9% at Week 12 to 34.8% at Week 46 in the evenamide 30 mg *bid* treated group, indicating the benefit of long-term use of evenamide in patients with TRS. The proportion of responders based on a CGI-C score ≤ 3 (indicating any improvement) at all visits within each treatment group was >70%. The proportion of responders was 76.2% at Week 12 and 78.6% at Week 46 in the evenamide 7.5 mg *bid* treated group, 81.1% at Week 12 and 71.7% at Week 46 in the evenamide 15 mg *bid* treated group, and 89.1% at Week 12 and 76.1% at Week 46 in the evenamide 30 mg *bid* treated group.

Strauss-Carpenter - Level of Functioning Scale (LOF)

The mean change from baseline in the LOF total score showed statistically significant ($p<0.001$; paired t-test) improvement (increase in score) over time across all study visits. The mean (SD) change from baseline in the LOF total score was 1.4 (2.03) (95% CI: 0.72, 1.99; $p<0.001$) at Week 12 and 1.5 (2.39) (95% CI: 0.71, 2.24; $p<0.001$) at Week 46 in the evenamide 7.5 mg *bid* treated group; 1.5 (2.70) (95% CI: 0.71, 2.23; $p<0.001$) at Week 12 and 2.2 (3.56)

(95% CI: 1.12, 3.23; p<0.001) at Week 46 in the evenamide 15 mg *bid* treated group; and 2.5 (3.26) (95% CI: 1.49, 3.43; p<0.001) at Week 12 and 3.6 (3.59) (95% CI: 2.45, 4.72; p<0.001) at Week 46 in the evenamide 30 mg *bid* treated group, indicating overall improvement in functioning.

Overall Efficacy Conclusions

The long-term efficacy of evenamide (7.5 mg, 15 mg and 30 mg *bid*) in patients with TRS was demonstrated by improvement in symptoms of schizophrenia assessed by the PANSS (total score and subscales), a decrease in disease severity assessed by the CGI-S score, overall improvement from baseline assessed by the CGI-C, and enhancement in functionality of patients assessed by the LOF. These beneficial effects, which increased over time across all the timepoints, were observed in patients with TRS not responding adequately to their stable, therapeutically active dose of a single antipsychotic medication.

13 Discussion and Overall Conclusions

13.1 Discussion

Despite the availability of numerous first (FGA) and second generation (SGA) antipsychotic drugs, the treatment of schizophrenia is still unsatisfactory, particularly for patients who are treatment-resistant. Currently, the only drug that has been approved for use in TRS patients is clozapine, that appears to act through multiple mechanisms, although the predominant activity appears to be through non-dopaminergic modulation. To date, no other first or second-generation antipsychotic, or any other psychotherapeutic agent, or new chemical entity, has demonstrated efficacy in this patient population, irrespective of whether it was used as monotherapy or as an add-on therapy (Buckley et al., 2001; Kane et al., 2022). However, ~30% of the patients with TRS remain symptomatic despite being treated with clozapine (Elkis and Buckley, 2016), and its overall usage in the US is limited to approximately 5% in the TRS population (Warnez et al., 2014).

A major finding that emerged is that patients who are responsive to 5-HT2/D2 modulators exhibit increased dopamine synthesis activity in the brain, while this is not noted in controls or in patients with TRS; conversely, TRS patients demonstrate increased levels of glutamine in the hippocampus, a finding not observed in healthy volunteers or in 5-HT2/D2 antipsychotic responders. This led to the exploration of selective glutamate modulation as a therapeutic modality for TRS patients. Evenamide, a highly selective VGSC blocker, is associated with inhibition of excessive release of glutamate: studies in rodents have established that ineffective doses of evenamide, when added to ineffective doses of clozapine, are able to reverse deficits in PPI noted with ketamine, or other glutamatergic antagonists (PCP, MK-801, etc.) (Anand et al., 2018; Bortolato et al., 2018). Evenamide Studies 014 and 015 were performed with the objective of determining tolerability and safety and preliminary evidence of efficacy of 3 fixed doses of evenamide used as add on to TRS patients not benefiting from their current antipsychotic medication (any oral or depot antipsychotics, except clozapine). The characteristics of the patients enrolled in Study 014 matched the demographic and disease characteristics noted in TRS patients in other studies.

The very low dropout rate in Study 014 (5%) led to 144 subjects continuing in Study 015 (i.e., the extension of Study 014). The data at 1-year again confirm the good tolerability of evenamide at all doses (7.5, 15, and 30 mg bid), as the retention rate for patients entering Study 015 was ~85%.

Safety results collected during the one-year treatment period, in addition to the high completion rate and the low dropout rate for adverse events (N=2), suggest that evenamide was very well tolerated at all doses. Laboratory tests, vital signs, physical, neurological and eye examinations, and ECG evaluations did not show any pattern of clinically notable effects associated with any of the three doses of evenamide. No increase in extrapyramidal symptoms (ESRS-A), or depressive symptoms (CDSS) was observed.

During the follow-up period of up to 1-year, only two subjects experienced SAEs. One patient experienced a SAE of dilutional hyponatremia leading to seizures 26 days after he received his last dose of evenamide (15 mg *bid*); according to the judgement of the investigator, the event was related to the ingestion of a large volume of water and was controlled by administration of 100 mL i.v. bolus of 3 percent saline. Another patient died suddenly due to unknown causes after 6-months of treatment with evenamide 30 mg *bid* as add-on to olanzapine and trihexyphenidyl; this patient was experiencing improvement of his psychotic symptoms (>20% improvement from baseline in PANSS Total), and no clinically significant abnormalities were noted in vital signs, ECG, or laboratory evaluations, and no adverse findings were reported. An autopsy indicated the presence of several atherosclerotic plaques suggestive of a possible contribution of cardiovascular dysfunction. Overall, no severe adverse events suggestive of involvement of evenamide were reported; however, as a definitive cause could not be established, a contribution of evenamide could not be fully excluded.

All efficacy measures showed a sustained and increasing improvement over time up to 1-year in the mean change from baseline, with no major differences noted between the three treatment groups, as already shown in Study 014. Similarly, the responder rate (≥20% improvement from baseline) for the PANSS Total Score increased from 15.4% (6-weeks) to 41.8% at 1-year, the proportion of patients with a CGI-S 2-category improvement increased from 10.3% (6-weeks) to 24.1% at 1-year, while the proportion who were responders on the CGI-C (at least “much improved”) increased from 24.4% (6-weeks) to 37.6 % at 1-year, indicating a dramatic increase in the proportion of patients with a clinically meaningful improvement compared Week 6 (endpoint of Study 014). This pattern of improvement with the addition of an antipsychotic to patients not responding to their current antipsychotic medication has never been reported in any prior study in patients with schizophrenia or with TRS.

Obviously, the caveats of Study 014/015 need to be addressed to justify the acceptability of the efficacy data. The study treatments were not blinded and not controlled by a placebo arm, and therefore, rater bias in efficacy ratings or a placebo effect cannot be excluded. However, the Sponsor is unaware of any study performed in patients with schizophrenia where the placebo (spontaneous) responder rate doubles or triples over a period of 1-year. Furthermore, the pattern of change from baseline is consistent across the efficacy measures, although the magnitude of the benefit varied among the PANSS, CGI-S, and CGI-C.

Another shortcoming of the study is that ~88% of patients were enrolled from a single country (i.e., India), also due to issues with the concurrence of the Covid-19 pandemic, raising the possibility that local practices may have precluded the generalizability of these results for a global audience. However, review of data from published placebo-controlled studies in patients with psychotic disorders with significant contribution from India did not detect any trend indicating that the results in India were more positive than in other countries. (Khanna et al., 2005; Potkin et al., 2006; Geffen et al., 2012; Cantillon et al., 2017).

13.2 Overall Conclusions

The results of Study 015 indicate that evenamide at doses of 7.5 to 30 mg *bid* is well tolerated and safe for up to and including 1-year of treatment, based on the high retention rate, very low number of patients discontinuing due to adverse events, and results of all safety evaluations indicating a lack of new treatment-emergent abnormalities. Preliminary evidence of efficacy of fixed doses of evenamide of 7.5, 15 and 30 mg *bid* as an add-on treatment up to 1-year in patients with TRS was demonstrated by the sustained improvement and clinically relevant benefit noted in all efficacy measures, indicating a pattern of unique improvement rarely observed in this patient population.

14 Tables, Figures, and Graphs Referred to but not included in the Text

14.1 Disposition, Demographic, and Baseline Data Summary Figures and Tables

14.2 Efficacy Data Summary Figures and Tables

14.3 Safety Data Summary Figures and Tables

Table 14.1.3.1.2
Demographics and Baseline Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Age (years)	n	42	53	46	141
	Mean (SD)	39.0 (10.48)	37.0 (10.13)	38.7 (9.36)	38.1 (9.96)
	Median	37.0	35.0	39.0	37.0
	Min, Max	23, 68	21, 62	20, 64	20, 68
Weight (kg)	n	42	53	46	141
	Mean (SD)	67.9 (15.38)	67.4 (12.65)	67.5 (13.43)	67.6 (13.67)
	Median	67.1	66.2	65.0	66.2
	Min, Max	42.6, 120.0	44.7, 91.0	42.0, 95.7	42.0, 120.0
Height (cm)	n	42	53	46	141
	Mean (SD)	164.3 (10.06)	164.2 (7.92)	163.4 (6.58)	164.0 (8.19)
	Median	164.9	165.9	164.0	164.0
	Min, Max	136.5, 183.0	145.0, 182.6	149.4, 181.0	136.5, 183.0

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.2
Demographics and Baseline Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
BMI (kg/m2)	n	42	53	46	141
	Mean (SD)	25.1 (4.91)	25.0 (4.67)	25.3 (4.86)	25.1 (4.77)
	Median	24.7	25.0	24.5	24.6
	Min, Max	17.28, 37.12	17.31, 34.79	15.62, 37.70	15.62, 37.70
Sex					
Male	n(%)	30(71.4)	38(71.7)	34(73.9)	102(72.3)
Female	n(%)	12(28.6)	15(28.3)	12(26.1)	39(27.7)
Childbearing Potential [a]					
Yes	n(%)	9(75.0)	9(60.0)	9(75.0)	27(69.2)
No	n(%)	3(25.0)	6(40.0)	3(25.0)	12(30.8)
Race					
American Indian or Alaska Native	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.2
Demographics and Baseline Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Asian	n(%)	41(97.6)	53(100.0)	45(97.8)	139(98.6)
Native Hawaiian or Other Pacific Islander	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Black or African American	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
White	n(%)	1(2.4)	0(0.0)	1(2.2)	2(1.4)
Other	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown or Not Reported	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ethnicity					
Hispanic or Latino	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Not Hispanic Or Latino	n(%)	42(100.0)	53(100.0)	46(100.0)	141(100.0)
Education					
1-8 years	n(%)	10(23.8)	10(18.9)	9(19.6)	29(20.6)
9-16 years	n(%)	32(76.2)	37(69.8)	31(67.4)	100(70.9)
>16 years	n(%)	0(0.0)	6(11.3)	6(13.0)	12(8.5)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.2
Demographics and Baseline Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Marital Status					
Married	n(%)	17(40.5)	23(43.4)	20(43.5)	60(42.6)
Single	n(%)	23(54.8)	24(45.3)	22(47.8)	69(48.9)
Stable union	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Widow / Widower	n(%)	0(0.0)	2(3.8)	0(0.0)	2(1.4)
Divorced	n(%)	2(4.8)	4(7.5)	4(8.7)	10(7.1)
Employment					
Full-Time Employment	n(%)	3(7.1)	6(11.3)	3(6.5)	12(8.5)
Not employed	n(%)	35(83.3)	42(79.2)	35(76.1)	112(79.4)
Part-Time Employment	n(%)	4(9.5)	5(9.4)	8(17.4)	17(12.1)
Housing Status					
Living alone	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.2
Demographics and Baseline Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Living with family	n(%)	42(100.0)	53(100.0)	46(100.0)	141(100.0)
Living with companion	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living in residential care	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living in institution	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living alone, with a caregiver	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Duration of Illness - Schizophrenia (Years)[a]	n	42	53	46	141
	Mean (SD)	7.0 (2.32)	6.2 (3.00)	7.2 (3.56)	6.8 (3.03)
	Median	7.6	6.2	7.3	6.7
	Min,Max	1,13	1,15	1,15	1,15
Duration of Current Episode of Schizophrenia (Months)[b]	n	42	53	46	141
	Mean (SD)	8.8 (5.68)	8.7 (5.07)	6.3 (3.32)	8.0 (4.88)
	Median	6.7	8.4	5.7	6.4
	Min,Max	3,25	2,23	2,15	2,25

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)

Source: Listing 16.2.4.3.1, Listing 16.2.15.
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
mITT = Modified intent-to-treat, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of randomization - Date of First diagnosis + 1)/365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1)/30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother’s brother, father's sister's son,son, uncle, brother of father, daughter, paternal side - father's brother.

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Number of Psychiatric Hospitalization	n	42	53	46	141
	Mean (SD)	0.2 (0.51)	0.3 (0.75)	0.4 (0.83)	0.3 (0.71)
	Median	0.0	0.0	0.0	0.0
	Min,Max	0,2	0,4	0,3	0,4

Source: Listing 16.2.4.3.1, Listing 16.2.15.
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
mITT = Modified intent-to-treat, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of randomization - Date of First diagnosis + 1)/365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1)/30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother’s brother, father's sister's son,son, uncle, brother of father, daughter, paternal side - father's brother.

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Family History of Schizophrenia					
None	n (%)	30 (71.4)	40 (75.5)	36 (78.3)	106 (75.2)
1st Degree Relatives [c]	n (%)	7 (16.7)	7 (13.2)	6 (13.0)	20 (14.2)
Father	n (%)	1 (2.4)	2 (3.8)	2 (4.3)	5 (3.5)
Mother	n (%)	2 (4.8)	4 (7.5)	1 (2.2)	7 (5.0)
Brother	n (%)	2 (4.8)	1 (1.9)	2 (4.3)	5 (3.5)
Sister	n (%)	2 (4.8)	0 (0.0)	1 (2.2)	3 (2.1)

Source: Listing 16.2.4.3.1, Listing 16.2.15.
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
mITT = Modified intent-to-treat, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of randomization - Date of First diagnosis + 1)/365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1)/30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother’s brother, father's sister's son,son, uncle, brother of father, daughter, paternal side - father's brother.

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
2nd Degree Relatives [d]	n (%)	2 (4.8)	2 (3.8)	0 (0.0)	4 (2.8)
Paternal Grandfather	n (%)	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.7)
Paternal Grandmother	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal Grandfather	n (%)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Maternal Grandmother	n (%)	1 (2.4)	1 (1.9)	0 (0.0)	2 (1.4)
other	n (%)	5 (11.9)	5 (9.4)	5 (10.9)	15 (10.6)
Number of subjects with other psychiatric disorders	n (%)	3 (7.1)	6 (11.3)	11 (23.9)	20 (14.2)

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)

Source: Listing 16.2.4.3.1, Listing 16.2.15.
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
mITT = Modified intent-to-treat, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of randomization - Date of First diagnosis + 1)/365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1)/30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother’s brother, father's sister's son,son, uncle, brother of father, daughter, paternal side - father's brother.

Table 14.1.3.2.2
Disease Characteristics
mITT Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=42)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=141)
Calgary Depression Scale for Schizophrenia (CDSS)					
CDSS Total Score	n	42	53	46	141
	Mean (SD)	0.4 (0.96)	0.6 (1.33)	0.8 (1.58)	0.6 (1.32)
	Median	0.0	0.0	0.0	0.0
	Min,Max	0,4	0,6	0,6	0,6

Source: Listing 16.2.4.3.1, Listing 16.2.15.
N - Total number of subjects in the mITT Population, n - Number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under mITT Population,
mITT = Modified intent-to-treat, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of Illness - Schizophrenia (Years) = (Date of randomization - Date of First diagnosis + 1)/365
[b] Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode + 1)/30.4167
[c] 1st degree relatives include patient's parents, siblings, and children.
[d] 2nd degree relatives include patient's grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings.
Other relatives include: maternal uncle, father's brother's son, mother’s brother, father's sister's son,son, uncle, brother of father, daughter, paternal side - father's brother.

Table 14.1.3.3.1
Medical History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Number of Subjects with any Medical History	8 (17.8)	12 (22.6)	9 (19.6)	29 (20.1)
Metabolism and nutrition disorders	4 (8.9)	4 (7.5)	2 (4.3)	10 (6.9)
Diabetes mellitus	4 (8.9)	3 (5.7)	2 (4.3)	9 (6.3)
Dyslipidaemia	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Hyperlipidaemia	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Type 2 diabetes mellitus	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Surgical and medical procedures	1 (2.2)	3 (5.7)	2 (4.3)	6 (4.2)
Salpingectomy	0 (0.0)	2 (3.8)	1 (2.2)	3 (2.1)
Female sterilisation	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Arm amputation	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Medical History is coded with MedDRA version 23.0.
Subjects counted only once for a given preferred term.

Table 14.1.3.3.1
Medical History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Otoplasty	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Endocrine disorders	0 (0.0)	1 (1.9)	3 (6.5)	4 (2.8)
Hypothyroidism	0 (0.0)	1 (1.9)	3 (6.5)	4 (2.8)
Vascular disorders	1 (2.2)	1 (1.9)	1 (2.2)	3 (2.1)
Hypertension	1 (2.2)	1 (1.9)	1 (2.2)	3 (2.1)
Gastrointestinal disorders	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Gastrooesophageal reflux disease	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Haemorrhoids	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)
Adenoma benign	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Medical History is coded with MedDRA version 23.0.
Subjects counted only once for a given preferred term.

Reference Datasets:ADSL,MH
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.1.3.3.1.sas
Programmer:SH
Date of Extraction:18DEC2023 Final - 18JAN2024:11:09

Table 14.1.3.3.1
Medical History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Benign breast neoplasm	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Nervous system disorders	1 (2.2)	1 (1.9)	0 (0.0)	2 (1.4)
Akathisia	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Extrapyramidal disorder	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Reproductive system and breast disorders	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Erectile dysfunction	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Sexual dysfunction	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Anaemia	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Eye disorders	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Medical History is coded with MedDRA version 23.0.
Subjects counted only once for a given preferred term.

Table 14.1.3.3.1
Medical History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Cataract	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Pterygium	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
General disorders and administration site conditions	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Atrophy	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Infections and infestations	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Chikungunya virus infection	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Skin and subcutaneous tissue disorders	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Eczema	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Lichen planus	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Medical History is coded with MedDRA version 23.0.
Subjects counted only once for a given preferred term.

Table 14.1.3.3.2
Summary of Other Psychiatric History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Number of Subjects with any Other Psychiatric History	3 (6.7)	6 (11.3)	11 (23.9)	20 (13.9)
Psychiatric disorders	3(6.7)	6(11.3)	11(23.9)	20(13.9)
Mental disorder	1 (2.2)	2 (3.8)	8 (17.4)	11 (7.6)
Depression	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Insomnia	2 (4.4)	1 (1.9)	0 (0.0)	3 (2.1)
Acute psychosis	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.3.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Reported term.
Psychiatric History is coded with MedDRA version 23.0.
The table summarizes all psychiatric history other than Schizophrenia.

Table 14.1.3.3.2
Summary of Other Psychiatric History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Anxiety	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Brief psychotic disorder, with postpartum onset	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Obsessive-compulsive disorder	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Sleep disorder	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.3.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Reported term.
Psychiatric History is coded with MedDRA version 23.0.
The table summarizes all psychiatric history other than Schizophrenia.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Any Prior Medication	8 (17.8)	14 (26.4)	16 (34.8)	38 (26.4)
Tertiary Amines	7 (15.6)	9 (17.0)	9 (19.6)	25 (17.4)
Trihexyphenidyl	7 (15.6)	9 (17.0)	9 (19.6)	25 (17.4)
Trihexyphenidyl Hydrochloride	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Benzodiazepine Derivatives	3 (6.7)	7 (13.2)	6 (13.0)	16 (11.1)
Nitrazepam	2 (4.4)	4 (7.5)	1 (2.2)	7 (4.9)
Lorazepam	1 (2.2)	2 (3.8)	3 (6.5)	6 (4.2)
Clonazepam	0 (0.0)	0 (0.0)	2 (4.3)	2 (1.4)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Diazepam	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Chlordiazepoxide	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Diazepines, Oxazepines, Thiazepines And Oxepines	1 (2.2)	1 (1.9)	2 (4.3)	4 (2.8)
Olanzapine	1 (2.2)	1 (1.9)	2 (4.3)	4 (2.8)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Vitamins, Other Combinations	1 (2.2)	2 (3.8)	1 (2.2)	4 (2.8)
Carbohydrates Nos;colecalciferol;copper;dexpanthenol ;iodine;lysine Hydrochloride;nicotinamide;potassium Iodide;pyridoxine Hydrochloride;retinol;riboflavin;selen ium;vitamin B1 Nos;vitamin B12 Nos;vitam	1 (2.2)	1 (1.9)	1 (2.2)	3 (2.1)
Ascorbic Acid;vitamin B Nos	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Phenothiazines With Piperazine Structure	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Trifluoperazine	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Vitamin B-Complex, Plain	0 (0.0)	2 (3.8)	1 (2.2)	3 (2.1)
Vitamin B Complex	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Biotin;cyanocobalamin;folic Acid;nicotinamide;pantothenic Acid;pyridoxine;riboflavin;thiamine	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Other Antipsychotics	0 (0.0)	0 (0.0)	2 (4.3)	2 (1.4)
Aripiprazole	0 (0.0)	0 (0.0)	2 (4.3)	2 (1.4)
Selective Serotonin Reuptake Inhibitors	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Escitalopram Oxalate	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Fluoxetine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Sertraline	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Benzodiazepine Related Drugs	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Zolpidem	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Biguanides	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Metformin	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Centrally Acting Sympathomimetics	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Armodafinil	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Modafinil	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Folic Acid And Derivatives	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Folic Acid	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Heparins Or Heparinoids For Topical Use	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Benzyl Nicotinate;heparin	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Influenza Vaccines	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Influenza Vaccine	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Iron Bivalent, Oral Preparations	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Ferrous Fumarate	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Iron In Other Combinations	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Copper Sulfate;cyanocobalamin;ferrous Fumarate;folic Acid;lysine Hydrochloride;manganese Sulfate;zinc Sulfate	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Other Antiallergics	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Olopatadine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Other Antidepressants	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Lamotrigine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Other Antihistamines For Systemic Use	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Azelastine Hydrochloride	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Sulfonylureas	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Glimepiride	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Zinc	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Zinc Sulfate	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Concomitant Medication				
Any Concomitant Medication	39 (86.7)	46 (86.8)	39 (84.8)	124 (86.1)
Tertiary Amines	28 (62.2)	38 (71.7)	30 (65.2)	96 (66.7)
Trihexyphenidyl	27 (60.0)	38 (71.7)	29 (63.0)	94 (65.3)
Biperiden	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Trihexyphenidyl Hydrochloride	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Benzodiazepine Derivatives	17 (37.8)	17 (32.1)	10 (21.7)	44 (30.6)
Lorazepam	15 (33.3)	16 (30.2)	5 (10.9)	36 (25.0)
Clonazepam	1 (2.2)	0 (0.0)	4 (8.7)	5 (3.5)
Alprazolam	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Benzodiazepine Derivatives	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Clobazam	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Diazepam	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Biguanides	5 (11.1)	4 (7.5)	5 (10.9)	14 (9.7)
Metformin	5 (11.1)	4 (7.5)	5 (10.9)	14 (9.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Diazepines, Oxazepines, Thiazepines And Oxepines	3 (6.7)	2 (3.8)	4 (8.7)	9 (6.3)
Quetiapine	3 (6.7)	2 (3.8)	4 (8.7)	9 (6.3)
Benzodiazepine Related Drugs	3 (6.7)	3 (5.7)	0 (0.0)	6 (4.2)
Zolpidem	3 (6.7)	3 (5.7)	0 (0.0)	6 (4.2)
Proton Pump Inhibitors	4 (8.9)	0 (0.0)	2 (4.3)	6 (4.2)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Domperidone;pantoprazole	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Domperidone;omeprazole	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Omeprazole	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Pantoprazole	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Rabeprazole	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Hmg Coa Reductase Inhibitors	2 (4.4)	2 (3.8)	1 (2.2)	5 (3.5)
Atorvastatin	2 (4.4)	2 (3.8)	1 (2.2)	5 (3.5)
Sulfonylureas	2 (4.4)	2 (3.8)	1 (2.2)	5 (3.5)
Glimepiride	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Gliclazide	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Progestogens And Estrogens, Fixed Combinations	0 (0.0)	2 (3.8)	2 (4.3)	4 (2.8)
Desogestrel;ethinylestradiol	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Ethinylestradiol;levonorgestrel	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Thyroid Hormones	0 (0.0)	1 (1.9)	3 (6.5)	4 (2.8)
Levothyroxine Sodium	0 (0.0)	1 (1.9)	3 (6.5)	4 (2.8)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Angiotensin Ii Receptor Blockers (Arbs), Plain	0 (0.0)	2 (3.8)	1 (2.2)	3 (2.1)
Losartan	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Telmisartan	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Anilides	1 (2.2)	0 (0.0)	2 (4.3)	3 (2.1)
Paracetamol	1 (2.2)	0 (0.0)	2 (4.3)	3 (2.1)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Multivitamins, Plain	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Vitamins Nos	1 (2.2)	2 (3.8)	0 (0.0)	3 (2.1)
Other Antipsychotics	0 (0.0)	2 (3.8)	1 (2.2)	3 (2.1)
Valproate Semisodium	0 (0.0)	2 (3.8)	1 (2.2)	3 (2.1)
Combinations Of Vitamins	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Cyanocobalamin;panthenol;pyridoxine Hydrochloride;thiamine Hydrochloride	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Vitamins Nos	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Expectorants	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Ambroxol;guaifenesin	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Hedera Helix	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Iron In Other Combinations	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Cyanocobalamin;ferrous Ascorbate;folic Acid	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Cyanocobalamin;folic Acid;iron;zinc	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Progestogens And Estrogens, Sequential Preparations	0 (0.0)	0 (0.0)	2 (4.3)	2 (1.4)
Desogestrel;ethinylestradiol	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Ethinylestradiol;levonorgestrel	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Tetracyclines	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Doxycycline	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Doxycycline;lactobacillus Nos	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Agents For Treatment Of Hemorrhoids And Anal Fissures For Topical Use	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Lidocaine Hydrochloride;metronidazole;sucralfate	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Amino Acids And Derivatives	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Amino Acids And Derivatives	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Bioflavonoids	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Diosmin;hesperidin	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Butyrophenone Derivatives	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Haloperidol	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Calcium, Combinations With Vitamin D And/Or Other Drugs	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Calcium Carbonate;colecalciferol;sodium	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Contact Laxatives	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Bisacodyl	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Corticosteroids, Very Potent, Other Combinations	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Clobetasol Propionate;salicylic Acid	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Enzymes	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Serrapeptase	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
H2-Receptor Antagonists	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Ranitidine Hydrochloride	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Influenza Vaccines	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Influenza Vaccine	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Local Anesthetics	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
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Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Lidocaine;nifedipine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Macrolides	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Azithromycin	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Opium Alkaloids And Derivatives	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Chlorphenamine Maleate;dextromethorphan Hydrobromide;phenylephrine	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Oral Rehydration Salt Formulations	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Oral Rehydration Salt Formulations	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Osmotically Acting Laxatives	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Lactulose	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Other Antidepressants	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Venlafaxine	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Other Antiinflammatory And Antirheumatic Agents, Non-Steroids	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Nimesulide	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Other Antiinflammatory/Antirheumatic Agents In Combination With Other Drugs	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Aceclofenac;paracetamol;serrapeptase	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Other Antivirals	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Favipiravir	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Other Anxiolytics	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Sertraline	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Other Dermatologicals	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Biotin;calcium Pantothenate;folic Acid;zinc Oxide	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Other Systemic Hemostatics	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Etamsilate	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Piperazine Derivatives	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Cetirizine Hydrochloride	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Second-Generation Cephalosporins	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Cefuroxime	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Selective Immunosuppressants	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Apremilast	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Selective Serotonin Reuptake Inhibitors	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Sertraline	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Vitamin B-Complex, Plain	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Biotin;cyanocobalamin;folic Acid;nicotinamide;pantothenic Acid;pyridoxine;riboflavin;thiamine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Vitamins	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Vitamins Nos	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Vitamins, Other Combinations	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)
Ascorbic Acid;vitamin B Nos	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.1.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
ATC4 = Anatomical Therapeutic Chemical Level 4
Medications are coded with WHO Drug Dictionary version B3 MAR2019.
Subjects counted only once if the medications belong to the same extended ATC4 classification.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medications
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Prior Antipsychotic Medication Any Prior Antipsychotic Medication During Last 5 Years	45 (100.0)	53 (100.0)	46 (100.0)	144 (100.0)
Risperidone	36 (80.0)	44 (83.0)	41 (89.1)	121 (84.0)
Olanzapine	34 (75.6)	40 (75.5)	29 (63.0)	103 (71.5)
Aripiprazole	10 (22.2)	15 (28.3)	16 (34.8)	41 (28.5)
Quetiapine	15 (33.3)	9 (17.0)	10 (21.7)	34 (23.6)

Source: Listing 16.2.4.4.3.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medications
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Trifluoperazine	8 (17.8)	10 (18.9)	9 (19.6)	27 (18.8)
Haloperidol	9 (20.0)	6 (11.3)	7 (15.2)	22 (15.3)
Amisulpride	7 (15.6)	3 (5.7)	8 (17.4)	18 (12.5)
Paliperidone	7 (15.6)	3 (5.7)	5 (10.9)	15 (10.4)
Fluphenazine	0 (0.0)	3 (5.7)	3 (6.5)	6 (4.2)

Source: Listing 16.2.4.4.3.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medications
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Chlorpromazine	1 (2.2)	2 (3.8)	2 (4.3)	5 (3.5)
Trifluoperazine Hydrochloride	0 (0.0)	1 (1.9)	3 (6.5)	4 (2.8)
Blonanserin	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Flupentixol	0 (0.0)	1 (1.9)	2 (4.3)	3 (2.1)
Fluphenazine Decanoate	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)

Source: Listing 16.2.4.4.3.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medications
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Lurasidone	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Quetiapine Fumarate	1 (2.2)	0 (0.0)	1 (2.2)	2 (1.4)
Zuclopenthixol	0 (0.0)	1 (1.9)	1 (2.2)	2 (1.4)
Cariprazine	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Fluoxetine;olanzapine	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.3.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medications
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Iloperidone	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.7)
Lurasidone Hydrochloride	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Risperidone;trihexyphenidyl	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.3.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Subjects counted only once for a Drug Name.

Table 14.1.4.3
Summary of Rescue Medications
Safety Population

Rescue Medication Name	Statistic	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
No. Of Subjects Who Received At Least One Rescue Medication	n (%)	2 (4.4)	0 (0.0)	0 (0.0)	2 (1.4)
Risperidone	n (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)
Trifluoperazine	n (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.7)

Source: Listing 16.2.4.4.3.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Dose adjustments for atypical antipsychotics of 25% or more, upwards, or downwards or any antipsychotic administered for Exacerbation Of Schizophrenia.
Not temporary (more than 5 days) in the treatment period due to significant worsening are considered rescue medications.
Refer to study protocol or statistical analysis plan for the full definition of rescue medication.

Table 14.2.1.2d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score Using Within Group Comparisons
(Supportive Estimand Hypothetical) mITT-C Population

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	39		41		40	
	Mean (SD)	79.8 (5.36)		79.0 (5.55)		78.7 (4.27)	
	Median	81.0		80.0		78.5	
	Min, Max	72, 89		70, 89		71, 87	
Week 12	n	36	36	41	41	40	40
	Mean (SD)	69.3 (9.88)	-10.4 (7.23)	67.7 (7.69)	-11.3 (7.74)	68.2 (6.00)	-10.5 (5.41)
	Median	69.0	-11.5	67.0	-10.0	68.0	-10.0
	Min, Max	51, 89	-28, 2	53, 87	-33, 3	58, 80	-25, -1
	95% CI		(-12.89, -8.00)		(-13.74, -8.85)		(-12.26, -8.79)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers,
Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score Using Within Group Comparisons
(Supportive Estimand Hypothetical) mITT-C Population

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	33	33	41	41	40	40
	Mean (SD)	67.9 (9.84)	-12.0 (6.54)	64.9 (8.06)	-14.1 (8.71)	65.6 (7.43)	-13.1 (7.30)
	Median	68.0	-13.0	64.0	-16.0	64.0	-12.5
	Min, Max	51, 89	-24, 0	46, 86	-40, -1	43, 82	-35, 0
	95% CI		(-14.35, -9.71)		(-16.82, -11.32)		(-15.44, -10.76)
	p-value		<.001		<.001		<.001
Week 36	n	29	29	41	41	40	40
	Mean (SD)	64.7 (8.68)	-14.8 (6.65)	63.0 (8.53)	-15.9 (9.39)	64.9 (8.63)	-13.9 (8.70)
	Median	63.0	-16.0	63.0	-16.0	63.5	-13.5
	Min, Max	51, 84	-27, -2	43, 85	-43, -2	47, 87	-34, 6
	95% CI		(-17.36, -12.30)		(-18.89, -12.96)		(-16.66, -11.09)

Table 14.2.1.2d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score Using Within Group Comparisons
(Supportive Estimand Hypothetical) mITT-C Population

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers,
Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score Using Within Group Comparisons
(Supportive Estimand Hypothetical) mITT-C Population

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	27	27	41	41	40	40
	Mean (SD)	62.2 (9.03)	-16.9 (7.48)	61.8 (9.85)	-17.2 (10.73)	63.3 (10.70)	-15.4 (10.87)
	Median	59.0	-18.0	60.0	-15.0	63.0	-14.0
	Min, Max	52, 83	-29, -3	39, 83	-47, 2	35, 85	-44, 4
	95% CI		(-19.89, -13.97)		(-20.58, -13.81)		(-18.88, -11.92)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers,
Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT Population - Overall

		Evenamide (N=141)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	141		
	Mean (SD)	79.5 (5.04)		
	Median	80.0		
	Min, Max	70, 89		
Week 12	n	136	136	136
	Mean (SD)	68.4 (8.18)	-11.1 (7.16)	-14.0 (8.79)
	Median	67.0	-10.5	-13.5
	Min, Max	51, 89	-33, 3	-39, 4
	95% CI		(-12.33, -9.90)	
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT Population - Overall

		Evenamide (N=141)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 24	n	125	125	125
	Mean (SD)	66.5 (8.45)	-12.8 (7.60)	-16.1 (9.30)
	Median	66.0	-13.0	-15.3
	Min, Max	43, 89	-40, 0	-47, 0
	95% CI		(-14.16, -11.47)	
	p-value		<.001	
Week 36	n	113	113	113
	Mean (SD)	64.2 (8.57)	-14.9 (8.47)	-18.7 (10.20)
	Median	63.0	-15.0	-19.3
	Min, Max	43, 87	-43, 6	-50, 7
	95% CI		(-16.45, -13.30)	

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT Population - Overall

			Evenamide (N=141)	
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT Population - Overall

		Evenamide (N=141)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 46	n	108	108	108
	Mean (SD)	62.5 (9.91)	-16.5 (10.02)	-20.7 (12.07)
	Median	61.5	-16.0	-20.4
	Min, Max	35, 85	-47, 4	-55, 5
	95% CI		(-18.37, -14.55)	
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, n = number of patients,
SD = Standard Deviation, CI = Confidence Interval, mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT-C Population - Overall

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	120		
	Mean (SD)	79.2 (5.07)		
	Median	79.0		
	Min, Max	70, 89		
Week 12	n	117	117	117
	Mean (SD)	68.3 (7.90)	-10.8 (6.81)	-13.6 (8.40)
	Median	67.0	-10.0	-13.3
	Min, Max	51, 89	-33, 3	-38, 4
	95% CI		(-12.02, -9.52)	
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients, SD = Standard Deviation,
CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADPANSS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.2.1.2cd.sas
Programmer:AG
Date of Extraction:18DEC2023 Final - 18JAN2024:14:24

Table 14.2.1.2cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT-C Population - Overall

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 24	n	114	114	114
	Mean (SD)	66.0 (8.43)	-13.1 (7.62)	-16.6 (9.29)
	Median	64.0	-13.0	-16.5
	Min, Max	43, 89	-40, 0	-47, 0
	95% CI		(-14.55, -11.73)	
	p-value		<.001	
Week 36	n	110	110	110
	Mean (SD)	64.1 (8.57)	-14.9 (8.46)	-18.7 (10.18)
	Median	63.0	-15.0	-19.1
	Min, Max	43, 87	-43, 6	-50, 7
	95% CI		(-16.49, -13.29)	

Table 14.2.1.2cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT-C Population - Overall

			Evenamide (N=120)	
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients, SD = Standard Deviation,
CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.2cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
(Supportive Estimand Hypothetical) mITT-C Population - Overall

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 46	n	108	108	108
	Mean (SD)	62.5 (9.91)	-16.5 (10.02)	-20.7 (12.07)
	Median	61.5	-16.0	-20.4
	Min, Max	35, 85	-47, 4	-55, 5
	95% CI		(-18.37, -14.55)	
	p-value		<.001	

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients, SD = Standard Deviation,
CI = Confidence Interval, mITT-C = Modified Intent-to-treat-Completers, Min = Minimum, Max = Maximum.
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	39		41		40	
	Mean (SD)	23.9 (3.82)		23.7 (3.71)		23.2 (2.96)	
	Median	24.0		24.0		23.0	
	Min, Max	17, 36		17, 30		17, 29	
Week 12	n	39	39	41	41	40	40
	Mean (SD)	19.1 (5.50)	-4.9 (3.81)	18.4 (4.13)	-5.3 (3.81)	18.7 (3.16)	-4.5 (2.74)
	Median	18.0	-4.0	17.0	-4.0	18.0	-4.5
	Min, Max	9, 34	-15, 2	9, 26	-13, 0	13, 27	-11, 0
	95% CI		(-6.11, -3.64)		(-6.54, -4.14)		(-5.40, -3.65)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADPANSS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.2.1.3d.sas
Programmer:AG
Date of Extraction:18DEC2023

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	39	39	41	41	40	40
	Mean (SD)	18.6 (5.27)	-5.3 (3.52)	17.2 (4.04)	-6.5 (4.07)	17.6 (3.37)	-5.6 (3.00)
	Median	18.0	-4.0	17.0	-7.0	17.0	-6.0
	Min, Max	9, 35	-13, 1	8, 24	-17, -1	10, 25	-11, 0
	95% CI		(-6.47, -4.19)		(-7.82, -5.25)		(-6.51, -4.59)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	41	41	40	40
	Mean (SD)	17.7 (5.07)	-6.2 (3.31)	16.3 (3.99)	-7.4 (4.21)	17.6 (3.67)	-5.6 (3.44)
	Median	16.0	-6.0	16.0	-6.0	17.0	-6.0
	Min, Max	9, 34	-13, 0	8, 24	-17, -1	10, 26	-13, 3
	95% CI		(-7.28, -5.13)		(-8.69, -6.04)		(-6.70, -4.50)

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	39	39	41	41	40	40
	Mean (SD)	17.8 (5.92)	-6.1 (4.06)	15.6 (3.94)	-8.1 (4.67)	17.0 (4.14)	-6.2 (3.83)
	Median	17.0	-6.0	16.0	-9.0	17.0	-6.0
	Min, Max	9, 40	-14, 4	8, 24	-17, -1	7, 26	-14, 2
	95% CI		(-7.42, -4.79)		(-9.62, -6.67)		(-7.37, -4.93)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	39		41		40	
	Mean (SD)	20.0 (3.42)		20.1 (3.58)		19.2 (3.20)	
	Median	20.0		20.0		19.5	
	Min, Max	12, 31		12, 29		12, 26	
Week 12	n	39	39	41	41	40	40
	Mean (SD)	17.7 (2.67)	-2.3 (3.01)	18.1 (3.44)	-2.0 (2.97)	17.1 (3.04)	-2.1 (2.05)
	Median	18.0	-1.0	19.0	-1.0	18.0	-2.0
	Min, Max	12, 24	-13, 2	11, 26	-11, 4	10, 22	-9, 1
	95% CI		(-3.23, -1.28)		(-2.91, -1.04)		(-2.76, -1.44)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADPANSS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.2.1.3d.sas
Programmer:AG
Date of Extraction:18DEC2023

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	39	39	41	41	40	40
	Mean (SD)	17.5 (2.72)	-2.4 (3.16)	17.6 (3.73)	-2.4 (3.59)	16.5 (2.89)	-2.8 (2.43)
	Median	17.0	-1.0	18.0	-2.0	17.0	-2.5
	Min, Max	11, 24	-14, 2	9, 25	-13, 6	10, 21	-9, 1
	95% CI		(-3.46, -1.41)		(-3.57, -1.31)		(-3.53, -1.97)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	41	41	40	40
	Mean (SD)	17.0 (2.73)	-3.0 (3.71)	17.4 (3.85)	-2.7 (3.72)	16.1 (3.10)	-3.2 (2.74)
	Median	17.0	-2.0	17.0	-2.0	16.5	-3.0
	Min, Max	11, 23	-16, 5	8, 25	-14, 6	9, 23	-9, 3
	95% CI		(-4.20, -1.80)		(-3.86, -1.51)		(-4.03, -2.27)

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	39	39	41	41	40	40
	Mean (SD)	16.9 (2.51)	-3.1 (3.47)	17.0 (4.13)	-3.0 (3.88)	15.6 (3.33)	-3.7 (3.21)
	Median	17.0	-3.0	17.0	-2.0	16.0	-3.5
	Min, Max	11, 23	-17, 2	8, 28	-14, 6	9, 23	-11, 3
	95% CI		(-4.18, -1.93)		(-4.27, -1.82)		(-4.68, -2.62)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: General psychopathology Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	39		41		40	
	Mean (SD)	35.9 (3.92)		35.2 (2.91)		36.4 (3.68)	
	Median	36.0		35.0		36.5	
	Min, Max	30, 49		29, 40		30, 43	
Week 12	n	39	39	41	41	40	40
	Mean (SD)	32.3 (4.93)	-3.6 (3.18)	31.2 (3.66)	-4.0 (3.49)	32.5 (3.91)	-3.9 (2.67)
	Median	31.0	-4.0	30.0	-4.0	32.5	-4.0
	Min, Max	23, 46	-11, 5	25, 39	-14, 4	26, 41	-11, 2
	95% CI		(-4.62, -2.56)		(-5.08, -2.87)		(-4.75, -3.05)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADPANSS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.2.1.3d.sas
Programmer:AG
Date of Extraction:18DEC2023

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: General psychopathology Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	39	39	41	41	40	40
	Mean (SD)	31.5 (5.15)	-4.4 (3.54)	30.1 (3.88)	-5.1 (3.56)	31.6 (4.61)	-4.8 (4.00)
	Median	31.0	-5.0	29.0	-5.0	32.0	-4.5
	Min, Max	23, 45	-12, 5	24, 39	-16, 2	20, 40	-20, 2
	95% CI		(-5.51, -3.21)		(-6.22, -3.97)		(-6.08, -3.52)
	p-value		<.001		<.001		<.001
Week 36	n	39	39	41	41	40	40
	Mean (SD)	30.5 (5.36)	-5.4 (3.85)	29.3 (3.88)	-5.9 (3.95)	31.2 (5.23)	-5.1 (4.47)
	Median	28.0	-5.0	28.0	-6.0	31.5	-5.0
	Min, Max	23, 45	-13, 2	21, 39	-17, 2	21, 46	-17, 3
	95% CI		(-6.63, -4.14)		(-7.13, -4.63)		(-6.55, -3.70)

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: General psychopathology Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3d
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparison
mITT-C Population

Scale: General psychopathology Scale

		Evenamide 7.5 mg BID (N=39)		Evenamide 15 mg BID (N=41)		Evenamide 30 mg BID (N=40)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	39	39	41	41	40	40
	Mean (SD)	29.9 (5.63)	-6.0 (4.39)	29.2 (4.77)	-6.0 (4.56)	30.8 (5.92)	-5.6 (5.52)
	Median	28.0	-5.0	28.0	-6.0	31.0	-5.0
	Min, Max	22, 43	-17, 2	21, 44	-19, 6	18, 47	-22, 4
	95% CI		(-7.40, -4.55)		(-7.44, -4.56)		(-7.37, -3.83)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation, CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline.
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Positive Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	120		
	Mean (SD)	23.6 (3.50)		
	Median	24.0		
	Min, Max	17, 36		
Week 12	n	120	120	120
	Mean (SD)	18.7 (4.33)	-4.9 (3.48)	-20.7 (14.03)
	Median	18.0	-4.0	-19.1
	Min, Max	9, 34	-15, 2	-56, 8
	95% CI		(-5.55, -4.29)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Positive Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 24	n	120	120	120
	Mean (SD)	17.8 (4.30)	-5.8 (3.57)	-24.5 (14.43)
	Median	17.0	-5.0	-24.5
	Min, Max	8, 35	-17, 1	-68, 4
	95% CI		(-6.46, -5.17)	
	p-value		<.001	
Week 36	n	120	120	120
	Mean (SD)	17.2 (4.29)	-6.4 (3.72)	-26.9 (14.94)
	Median	17.0	-6.0	-25.0
	Min, Max	8, 34	-17, 3	-68, 14
	95% CI		(-7.07, -5.73)	

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Positive Scale

			Evenamide (N=120)	
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Positive Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 46	n	120	120	120
	Mean (SD)	16.8 (4.79)	-6.8 (4.28)	-28.7 (16.90)
	Median	16.0	-6.0	-27.8
	Min, Max	7, 40	-17, 4	-68, 11
	95% CI		(-7.59, -6.04)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Negative Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	120		
	Mean (SD)	19.8 (3.40)		
	Median	20.0		
	Min, Max	12, 31		
Week 12	n	120	120	120
	Mean (SD)	17.6 (3.08)	-2.1 (2.69)	-9.8 (12.47)
	Median	18.0	-1.0	-5.9
	Min, Max	10, 26	-13, 4	-50, 33
	95% CI		(-2.59, -1.62)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Negative Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 24	n	120	120	120
	Mean (SD)	17.2 (3.17)	-2.5 (3.08)	-11.9 (14.30)
	Median	17.0	-2.0	-10.0
	Min, Max	9, 25	-14, 6	-59, 35
	95% CI		(-3.10, -1.99)	
	p-value		<.001	
Week 36	n	120	120	120
	Mean (SD)	16.8 (3.29)	-2.9 (3.40)	-13.8 (15.99)
	Median	17.0	-2.5	-13.6
	Min, Max	8, 25	-16, 6	-64, 35
	95% CI		(-3.56, -2.33)	

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Negative Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: Negative Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 46	n	120	120	120
	Mean (SD)	16.5 (3.44)	-3.3 (3.52)	-15.4 (16.27)
	Median	17.0	-3.0	-14.3
	Min, Max	8, 28	-17, 6	-64, 35
	95% CI		(-3.89, -2.61)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: General psychopathology Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	120		
	Mean (SD)	35.8 (3.53)		
	Median	36.0		
	Min, Max	29, 49		
Week 12	n	120	120	120
	Mean (SD)	32.0 (4.19)	-3.8 (3.11)	-10.6 (8.57)
	Median	31.0	-4.0	-11.5
	Min, Max	23, 46	-14, 5	-35, 15
	95% CI		(-4.39, -3.26)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: General psychopathology Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 24	n	120	120	120
	Mean (SD)	31.0 (4.58)	-4.8 (3.69)	-13.2 (9.87)
	Median	30.5	-5.0	-13.3
	Min, Max	20, 45	-20, 5	-50, 15
	95% CI		(-5.43, -4.09)	
	p-value		<.001	
Week 36	n	120	120	120
	Mean (SD)	30.3 (4.89)	-5.5 (4.08)	-15.2 (10.88)
	Median	29.0	-5.0	-14.7
	Min, Max	21, 46	-17, 3	-45, 7
	95% CI		(-6.20, -4.73)	

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: General psychopathology Scale

			Evenamide (N=120)	
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.3cd
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales
mITT-C Population - Overall

Scale: General psychopathology Scale

		Evenamide (N=120)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Week 46	n	120	120	120
	Mean (SD)	29.9 (5.45)	-5.9 (4.81)	-16.3 (12.67)
	Median	28.0	-5.0	-15.5
	Min, Max	18, 47	-22, 6	-55, 16
	95% CI		(-6.73, -4.99)	
	p-value		<.001	

Source: Listing 16.2.6.1.1
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers, SD = Standard Deviation,CI = Confidence Interval, Min = Minimum, Max = Maximum. Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
p-value = Paired t-test. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.2.1.7d
Responder Analysis by Visit - Positive and Negative Syndrome Scale (PANSS)
mITT-C Population

Visit	PANSS	Improvement Category	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
Week 12	Total Score	Change >=20%	n (%)	9 (23.1)	11 (26.8)	7 (17.5)	27 (22.5)
	Total Positive Score	>=4-Point Improvement	n (%)	22 (56.4)	22 (53.7)	24 (60.0)	68 (56.7)
Week 24	Total Score	Change >=20%	n (%)	12 (30.8)	21 (51.2)	14 (35.0)	47 (39.2)
	Total Positive Score	>=4-Point Improvement	n (%)	24 (61.5)	27 (65.9)	29 (72.5)	80 (66.7)
Week 36	Total Score	Change >=20%	n (%)	21 (53.8)	20 (48.8)	17 (42.5)	58 (48.3)
	Total Positive Score	>=4-Point Improvement	n (%)	31 (79.5)	33 (80.5)	29 (72.5)	93 (77.5)
Week 46	Total Score	Change >=20%	n (%)	20 (51.3)	20 (48.8)	18 (45.0)	58 (48.3)
	Total Positive Score	>=4-Point Improvement	n (%)	29 (74.4)	34 (82.9)	32 (80.0)	95 (79.2)

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified intent-to-treat-Completers.
Responder analyses will be performed by summarizing the proportion of patients in each of the evenamide groups with different categories of improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale.
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

Reference Datasets:ADPANSS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.2.1.7d.sas
Programmer:AG
Date of Extraction:18DEC2023 Final - 18JAN2024:17:57

Table 14.2.1.7d
Responder Analysis by Visit - Positive and Negative Syndrome Scale (PANSS)
mITT-C Population

Table 14.2.2.5d
Responder Analysis (Improvement) - Clinical Global Impression – Severity of Illness (CGI-S) Score
mITT-C Population

Visit	Improvement Category	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
Week 12	Improvement of at least 2 categories	n (%)	4 (10.3)	8 (19.5)	3 (7.5)	15 (12.5)
	Improvement of at least 1 category	n (%)	27 (69.2)	33 (80.5)	28 (70.0)	88 (73.3)
Week 24	Improvement of at least 2 categories	n (%)	5 (12.8)	10 (24.4)	5 (12.5)	20 (16.7)
	Improvement of at least 1 category	n (%)	30 (76.9)	36 (87.8)	33 (82.5)	99 (82.5)
Week 36	Improvement of at least 2 categories	n (%)	8 (20.5)	16 (39.0)	7 (17.5)	31 (25.8)
	Improvement of at least 1 category	n (%)	34 (87.2)	36 (87.8)	34 (85.0)	104 (86.7)
Week 46	Improvement of at least 2 categories	n (%)	9 (23.1)	16 (39.0)	9 (22.5)	34 (28.3)
	Improvement of at least 1 category	n (%)	34 (87.2)	35 (85.4)	33 (82.5)	102 (85.0)

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified intent-to-treat-Completers.
Improvement at least 2 Category = Change = (Post Dose - Baseline) CGI-S Score is -2 or below.
Similarly, improvement at least 1 Category = Change is -1 or below.Percentages are calculated by all patient in the respective mITT-C population in denominator (N).
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

Table 14.2.2.5d
Responder Analysis (Improvement) - Clinical Global Impression – Severity of Illness (CGI-S) Score
mITT-C Population

Table 14.2.3.2d
Responder Analysis - Clinical Global Impression - Change from Baseline (CGI-C)
mITT -C Population

Visit	Category	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
Week 12	CGI-C score <= 3	n (%)	31 (79.5)	35 (85.4)	37 (92.5)	103 (85.8)
	CGI-C score <= 2	n (%)	12 (30.8)	11 (26.8)	9 (22.5)	32 (26.7)
Week 24	CGI-C score <= 3	n (%)	31 (79.5)	38 (92.7)	37 (92.5)	106 (88.3)
	CGI-C score <= 2	n (%)	13 (33.3)	17 (41.5)	11 (27.5)	41 (34.2)

Source: Listing 16.2.6.3
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers.
CGI-C score <=3 Category = patients rated as 1 = Very much improved, or 2 = Much improved, or 3 = Minimally improved.
CGI-C score <=2 Category = patients rated as 1 = Very much improved, or 2 = Much improved.
Percentages are calculated by all patients in the respective mITT population in denominator (N).
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

Table 14.2.3.2d
Responder Analysis - Clinical Global Impression - Change from Baseline (CGI-C)
mITT -C Population

Visit	Category	Statistic	Evenamide 7.5 mg BID (N=39)	Evenamide 15 mg BID (N=41)	Evenamide 30 mg BID (N=40)	Total [a] (N=120)
Week 36	CGI-C score <= 3	n (%)	33 (84.6)	38 (92.7)	36 (90.0)	107 (89.2)
	CGI-C score <= 2	n (%)	18 (46.2)	19 (46.3)	14 (35.0)	51 (42.5)
Week 46	CGI-C score <= 3	n (%)	33 (84.6)	36 (87.8)	35 (87.5)	104 (86.7)
	CGI-C score <= 2	n (%)	18 (46.2)	19 (46.3)	16 (40.0)	53 (44.2)

Source: Listing 16.2.6.3
N - Total number of subjects in the mITT-C Population, n = number of patients, mITT-C = Modified Intent-to-treat-Completers.
CGI-C score <=3 Category = patients rated as 1 = Very much improved, or 2 = Much improved, or 3 = Minimally improved.
CGI-C score <=2 Category = patients rated as 1 = Very much improved, or 2 = Much improved.
Percentages are calculated by all patients in the respective mITT population in denominator (N).
[a] Total is the total number of subjects taking the active treatment Evenamide included in each category.

Table 14.3.0.2
Summary of Dose Adjustments or Kit Replacement
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=45)	Evenamide 15 mg BID (N=53)	Evenamide 30 mg BID (N=46)	Total (N=144)
Number of Subjects with Dose Adjustments or Kit Replacement	n(%)	43 (95.6)	50 (94.3)	41 (89.1)	134 (93.1)
Number of Subjects with Dose Adjustments	n(%)	0(0.0)	0(0.0)	1(2.2)	1(0.7)
Number of Subjects with Kit Replacement	n(%)	43(95.6)	50(94.3)	41(89.1)	134(93.1)
Number of Subjects with Other	n(%)	42 (93.3)	48 (90.6)	39 (84.8)	129 (89.6)
Reason for Adjustments					
As Per Pi, Unscheduled Visit Was Performed To Dispense 30mg Ip	n(%)	0(0.0)	0(0.0)	1(2.2)	1(0.7)
Start Of Adverse Event	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
End of adverse event	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.5.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Note that more than one reason per subject may be provided for dose adjustment due to multiple modifications.
Other data is in long text and are available in listing 16.2.5.3

Reference Datasets:ADSL,DA,SUPPDA,SUPPEX
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.0.2.sas
Programmer:SH
Date of Extraction:18DEC2023 Final - 18JAN2024:11:43

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	43		53		45	
	Mean (SD)	0.05 (0.05)		0.04 (0.04)		0.04 (0.03)	
	Median	0.06		0.05		0.05	
	Min, Max	0, 0.21		0, 0.101		0, 0.095	
Week 12	n	34	34	50	50	43	43
	Mean (SD)	0.05 (0.04)	0.01 (0.05)	0.05 (0.04)	0.01 (0.05)	0.04 (0.03)	-0.00 (0.04)
	Median	0.06	0.00	0.06	0.00	0.04	0.00
	Min, Max	0, 0.11	-0.108, 0.107	0, 0.114	-0.096, 0.099	0, 0.11	-0.09, 0.105

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	37	37	44	44	39	39
	Mean (SD)	0.04 (0.04)	-0.01 (0.06)	0.05 (0.04)	0.00 (0.05)	0.04 (0.03)	0.00 (0.04)
	Median	0.04	0.00	0.05	0.00	0.05	0.00
	Min, Max	0, 0.122	-0.108, 0.122	0, 0.192	-0.101, 0.192	0, 0.105	-0.09, 0.105
Week 36	n	38	37	37	37	40	40
	Mean (SD)	0.05 (0.04)	-0.00 (0.05)	0.05 (0.03)	0.01 (0.04)	0.04 (0.04)	0.00 (0.05)
	Median	0.05	0.00	0.06	0.00	0.05	0.00
	Min, Max	0, 0.125	-0.107, 0.125	0, 0.099	-0.089, 0.091	0, 0.117	-0.095, 0.117

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	39	44	44	37	37
	Mean (SD)	0.05 (0.04)	-0.00 (0.05)	0.05 (0.03)	0.00 (0.05)	0.05 (0.04)	0.01 (0.05)
	Median	0.05	0.00	0.05	0.00	0.05	0.00
	Min, Max	0, 0.136	-0.112, 0.092	0, 0.094	-0.101, 0.094	0, 0.113	-0.095, 0.113

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	0.63 (0.52)		0.58 (0.48)		0.61 (0.45)	
	Median	1.00		1.00		0.95	
	Min, Max	0, 2		0, 1		0, 1	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	0.69 (0.56)	0.10 (0.66)	0.70 (0.45)	0.09 (0.65)	0.59 (0.46)	-0.03 (0.59)
	Median	1.00	0.00	1.00	0.00	0.95	0.00
	Min, Max	0, 2.4	-1, 2	0, 1	-1, 1	0, 1	-1, 1
Week 24	n	38	38	44	44	40	40
	Mean (SD)	0.60 (0.51)	0.00 (0.71)	0.67 (0.55)	0.02 (0.67)	0.65 (0.44)	0.06 (0.53)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 1.5	-1, 1.2	0, 2	-1, 2	0, 1	-1, 1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Basophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	0.61 (0.48)	0.00 (0.61)	0.78 (0.41)	0.13 (0.59)	0.60 (0.45)	0.02 (0.60)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 1	-1, 1	0, 1	-1, 1	0, 1	-1, 1
Week 46	n	41	41	44	44	38	38
	Mean (SD)	0.66 (0.51)	0.06 (0.66)	0.67 (0.46)	0.05 (0.68)	0.67 (0.43)	0.10 (0.62)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 2	-1, 1	0, 1.1	-1, 1	0, 1	-1, 1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	43		53		45	
	Mean (SD)	0.43 (0.61)		0.25 (0.25)		0.25 (0.23)	
	Median	0.25		0.16		0.15	
	Min, Max	0, 2.912		0, 1.056		0, 0.91	
Week 12	n	34	34	50	50	43	43
	Mean (SD)	0.37 (0.54)	0.00 (0.28)	0.26 (0.22)	-0.00 (0.20)	0.26 (0.33)	0.02 (0.30)
	Median	0.22	-0.00	0.21	0.01	0.14	-0.02
	Min, Max	0, 2.925	-0.627, 0.98	0, 0.93	-0.78, 0.32	0, 1.54	-0.78, 1.245

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	37	37	44	44	39	39
	Mean (SD)	0.35 (0.42)	-0.09 (0.51)	0.25 (0.22)	-0.01 (0.24)	0.26 (0.23)	-0.00 (0.20)
	Median	0.20	-0.02	0.20	0.00	0.19	0.00
	Min, Max	0, 2.31	-2.711, 0.654	0, 1	-0.822, 0.67	0, 1.03	-0.64, 0.568
Week 36	n	38	37	37	37	40	40
	Mean (SD)	0.41 (0.42)	-0.03 (0.54)	0.22 (0.26)	-0.00 (0.26)	0.24 (0.26)	-0.01 (0.24)
	Median	0.28	-0.00	0.16	0.01	0.18	0.01
	Min, Max	0, 1.909	-2.641, 0.819	0, 1.455	-0.844, 1.01	0, 1.56	-0.66, 0.76

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	39	44	44	37	37
	Mean (SD)	0.29 (0.26)	-0.15 (0.60)	0.22 (0.17)	-0.04 (0.23)	0.25 (0.24)	0.01 (0.22)
	Median	0.23	-0.04	0.15	-0.01	0.16	0.00
	Min, Max	0, 1.092	-2.745, 0.505	0, 0.81	-0.78, 0.365	0, 1.22	-0.526, 0.59

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	5.01 (6.32)		3.34 (2.90)		3.62 (3.42)	
	Median	3.00		3.00		2.40	
	Min, Max	0, 33		0, 14		0, 15	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	4.57 (7.04)	0.23 (3.61)	3.44 (2.58)	-0.01 (2.75)	3.63 (4.06)	0.09 (3.61)
	Median	3.00	0.00	3.00	0.00	2.00	0.00
	Min, Max	0, 39	-9, 12	0, 10	-11, 6	0, 18.4	-8.5, 13
Week 24	n	38	38	44	44	40	40
	Mean (SD)	4.67 (5.62)	-0.48 (4.80)	3.61 (3.16)	0.11 (2.97)	3.81 (3.04)	-0.01 (2.64)
	Median	3.00	0.00	3.00	0.00	3.00	0.00
	Min, Max	0, 33	-23, 7	0, 14	-8, 7	0, 11	-6.1, 8

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Eosinophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	5.16 (4.96)	0.15 (5.52)	3.09 (2.85)	-0.11 (3.10)	3.49 (3.26)	-0.15 (2.98)
	Median	4.00	0.00	2.00	0.00	3.00	0.40
	Min, Max	0, 23	-21, 12	0, 15	-11, 10	0, 17.1	-7.4, 9
Week 46	n	41	41	44	44	38	38
	Mean (SD)	4.16 (3.36)	-0.86 (6.20)	3.17 (2.28)	-0.28 (2.75)	3.60 (3.28)	-0.11 (2.79)
	Median	3.00	0.00	2.40	0.00	3.00	0.00
	Min, Max	0, 13	-27, 8	0, 10	-10, 5	0, 17.1	-8, 6

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hemoglobin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	132.27 (15.41)		132.09 (18.01)		135.91 (17.73)	
	Median	133.50		135.00		136.00	
	Min, Max	88, 161		81, 157		85, 174	
Week 12	n	35	35	50	50	44	44
	Mean (SD)	131.71 (14.69)	0.11 (7.80)	131.20 (19.42)	-0.42 (7.36)	134.45 (15.76)	-1.39 (8.67)
	Median	130.00	0.00	134.00	1.00	136.50	-1.00
	Min, Max	107, 166	-18, 16	68, 158	-21, 14	77, 165	-18, 22

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hemoglobin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	38	38	44	44	40	40
	Mean (SD)	130.76 (15.71)	-0.92 (7.78)	132.66 (18.99)	0.09 (10.06)	137.13 (13.32)	-0.95 (10.50)
	Median	135.00	0.00	135.50	0.50	139.00	-1.00
	Min, Max	98, 153	-15, 15	89, 161	-31, 22	114, 169	-24, 31
Week 36	n	39	39	37	37	41	41
	Mean (SD)	131.36 (16.22)	-1.82 (9.31)	132.70 (18.56)	0.35 (8.85)	132.39 (12.89)	-3.61 (11.03)
	Median	133.00	0.00	135.00	0.00	132.00	-2.00
	Min, Max	99, 158	-27, 16	90, 167	-21, 24	107, 164	-42, 19

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hemoglobin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	44	44	38	38
	Mean (SD)	130.15 (17.09)	-2.85 (10.94)	132.82 (17.33)	0.64 (10.97)	134.05 (14.57)	-1.68 (10.79)
	Median	131.00	-2.00	137.50	-1.50	133.00	-1.00
	Min, Max	85, 164	-34, 18	93, 161	-27, 30	93, 157	-36, 21

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hematocrit (fraction of 1)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	0.43 (0.05)		0.42 (0.06)		0.42 (0.05)	
	Median	0.42		0.43		0.42	
	Min, Max	0.319, 0.516		0.282, 0.519		0.29, 0.553	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hematocrit (fraction of 1)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	0.42 (0.04)	-0.01 (0.02)	0.42 (0.05)	-0.01 (0.03)	0.42 (0.05)	-0.00 (0.03)
	Median	0.42	-0.01	0.42	-0.00	0.42	0.00
	Min, Max	0.334, 0.48	-0.05, 0.032	0.244, 0.517	-0.076, 0.061	0.253, 0.527	-0.059, 0.058
Week 24	n	38	38	44	44	40	40
	Mean (SD)	0.41 (0.04)	-0.01 (0.03)	0.42 (0.05)	-0.01 (0.04)	0.42 (0.04)	-0.00 (0.03)
	Median	0.41	-0.01	0.42	-0.01	0.43	-0.01
	Min, Max	0.304, 0.483	-0.072, 0.052	0.302, 0.521	-0.103, 0.099	0.351, 0.533	-0.059, 0.088

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Hematocrit (fraction of 1)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	0.41 (0.04)	-0.02 (0.04)	0.41 (0.05)	-0.01 (0.03)	0.41 (0.04)	-0.01 (0.04)
	Median	0.41	-0.02	0.42	-0.01	0.41	-0.01
	Min, Max	0.321, 0.486	-0.128, 0.085	0.288, 0.532	-0.076, 0.061	0.312, 0.525	-0.104, 0.083
Week 46	n	41	41	44	44	38	38
	Mean (SD)	0.41 (0.05)	-0.02 (0.04)	0.42 (0.05)	-0.01 (0.04)	0.42 (0.04)	-0.00 (0.03)
	Median	0.42	-0.02	0.43	-0.01	0.41	0.00
	Min, Max	0.298, 0.489	-0.105, 0.083	0.314, 0.517	-0.076, 0.099	0.3, 0.494	-0.087, 0.059

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	43		53		45	
	Mean (SD)	1.84 (0.62)		1.87 (0.62)		1.99 (0.84)	
	Median	1.74		1.73		1.83	
	Min, Max	0.7, 3.567		0.697, 3.3		0.476, 4.62	
Week 12	n	34	34	50	50	43	43
	Mean (SD)	1.90 (0.70)	0.07 (0.47)	1.77 (0.66)	-0.05 (0.38)	2.00 (0.85)	-0.02 (0.49)
	Median	1.79	0.05	1.74	0.08	1.89	-0.03
	Min, Max	0.748, 4.07	-1.071, 1.298	0.44, 3.25	-0.896, 0.546	0.468, 4.97	-1.034, 2.096

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	37	37	44	44	39	39
	Mean (SD)	1.88 (0.70)	0.06 (0.65)	1.77 (0.63)	-0.01 (0.52)	2.02 (0.82)	0.08 (0.60)
	Median	1.74	0.15	1.59	-0.11	1.85	0.11
	Min, Max	0.855, 4.346	-2.161, 1.574	0.87, 3.69	-1.148, 1.988	0.828, 4.63	-1.224, 2.219
Week 36	n	38	37	37	37	40	40
	Mean (SD)	1.77 (0.80)	-0.03 (0.59)	1.71 (0.71)	-0.04 (0.47)	1.98 (0.94)	0.02 (0.72)
	Median	1.61	-0.06	1.56	-0.00	1.85	0.06
	Min, Max	0.413, 4.708	-1.425, 1.936	0.781, 3.977	-1.682, 1.129	0.816, 5.87	-1.21, 1.744

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	39	44	44	37	37
	Mean (SD)	1.84 (0.71)	0.04 (0.56)	1.82 (0.70)	-0.05 (0.48)	2.04 (0.85)	0.03 (0.62)
	Median	1.67	-0.02	1.61	-0.03	1.96	0.02
	Min, Max	1.071, 4.872	-1.377, 2.1	1.014, 3.564	-1.918, 0.903	0.273, 4.97	-1.399, 1.426

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	24.25 (6.72)		25.65 (8.57)		28.24 (9.76)	
	Median	25.50		26.00		28.00	
	Min, Max	10, 37.4		11, 52		7, 49	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	25.27 (7.26)	1.02 (5.07)	25.41 (8.33)	-0.04 (7.83)	29.39 (9.75)	0.61 (6.92)
	Median	25.00	1.00	26.00	1.00	28.00	0.50
	Min, Max	11, 46.7	-9, 9.3	10, 43	-20, 18	9, 62	-18, 17
Week 24	n	38	38	44	44	40	40
	Mean (SD)	26.70 (9.99)	2.75 (8.82)	25.22 (8.60)	0.00 (6.37)	29.21 (7.69)	1.98 (7.73)
	Median	26.00	2.50	24.30	0.00	28.25	2.50
	Min, Max	14, 68	-11, 39	12, 63	-11, 18	18, 47.3	-20, 20

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Lymphocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	24.42 (8.15)	0.44 (7.86)	25.69 (9.01)	0.25 (7.17)	29.67 (9.96)	2.01 (10.51)
	Median	24.00	1.00	24.00	0.00	29.00	1.00
	Min, Max	7, 44	-14, 16	10, 43	-18, 16	11, 60	-21, 32
Week 46	n	41	41	44	44	38	38
	Mean (SD)	26.90 (7.67)	2.71 (8.84)	26.99 (8.31)	0.93 (8.28)	28.32 (8.69)	-0.24 (7.76)
	Median	25.00	1.40	25.00	1.50	29.00	-0.10
	Min, Max	15, 50	-14, 32	15, 57.4	-30, 18	3, 45	-17, 17

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	43		53		45	
	Mean (SD)	0.37 (0.16)		0.38 (0.18)		0.36 (0.20)	
	Median	0.36		0.40		0.31	
	Min, Max	0.07, 0.861		0, 0.84		0, 0.897	
Week 12	n	34	34	50	50	43	43
	Mean (SD)	0.35 (0.17)	0.00 (0.18)	0.36 (0.18)	-0.02 (0.21)	0.37 (0.18)	0.01 (0.15)
	Median	0.35	-0.01	0.35	-0.00	0.35	0.01
	Min, Max	0.084, 0.768	-0.411, 0.492	0.088, 0.798	-0.56, 0.65	0.098, 0.888	-0.507, 0.447

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	37	37	44	44	39	39
	Mean (SD)	0.33 (0.14)	-0.05 (0.19)	0.40 (0.19)	0.01 (0.19)	0.42 (0.20)	0.06 (0.16)
	Median	0.30	-0.04	0.39	0.02	0.38	0.06
	Min, Max	0.086, 0.67	-0.713, 0.469	0.086, 0.93	-0.428, 0.467	0.106, 0.84	-0.29, 0.546
Week 36	n	38	37	37	37	40	40
	Mean (SD)	0.39 (0.19)	0.02 (0.20)	0.35 (0.16)	0.01 (0.18)	0.43 (0.21)	0.07 (0.21)
	Median	0.34	0.01	0.33	-0.04	0.39	0.06
	Min, Max	0.09, 0.952	-0.342, 0.764	0.088, 0.63	-0.378, 0.627	0.102, 0.91	-0.705, 0.684

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	39	44	44	37	37
	Mean (SD)	0.36 (0.15)	-0.01 (0.17)	0.39 (0.16)	0.01 (0.18)	0.39 (0.16)	0.03 (0.18)
	Median	0.30	-0.03	0.37	-0.01	0.39	0.04
	Min, Max	0.092, 0.693	-0.305, 0.426	0.118, 0.736	-0.371, 0.456	0.126, 0.728	-0.618, 0.429

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	4.87 (1.96)		5.17 (2.44)		5.08 (2.51)	
	Median	5.00		5.00		5.00	
	Min, Max	1, 9		0, 11		0, 13	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	4.62 (1.74)	0.01 (2.21)	5.20 (2.48)	0.01 (2.53)	5.51 (2.30)	0.37 (2.04)
	Median	4.40	0.00	4.00	0.00	6.00	0.75
	Min, Max	1, 8	-5, 6	2, 12	-8, 5	1, 12	-7, 5
Week 24	n	38	38	44	44	40	40
	Mean (SD)	4.70 (2.01)	-0.15 (2.00)	5.74 (2.36)	0.32 (2.27)	5.99 (1.87)	0.98 (2.09)
	Median	5.00	0.00	6.00	1.00	6.00	1.00
	Min, Max	2, 10	-5, 5	1, 10.7	-6, 4	2, 10	-5, 5

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Monocytes/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	5.27 (2.22)	0.31 (2.55)	5.24 (2.39)	0.32 (2.72)	6.35 (2.51)	1.34 (2.70)
	Median	5.00	0.00	5.00	0.00	6.00	1.00
	Min, Max	2, 11	-6, 5	1, 11	-5, 11	1, 12	-8, 8
Week 46	n	41	41	44	44	38	38
	Mean (SD)	5.36 (2.31)	0.33 (2.74)	5.74 (2.00)	0.60 (2.29)	5.46 (1.75)	0.31 (2.41)
	Median	5.00	0.00	6.00	0.05	5.90	0.35
	Min, Max	2, 11	-6, 5	2, 10.9	-4, 6	2, 8.8	-7, 5

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	43		53		45	
	Mean (SD)	5.06 (1.43)		5.01 (1.79)		4.44 (1.37)	
	Median	4.76		4.96		4.26	
	Min, Max	2.454, 8.176		1.947, 9.605		1.887, 7.742	
Week 12	n	34	34	50	50	43	43
	Mean (SD)	4.96 (1.65)	-0.16 (1.05)	4.68 (1.50)	-0.27 (1.83)	4.21 (1.45)	-0.17 (1.16)
	Median	4.94	-0.35	4.54	-0.41	4.08	0.08
	Min, Max	1.97, 9.216	-2.64, 2.641	1.584, 8.208	-5.622, 3.694	1.925, 8.346	-2.693, 1.547

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	37	37	44	44	39	39
	Mean (SD)	4.78 (1.96)	-0.32 (2.02)	4.67 (1.44)	-0.24 (1.55)	4.22 (1.29)	-0.35 (1.29)
	Median	4.65	-0.28	4.52	-0.15	4.08	-0.40
	Min, Max	0.361, 10.854	-5.952, 6.499	0.951, 7.626	-4.42, 2.668	2.448, 8.378	-3.12, 3.06
Week 36	n	38	37	37	37	40	40
	Mean (SD)	4.79 (1.74)	-0.23 (1.67)	4.50 (1.59)	-0.27 (1.34)	4.30 (1.87)	-0.22 (1.56)
	Median	4.55	-0.34	4.24	-0.23	4.08	-0.17
	Min, Max	2.04, 9.656	-3.722, 3.452	1.833, 8.245	-3.641, 2.165	0.499, 8.892	-4.669, 2.437

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	39	44	44	37	37
	Mean (SD)	4.35 (1.44)	-0.60 (1.89)	4.34 (1.29)	-0.58 (1.57)	4.56 (1.61)	0.20 (1.17)
	Median	4.25	-0.55	4.40	-0.39	4.41	0.31
	Min, Max	1.617, 7.81	-6.559, 2.705	1.887, 6.9	-5.091, 1.912	2.268, 8.588	-3.353, 2.632

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	65.23 (7.73)		65.25 (10.26)		62.45 (11.56)	
	Median	66.00		64.00		61.50	
	Min, Max	45, 80		35, 85		39.2, 86	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	64.85 (9.98)	-1.36 (8.02)	65.24 (9.84)	-0.05 (9.45)	60.88 (11.02)	-1.04 (7.68)
	Median	67.00	-1.00	65.00	-0.70	63.00	-1.55
	Min, Max	41.3, 86	-22, 16	46, 86	-21, 27	35, 83	-17, 14
Week 24	n	38	38	44	44	40	40
	Mean (SD)	63.33 (12.95)	-2.12 (11.01)	64.76 (10.74)	-0.46 (7.67)	60.34 (9.34)	-3.01 (9.27)
	Median	65.00	-1.00	65.00	1.00	60.00	-2.50
	Min, Max	14, 81	-45, 16	21, 85	-20, 12	40.8, 75	-28, 21

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Neutrophils/Leukocytes (%)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	64.54 (10.57)	-0.91 (9.78)	65.21 (11.73)	-0.59 (9.66)	59.82 (11.73)	-3.29 (12.27)
	Median	65.00	0.00	68.00	0.00	60.00	-2.00
	Min, Max	43, 88	-24, 20	37, 85	-25, 22	29, 83	-39, 18
Week 46	n	41	41	44	44	38	38
	Mean (SD)	62.91 (9.43)	-2.24 (10.80)	63.43 (9.39)	-1.30 (9.98)	61.95 (10.81)	-0.06 (9.12)
	Median	65.00	-2.00	63.50	-1.00	63.00	-0.30
	Min, Max	33, 79	-40, 19	34, 82	-24, 36	34.1, 88	-19, 17

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Platelets (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		52		46	
	Mean (SD)	280.82 (76.23)		282.04 (93.37)		256.87 (64.70)	
	Median	283.00		277.00		257.00	
	Min, Max	144, 450		144, 652		151, 376	
Week 12	n	35	35	49	49	44	44
	Mean (SD)	291.20 (70.71)	12.34 (46.01)	284.47 (79.98)	0.51 (47.23)	261.45 (74.42)	6.32 (37.08)
	Median	289.00	5.00	265.00	7.00	263.00	-2.00
	Min, Max	182, 452	-92, 148	135, 559	-127, 128	149, 498	-53, 137

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Platelets (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	38	38	44	44	40	40
	Mean (SD)	271.11 (80.90)	-8.87 (43.85)	292.30 (85.72)	-5623 (37366)	258.83 (58.51)	-3.20 (47.73)
	Median	264.50	-7.00	288.00	9.50	273.00	-7.50
	Min, Max	170, 476	-112, 91	150, 600	-247850, 154	145, 413	-114, 144
Week 36	n	39	39	37	37	41	41
	Mean (SD)	281.74 (79.28)	7.23 (65.29)	287.78 (80.73)	3.32 (65.70)	262.76 (64.92)	3.90 (40.76)
	Median	274.00	-2.00	282.00	20.00	271.00	-3.00
	Min, Max	169, 493	-77, 276	152, 547	-195, 96	146, 460	-103, 112

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Platelets (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	44	44	38	38
	Mean (SD)	273.95 (76.84)	1.39 (65.93)	279.09 (88.52)	-5.70 (63.10)	266.08 (62.99)	6.21 (55.82)
	Median	261.00	3.00	268.50	10.00	264.50	3.00
	Min, Max	157, 466	-152, 248	150, 666	-210, 92	152, 463	-151, 111

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Erythrocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	4.75 (0.47)		4.75 (0.56)		4.80 (0.46)	
	Median	4.73		4.87		4.75	
	Min, Max	3.71, 6.25		3.66, 5.73		3.65, 5.64	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Erythrocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	35	35	50	50	44	44
	Mean (SD)	4.67 (0.59)	-0.07 (0.28)	4.69 (0.56)	-0.06 (0.28)	4.76 (0.49)	-0.06 (0.38)
	Median	4.56	-0.06	4.80	-0.03	4.84	0.02
	Min, Max	3.74, 6.31	-0.87, 0.49	3.37, 5.58	-0.55, 0.55	3.37, 5.72	-1.32, 0.59
Week 24	n	38	38	44	44	40	40
	Mean (SD)	4.67 (0.51)	-0.09 (0.32)	4.71 (0.61)	-0.07 (0.44)	4.79 (0.44)	-0.07 (0.34)
	Median	4.63	-0.15	4.68	0.00	4.81	-0.06
	Min, Max	3.6, 6.02	-0.93, 0.69	3.33, 5.75	-1.99, 0.74	3.84, 5.74	-0.9, 0.76

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Erythrocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	37	37	41	41
	Mean (SD)	4.73 (0.55)	-0.03 (0.37)	4.78 (0.57)	0.04 (0.38)	4.66 (0.44)	-0.14 (0.37)
	Median	4.70	-0.03	4.72	0.03	4.64	-0.12
	Min, Max	3.76, 5.82	-0.88, 0.9	3.18, 5.99	-0.67, 1.33	3.72, 5.49	-1.32, 0.82
Week 46	n	41	41	44	44	38	38
	Mean (SD)	4.70 (0.55)	-0.06 (0.34)	4.78 (0.52)	0.02 (0.37)	4.70 (0.48)	-0.09 (0.39)
	Median	4.62	-0.02	4.80	-0.01	4.67	-0.09
	Min, Max	3.72, 6.04	-1.05, 0.65	3.64, 5.94	-0.7, 0.94	3.45, 5.7	-1.11, 0.82

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Leukocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	44		53		46	
	Mean (SD)	7.69 (1.98)		7.55 (1.95)		7.10 (1.62)	
	Median	7.10		7.58		7.10	
	Min, Max	4.3, 12.3		3.3, 11.6		3.7, 10.39	
Week 12	n	35	35	50	50	44	44
	Mean (SD)	7.56 (2.15)	-0.07 (1.09)	7.12 (1.87)	-0.34 (1.89)	6.91 (1.87)	-0.15 (1.55)
	Median	7.50	-0.30	7.11	-0.40	6.78	-0.15
	Min, Max	4.7, 13.7	-1.6, 2.9	3.3, 11.4	-5.4, 4	3.9, 11	-3.52, 5.1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Leukocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	38	38	44	44	40	40
	Mean (SD)	7.34 (2.32)	-0.37 (2.48)	7.15 (1.70)	-0.25 (1.85)	6.97 (1.88)	-0.22 (1.47)
	Median	7.05	-0.05	7.20	-0.25	6.60	-0.40
	Min, Max	2.58, 13.4	-8.12, 6.7	3.2, 12.3	-5.07, 4.9	3.6, 11.8	-4.32, 3.1
Week 36	n	39	39	37	37	41	41
	Mean (SD)	7.34 (2.31)	-0.31 (1.93)	6.83 (1.81)	-0.30 (1.42)	7.03 (2.43)	-0.12 (1.85)
	Median	6.70	-0.30	6.80	-0.30	6.50	-0.10
	Min, Max	4.29, 13.6	-5.78, 4.2	3.4, 10.5	-4.2, 2.6	1.72, 13.2	-5.88, 3.2

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: Leukocytes (10/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	44	44	38	38
	Mean (SD)	6.92 (1.90)	-0.62 (2.17)	6.82 (1.68)	-0.66 (1.61)	7.33 (1.94)	0.29 (1.34)
	Median	6.50	-0.64	7.00	-0.46	7.65	0.50
	Min, Max	4.3, 11.6	-6.3, 3.22	3.7, 10	-5.9, 1.9	4.1, 11.86	-3.5, 2.8

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	0.04 (0.04)	
	Median	0.05	
	Min, Max	0, 0.21	
Week 12	n	127	127
	Mean (SD)	0.05 (0.04)	0.00 (0.05)
	Median	0.05	0.00
	Min, Max	0, 0.114	-0.108, 0.107

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	120	120
	Mean (SD)	0.04 (0.04)	0.00 (0.05)
	Median	0.05	0.00
	Min, Max	0, 0.192	-0.108, 0.192
Week 36	n	115	114
	Mean (SD)	0.05 (0.04)	0.00 (0.05)
	Median	0.05	0.00
	Min, Max	0, 0.125	-0.107, 0.125

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	121	120
	Mean (SD)	0.05 (0.04)	0.00 (0.05)
	Median	0.05	0.00
	Min, Max	0, 0.136	-0.112, 0.113

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	0.61 (0.48)	
	Median	1.00	
	Min, Max	0, 2	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	0.66 (0.48)	0.05 (0.63)
	Median	1.00	0.00
	Min, Max	0, 2.4	-1, 2
Week 24	n	122	122
	Mean (SD)	0.64 (0.50)	0.03 (0.63)
	Median	1.00	0.00
	Min, Max	0, 2	-1, 2

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Basophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	0.66 (0.45)	0.05 (0.60)
	Median	1.00	0.00
	Min, Max	0, 1	-1, 1
Week 46	n	123	123
	Mean (SD)	0.67 (0.46)	0.07 (0.65)
	Median	1.00	0.00
	Min, Max	0, 2	-1, 1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	0.31 (0.40)	
	Median	0.20	
	Min, Max	0, 2.912	
Week 12	n	127	127
	Mean (SD)	0.29 (0.37)	0.00 (0.26)
	Median	0.18	-0.00
	Min, Max	0, 2.925	-0.78, 1.245

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	120	120
	Mean (SD)	0.28 (0.30)	-0.03 (0.34)
	Median	0.20	-0.00
	Min, Max	0, 2.31	-2.711, 0.67
Week 36	n	115	114
	Mean (SD)	0.29 (0.33)	-0.01 (0.37)
	Median	0.18	0.00
	Min, Max	0, 1.909	-2.641, 1.01

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	121	120
	Mean (SD)	0.25 (0.23)	-0.06 (0.39)
	Median	0.17	-0.01
	Min, Max	0, 1.22	-2.745, 0.59

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	3.95 (4.40)	
	Median	3.00	
	Min, Max	0, 33	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	3.81 (4.63)	0.09 (3.28)
	Median	3.00	0.00
	Min, Max	0, 39	-11, 13
Week 24	n	122	122
	Mean (SD)	4.01 (4.05)	-0.11 (3.53)
	Median	3.00	0.00
	Min, Max	0, 33	-23, 8

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Eosinophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	3.92 (3.88)	-0.04 (4.01)
	Median	3.00	0.00
	Min, Max	0, 23	-21, 12
Week 46	n	123	123
	Mean (SD)	3.63 (2.99)	-0.42 (4.21)
	Median	3.00	0.00
	Min, Max	0, 17.1	-27, 8

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hemoglobin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	133.38 (17.13)	
	Median	135.00	
	Min, Max	81, 174	
Week 12	n	129	129
	Mean (SD)	132.45 (16.95)	-0.60 (7.91)
	Median	134.00	1.00
	Min, Max	68, 166	-21, 22

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hemoglobin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	122	122
	Mean (SD)	133.53 (16.37)	-0.57 (9.50)
	Median	135.50	0.00
	Min, Max	89, 169	-31, 31
Week 36	n	117	117
	Mean (SD)	132.15 (15.83)	-1.76 (9.86)
	Median	133.00	-1.00
	Min, Max	90, 167	-42, 24

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hemoglobin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	123	123
	Mean (SD)	132.31 (16.39)	-1.24 (10.92)
	Median	133.00	-2.00
	Min, Max	85, 164	-36, 30

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hematocrit (fraction of 1)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	0.42 (0.05)	
	Median	0.42	
	Min, Max	0.282, 0.553	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hematocrit (fraction of 1)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	0.42 (0.05)	-0.01 (0.03)
	Median	0.42	-0.01
	Min, Max	0.244, 0.527	-0.076, 0.061
Week 24	n	122	122
	Mean (SD)	0.42 (0.05)	-0.01 (0.03)
	Median	0.42	-0.01
	Min, Max	0.302, 0.533	-0.103, 0.099

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Hematocrit (fraction of 1)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	0.41 (0.05)	-0.01 (0.03)
	Median	0.41	-0.01
	Min, Max	0.288, 0.532	-0.128, 0.085
Week 46	n	123	123
	Mean (SD)	0.42 (0.05)	-0.01 (0.04)
	Median	0.42	-0.01
	Min, Max	0.298, 0.517	-0.105, 0.099

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	1.90 (0.70)	
	Median	1.76	
	Min, Max	0.476, 4.62	
Week 12	n	127	127
	Mean (SD)	1.88 (0.74)	-0.01 (0.44)
	Median	1.80	0.02
	Min, Max	0.44, 4.97	-1.071, 2.096

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	120	120
	Mean (SD)	1.88 (0.72)	0.04 (0.58)
	Median	1.74	-0.05
	Min, Max	0.828, 4.63	-2.161, 2.219
Week 36	n	115	114
	Mean (SD)	1.82 (0.83)	-0.02 (0.60)
	Median	1.60	0.00
	Min, Max	0.413, 5.87	-1.682, 1.936

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	121	120
	Mean (SD)	1.89 (0.75)	0.00 (0.55)
	Median	1.78	-0.01
	Min, Max	0.273, 4.97	-1.918, 2.1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	26.05 (8.57)	
	Median	26.50	
	Min, Max	7, 52	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	26.73 (8.73)	0.47 (6.82)
	Median	27.00	1.00
	Min, Max	9, 62	-20, 18
Week 24	n	122	122
	Mean (SD)	26.99 (8.87)	1.50 (7.67)
	Median	26.00	1.00
	Min, Max	12, 68	-20, 39

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Lymphocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	26.66 (9.29)	0.93 (8.65)
	Median	26.00	1.00
	Min, Max	7, 60	-21, 32
Week 46	n	123	123
	Mean (SD)	27.37 (8.18)	1.16 (8.34)
	Median	26.00	1.00
	Min, Max	3, 57.4	-30, 32

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	0.37 (0.18)	
	Median	0.36	
	Min, Max	0, 0.897	
Week 12	n	127	127
	Mean (SD)	0.36 (0.17)	-0.00 (0.18)
	Median	0.35	0.01
	Min, Max	0.084, 0.888	-0.56, 0.65

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	120	120
	Mean (SD)	0.39 (0.18)	0.01 (0.18)
	Median	0.37	0.02
	Min, Max	0.086, 0.93	-0.713, 0.546
Week 36	n	115	114
	Mean (SD)	0.39 (0.19)	0.04 (0.20)
	Median	0.37	0.02
	Min, Max	0.088, 0.952	-0.705, 0.764

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	121	120
	Mean (SD)	0.38 (0.16)	0.01 (0.18)
	Median	0.36	0.00
	Min, Max	0.092, 0.736	-0.618, 0.456

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	5.05 (2.31)	
	Median	5.00	
	Min, Max	0, 13	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	5.15 (2.25)	0.13 (2.28)
	Median	5.00	0.00
	Min, Max	1, 12	-8, 6
Week 24	n	122	122
	Mean (SD)	5.50 (2.16)	0.39 (2.16)
	Median	6.00	0.95
	Min, Max	1, 10.7	-6, 5

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Monocytes/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	5.64 (2.41)	0.67 (2.68)
	Median	5.40	0.00
	Min, Max	1, 12	-8, 11
Week 46	n	123	123
	Mean (SD)	5.53 (2.03)	0.42 (2.47)
	Median	5.10	0.00
	Min, Max	2, 11	-7, 6

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	141	
	Mean (SD)	4.84 (1.57)	
	Median	4.76	
	Min, Max	1.887, 9.605	
Week 12	n	127	127
	Mean (SD)	4.59 (1.54)	-0.20 (1.43)
	Median	4.48	-0.27
	Min, Max	1.584, 9.216	-5.622, 3.694

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	120	120
	Mean (SD)	4.56 (1.58)	-0.30 (1.62)
	Median	4.44	-0.24
	Min, Max	0.361, 10.854	-5.952, 6.499
Week 36	n	115	114
	Mean (SD)	4.53 (1.74)	-0.24 (1.52)
	Median	4.28	-0.18
	Min, Max	0.499, 9.656	-4.669, 3.452

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	121	120
	Mean (SD)	4.41 (1.44)	-0.34 (1.60)
	Median	4.40	-0.26
	Min, Max	1.617, 8.588	-6.559, 2.705

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	64.35 (10.03)	
	Median	65.00	
	Min, Max	35, 86	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	63.65 (10.41)	-0.74 (8.45)
	Median	65.00	-1.00
	Min, Max	35, 86	-22, 27
Week 24	n	122	122
	Mean (SD)	62.87 (11.13)	-1.81 (9.32)
	Median	64.00	-1.00
	Min, Max	14, 85	-45, 21

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Neutrophils/Leukocytes (%)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	63.10 (11.52)	-1.64 (10.66)
	Median	64.00	0.00
	Min, Max	29, 88	-39, 22
Week 46	n	123	123
	Mean (SD)	62.80 (9.80)	-1.23 (9.97)
	Median	64.00	-1.00
	Min, Max	33, 88	-40, 36

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Platelets (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	142	
	Mean (SD)	273.51 (79.97)	
	Median	272.00	
	Min, Max	144, 652	
Week 12	n	128	128
	Mean (SD)	278.40 (76.09)	5.74 (43.57)
	Median	270.00	4.00
	Min, Max	135, 559	-127, 148

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Platelets (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	122	122
	Mean (SD)	274.72 (76.91)	-2032 (22439)
	Median	272.50	-5.00
	Min, Max	145, 600	-247850, 154
Week 36	n	117	117
	Mean (SD)	277.00 (75.17)	4.83 (57.55)
	Median	276.00	1.00
	Min, Max	146, 547	-195, 276

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Platelets (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	123	123
	Mean (SD)	273.36 (77.00)	0.34 (61.63)
	Median	264.00	6.00
	Min, Max	150, 666	-210, 248

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Erythrocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	4.77 (0.50)	
	Median	4.76	
	Min, Max	3.65, 6.25	

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Erythrocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	129	129
	Mean (SD)	4.71 (0.54)	-0.06 (0.31)
	Median	4.71	-0.03
	Min, Max	3.37, 6.31	-1.32, 0.59
Week 24	n	122	122
	Mean (SD)	4.72 (0.53)	-0.08 (0.37)
	Median	4.71	-0.08
	Min, Max	3.33, 6.02	-1.99, 0.76

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Erythrocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	117	117
	Mean (SD)	4.72 (0.52)	-0.05 (0.38)
	Median	4.71	-0.03
	Min, Max	3.18, 5.99	-1.32, 1.33
Week 46	n	123	123
	Mean (SD)	4.73 (0.51)	-0.04 (0.37)
	Median	4.68	-0.06
	Min, Max	3.45, 6.04	-1.11, 0.94

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Leukocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	7.45 (1.87)	
	Median	7.40	
	Min, Max	3.3, 12.3	
Week 12	n	129	129
	Mean (SD)	7.17 (1.95)	-0.20 (1.58)
	Median	7.00	-0.30
	Min, Max	3.3, 13.7	-5.4, 5.1

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Leukocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	122	122
	Mean (SD)	7.15 (1.96)	-0.28 (1.95)
	Median	7.05	-0.20
	Min, Max	2.58, 13.4	-8.12, 6.7
Week 36	n	117	117
	Mean (SD)	7.07 (2.20)	-0.24 (1.74)
	Median	6.60	-0.20
	Min, Max	1.72, 13.6	-5.88, 4.2

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.1c
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population - Overall

Test: Leukocytes (10/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	123	123
	Mean (SD)	7.01 (1.83)	-0.35 (1.79)
	Median	6.90	-0.24
	Min, Max	3.7, 11.86	-6.3, 3.22

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Albumin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	45.06 (3.53)		44.91 (3.26)		45.44 (3.32)	
	Median	44.80		44.50		45.45	
	Min, Max	34.7, 51.2		38.6, 51.2		38, 53.6	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	44.49 (3.09)	-0.45 (2.98)	44.99 (3.12)	0.10 (2.66)	45.00 (2.80)	-0.58 (3.59)
	Median	44.90	0.10	45.80	0.20	45.00	-0.50
	Min, Max	37.9, 51.3	-6.1, 8.1	37.9, 50.8	-5.2, 6.7	38.8, 52.5	-11, 6.1

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Albumin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	44.19 (4.58)	-0.67 (3.73)	45.56 (3.18)	0.74 (2.75)	45.23 (2.90)	-0.03 (3.98)
	Median	44.70	-0.40	46.20	0.70	45.90	-0.20
	Min, Max	30.8, 51.5	-13.5, 6.5	37.1, 51.4	-3.4, 8.4	38.2, 49.8	-7.8, 8
Week 36	n	39	39	41	41	42	42
	Mean (SD)	45.05 (3.20)	0.22 (3.11)	45.52 (2.83)	0.72 (3.11)	44.86 (2.88)	-0.37 (3.91)
	Median	45.20	0.00	46.20	0.40	44.55	-0.60
	Min, Max	36.8, 51.1	-6, 7.4	38.6, 50	-5, 8	38.8, 53.9	-8.6, 8.2

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Albumin (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	40
	Mean (SD)	45.41 (3.21)	0.48 (3.24)	45.31 (3.17)	0.37 (2.63)	45.25 (3.94)	0.05 (4.13)
	Median	45.70	0.00	45.70	-0.30	45.15	-0.30
	Min, Max	37.3, 51	-5, 9.4	35.8, 50.3	-3.6, 7.5	38.3, 56.4	-8.6, 10.3

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alkaline Phosphatase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	82.29 (26.76)		90.00 (28.39)		77.70 (19.48)	
	Median	79.00		84.00		79.50	
	Min, Max	51, 160		43, 190		40, 139	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alkaline Phosphatase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	42	42	51	51	45	45
	Mean (SD)	85.31 (30.21)	2.17 (18.15)	92.41 (24.13)	2.12 (25.12)	77.71 (19.40)	0.07 (12.16)
	Median	78.00	1.00	90.00	1.00	75.00	0.00
	Min, Max	52, 176	-49, 72	48, 144	-130, 41	42, 132	-23, 33
Week 24	n	42	42	47	47	40	40
	Mean (SD)	84.52 (34.22)	1.24 (23.55)	94.28 (24.68)	3.66 (24.79)	78.18 (22.27)	0.73 (14.70)
	Median	77.00	3.00	91.00	5.00	76.50	-1.50
	Min, Max	37, 188	-71, 88	52, 176	-119, 56	38, 154	-24, 49

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alkaline Phosphatase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	41	41	42	42
	Mean (SD)	89.00 (31.41)	5.26 (15.12)	92.05 (19.64)	1.12 (28.54)	73.21 (20.96)	-4.21 (17.19)
	Median	85.00	6.00	89.00	4.00	73.50	-5.00
	Min, Max	52, 185	-34, 30	55, 149	-114, 74	26, 125	-79, 28
Week 46	n	40	40	45	45	40	40
	Mean (SD)	82.33 (26.36)	-0.30 (25.78)	88.49 (22.14)	-2.40 (29.05)	76.73 (19.60)	-2.10 (14.20)
	Median	78.00	4.00	88.00	0.00	74.00	-1.50
	Min, Max	39, 183	-98, 41	46, 146	-115, 50	36, 129	-45, 22

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alanine Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	24.11 (18.41)		25.87 (16.56)		24.24 (16.57)	
	Median	19.00		20.00		18.00	
	Min, Max	9, 87		7, 78		7, 74	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	24.33 (15.84)	0.02 (15.01)	24.61 (14.26)	-1.73 (14.36)	31.04 (19.88)	6.47 (17.07)
	Median	19.00	2.00	19.00	1.00	23.00	5.00
	Min, Max	8, 93	-72, 33	8, 67	-53, 35	8, 81	-55, 60

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alanine Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	22.24 (13.53)	-2.22 (17.16)	27.91 (21.09)	0.66 (22.67)	28.78 (16.78)	4.63 (17.44)
	Median	19.00	-2.00	20.00	0.00	25.00	3.00
	Min, Max	5, 72	-64, 62	7, 130	-53, 110	8, 69	-57, 40
Week 36	n	39	39	41	41	42	42
	Mean (SD)	23.49 (14.50)	0.13 (11.39)	25.95 (14.01)	-2.39 (17.75)	28.55 (19.22)	4.57 (18.16)
	Median	20.00	-1.00	24.00	1.00	23.50	3.00
	Min, Max	8, 71	-37, 25	9, 79	-51, 35	7, 93	-56, 54

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Alanine Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	40
	Mean (SD)	24.27 (13.89)	-0.32 (15.55)	24.62 (16.48)	-2.91 (19.25)	27.50 (15.87)	4.10 (16.79)
	Median	22.00	-1.00	19.00	0.00	23.50	4.50
	Min, Max	7, 74	-63, 31	8, 69	-52, 47	6, 68	-51, 34

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Aspartate Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	21.67 (8.51)		24.34 (9.70)		21.85 (9.25)	
	Median	20.00		22.00		19.00	
	Min, Max	8.1, 48		11, 51		9, 50	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Aspartate Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	45
	Mean (SD)	23.47 (10.54)	2.07 (10.82)	23.59 (9.03)	-1.08 (8.84)	24.44 (10.34)	2.53 (10.32)
	Median	20.00	1.00	22.00	1.00	21.00	2.00
	Min, Max	12, 69	-27, 34	10, 56	-24, 21	10, 56	-27, 31
Week 24	n	42	42	47	47	41	41
	Mean (SD)	21.38 (7.43)	-0.10 (9.50)	24.91 (11.60)	-0.11 (12.64)	22.80 (7.26)	1.22 (9.47)
	Median	20.00	1.00	22.00	0.00	22.00	1.00
	Min, Max	12, 52	-26, 35	11, 69	-23, 53	12, 40	-31, 27

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Aspartate Aminotransferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	41	41	42	42
	Mean (SD)	21.23 (8.36)	0.15 (8.73)	23.85 (7.56)	-1.68 (10.51)	23.93 (10.23)	2.38 (11.30)
	Median	20.00	0.00	23.00	1.00	21.00	1.50
	Min, Max	12, 55	-22, 32	12, 49	-23, 17	10, 56	-29, 36
Week 46	n	41	41	45	45	40	40
	Mean (SD)	22.20 (7.72)	0.58 (8.99)	24.13 (12.11)	-1.18 (13.15)	23.53 (9.29)	2.58 (9.60)
	Median	21.00	0.00	21.00	-2.00	22.50	0.50
	Min, Max	9, 45	-22, 23	12, 72	-25, 42	10, 48	-25, 28

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bicarbonate (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	24.40 (3.41)		23.53 (3.05)		22.85 (2.89)	
	Median	24.00		24.00		23.00	
	Min, Max	17, 30		10, 30		16, 30	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	23.65 (3.76)	-0.86 (4.95)	22.84 (3.48)	-0.76 (4.11)	22.98 (3.60)	0.16 (3.78)
	Median	23.00	-2.00	23.00	-1.00	23.00	0.00
	Min, Max	16, 33	-11, 11	15, 29	-10, 11	14, 31	-12, 7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bicarbonate (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	23.55 (3.08)	-1.00 (4.11)	22.85 (3.11)	-0.62 (4.16)	23.80 (3.12)	0.83 (3.74)
	Median	24.00	-2.00	23.00	0.00	24.00	1.00
	Min, Max	17, 29	-11, 8	13, 28	-11, 9	16, 29	-7, 9
Week 36	n	39	39	41	41	42	42
	Mean (SD)	23.18 (4.04)	-1.62 (5.53)	23.80 (3.16)	0.51 (3.94)	23.40 (2.99)	0.40 (3.70)
	Median	24.00	-1.00	24.00	1.00	24.00	1.00
	Min, Max	14, 33	-12, 13	16, 30	-9, 11	16, 29	-8, 7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bicarbonate (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	40
	Mean (SD)	22.86 (3.68)	-1.77 (4.24)	22.62 (2.84)	-0.64 (3.71)	23.00 (2.44)	0.03 (3.22)
	Median	23.00	-1.00	22.00	-1.00	23.00	0.00
	Min, Max	12, 30	-12, 5	16, 30	-7, 11	15, 27	-8, 6

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bilirubin (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	7.64 (4.55)		7.45 (6.05)		8.33 (6.00)	
	Median	6.84		5.99		5.90	
	Min, Max	1.71, 22.401		0.15, 37.107		2.565, 25.479	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bilirubin (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	45
	Mean (SD)	7.22 (3.46)	-0.43 (3.12)	7.11 (5.21)	-0.36 (3.80)	9.13 (6.00)	1.02 (3.49)
	Median	6.67	-0.68	5.64	-0.34	7.52	1.54
	Min, Max	2.565, 18.81	-11.286, 5.985	1.71, 21.717	-15.561, 11.628	3.078, 35.226	-7.695, 11.97
Week 24	n	42	42	47	47	41	41
	Mean (SD)	7.41 (3.83)	-0.22 (3.22)	7.52 (4.05)	0.14 (4.98)	9.08 (6.17)	1.03 (3.99)
	Median	7.27	0.51	6.16	0.34	6.84	0.51
	Min, Max	1.71, 21.204	-14.364, 3.762	2.565, 18.981	-18.126, 14.022	2.736, 30.951	-9.234, 10.602

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Bilirubin (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	41	41	42	42
	Mean (SD)	7.31 (3.63)	-0.43 (3.68)	7.03 (3.38)	0.30 (2.99)	9.16 (8.53)	1.17 (5.25)
	Median	6.84	0.00	6.50	0.86	6.24	0.26
	Min, Max	2.565, 20.178	-15.39, 4.788	2.565, 15.048	-10.089, 6.669	3.078, 52.497	-5.814, 27.018
Week 46	n	41	41	45	45	40	40
	Mean (SD)	8.46 (4.73)	0.72 (4.94)	8.14 (4.62)	1.11 (4.27)	9.49 (7.33)	1.50 (3.86)
	Median	7.35	0.00	6.84	0.34	6.84	1.45
	Min, Max	2.907, 27.873	-6.84, 26.163	2.565, 25.65	-11.286, 13.338	3.078, 35.568	-5.643, 11.115

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Calcium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	2.28 (0.14)		2.29 (0.11)		2.32 (0.11)	
	Median	2.28		2.30		2.30	
	Min, Max	1.75, 2.525		2.075, 2.725		1.925, 2.525	
Week 12	n	42	42	51	51	45	45
	Mean (SD)	2.28 (0.14)	-0.01 (0.13)	2.31 (0.10)	0.02 (0.10)	2.31 (0.08)	-0.02 (0.12)
	Median	2.30	-0.02	2.30	0.02	2.33	-0.02
	Min, Max	1.8, 2.525	-0.375, 0.325	2.125, 2.575	-0.175, 0.25	2.175, 2.475	-0.225, 0.4

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Calcium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	40	40
	Mean (SD)	2.24 (0.17)	-0.04 (0.17)	2.32 (0.11)	0.03 (0.11)	2.29 (0.13)	-0.03 (0.16)
	Median	2.28	0.00	2.33	0.02	2.30	-0.02
	Min, Max	1.775, 2.475	-0.55, 0.275	2.125, 2.625	-0.175, 0.275	1.725, 2.525	-0.475, 0.45
Week 36	n	38	38	41	41	41	41
	Mean (SD)	2.27 (0.16)	-0.01 (0.12)	2.28 (0.12)	-0.01 (0.12)	2.28 (0.12)	-0.04 (0.14)
	Median	2.28	0.00	2.28	0.00	2.28	-0.05
	Min, Max	1.65, 2.55	-0.25, 0.2	2.075, 2.6	-0.325, 0.225	1.95, 2.475	-0.3, 0.275

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Calcium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	40	45	45	40	40
	Mean (SD)	2.27 (0.19)	-0.01 (0.16)	2.28 (0.15)	-0.02 (0.15)	2.29 (0.11)	-0.03 (0.14)
	Median	2.30	0.02	2.30	0.00	2.28	-0.05
	Min, Max	1.575, 2.5	-0.575, 0.25	1.725, 2.475	-0.425, 0.3	2.1, 2.575	-0.275, 0.3

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		45	
	Mean (SD)	4.46 (0.95)		4.47 (0.94)		4.50 (0.92)	
	Median	4.35		4.43		4.33	
	Min, Max	2.745, 7.382		2.461, 6.993		2.901, 7.382	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	44
	Mean (SD)	4.53 (0.93)	0.07 (0.68)	4.47 (1.05)	0.02 (1.02)	4.73 (1.07)	0.17 (0.61)
	Median	4.38	0.13	4.40	0.00	4.46	0.15
	Min, Max	2.357, 6.397	-2.046, 1.295	2.15, 8.107	-3.108, 4.947	2.642, 7.278	-1.269, 1.631
Week 24	n	42	42	47	47	41	40
	Mean (SD)	4.61 (1.00)	0.15 (0.66)	4.53 (0.99)	0.06 (0.84)	4.62 (0.91)	0.08 (0.77)
	Median	4.49	0.21	4.46	0.21	4.58	0.03
	Min, Max	2.124, 7.123	-2.046, 1.528	2.202, 7.148	-4.014, 1.269	2.668, 6.579	-1.347, 2.331

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	41	41	42	41
	Mean (SD)	4.61 (1.04)	0.15 (0.73)	4.45 (0.94)	-0.02 (1.03)	4.41 (0.88)	-0.14 (0.68)
	Median	4.55	0.27	4.20	0.00	4.48	-0.21
	Min, Max	2.927, 7.615	-2.746, 1.528	2.331, 6.734	-3.237, 3.237	2.771, 6.475	-1.088, 2.072
Week 46	n	40	40	45	45	40	39
	Mean (SD)	4.45 (0.84)	-0.02 (0.79)	4.48 (0.90)	-0.03 (0.93)	4.66 (1.01)	0.09 (0.74)
	Median	4.47	0.22	4.25	0.03	4.75	-0.03
	Min, Max	2.331, 6.216	-3.005, 1.295	2.823, 6.63	-3.237, 1.916	3.004, 7.382	-1.062, 2.202

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Chloride (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	103.78 (2.91)		103.62 (3.48)		103.43 (3.02)	
	Median	103.00		104.00		103.50	
	Min, Max	98, 114		96, 112		98, 110	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	103.30 (3.13)	-0.44 (3.22)	103.55 (2.91)	-0.16 (3.81)	102.58 (2.58)	-0.84 (2.70)
	Median	104.00	0.00	104.00	1.00	102.00	-1.00
	Min, Max	97, 110	-7, 6	93, 114	-9, 8	95, 108	-6, 4

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Chloride (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	41	41	47	47	41	41
	Mean (SD)	102.76 (3.40)	-1.07 (4.17)	103.15 (2.55)	-0.89 (4.06)	102.66 (3.31)	-0.63 (2.98)
	Median	103.00	-1.00	103.00	-1.00	103.00	0.00
	Min, Max	94, 111	-17, 7	98, 114	-12, 11	97, 109	-8, 5
Week 36	n	39	39	41	41	42	42
	Mean (SD)	102.72 (3.10)	-0.95 (3.48)	103.17 (2.23)	-0.88 (3.47)	102.79 (2.37)	-0.52 (3.12)
	Median	103.00	0.00	103.00	-1.00	103.00	0.00
	Min, Max	94, 110	-12, 5	98, 109	-7, 5	98, 108	-6, 6

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Chloride (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	44	44	40	40
	Mean (SD)	102.32 (4.47)	-1.37 (4.37)	103.20 (2.27)	-0.48 (3.90)	102.38 (3.07)	-0.88 (3.57)
	Median	102.00	-1.00	104.00	0.00	102.00	-1.00
	Min, Max	82, 108	-20, 6	98, 107	-8, 8	96, 109	-11, 7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatine Kinase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	125.69 (68.77)		161.36 (176.0)		152.00 (87.20)	
	Median	104.00		115.00		130.50	
	Min, Max	1.17, 385		46, 1246		48, 397	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatine Kinase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	45
	Mean (SD)	136.56 (74.05)	12.79 (67.86)	152.24 (105.5)	8.10 (86.05)	144.77 (107.2)	-7.35 (74.69)
	Median	127.00	11.00	110.00	1.00	118.00	6.00
	Min, Max	34, 325	-181, 243.83	48, 526	-234, 342	1.45, 528	-163, 282
Week 24	n	42	42	47	47	41	41
	Mean (SD)	150.55 (96.11)	26.62 (87.62)	132.36 (63.01)	-13.70 (69.91)	165.78 (115.2)	14.85 (82.81)
	Median	126.50	4.50	119.00	3.00	139.00	-2.00
	Min, Max	40, 467	-195, 241	42, 314	-262, 86	47, 546	-163, 300

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatine Kinase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	41	41	42	42
	Mean (SD)	132.79 (70.06)	8.61 (66.63)	195.17 (202.9)	43.10 (187.0)	163.62 (103.3)	10.45 (60.73)
	Median	121.00	-7.00	145.00	9.00	130.00	3.00
	Min, Max	37, 311	-144, 205.83	30, 1245	-216, 1004	33, 517	-147, 160
Week 46	n	41	41	45	45	40	40
	Mean (SD)	160.05 (97.76)	35.46 (89.54)	254.84 (596.7)	110.73 (580.9)	168.60 (116.1)	11.85 (71.50)
	Median	147.00	21.00	126.00	11.00	140.00	1.50
	Min, Max	41, 502	-214, 254	51, 4076	-241, 3832	32, 621	-131, 255

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatinine (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		45	
	Mean (SD)	96.08 (130.6)		77.29 (33.49)		75.89 (16.20)	
	Median	74.26		70.72		74.26	
	Min, Max	46.852, 923.78		47.736, 292.604		42.432, 114.92	
Week 12	n	43	43	51	51	44	43
	Mean (SD)	76.93 (14.43)	-15.77 (130.7)	72.51 (15.23)	-4.91 (33.67)	76.00 (16.83)	0.64 (10.28)
	Median	76.91	3.54	71.60	-0.88	76.91	0.88
	Min, Max	45.084, 109.616	-848.64, 39.78	47.736, 130.832	-222.768, 32.708	45.084, 128.18	-25.636, 18.564

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatinine (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	40
	Mean (SD)	96.10 (117.2)	2.48 (180.1)	74.86 (18.40)	-3.71 (37.09)	87.19 (76.09)	12.44 (74.28)
	Median	80.44	3.54	71.60	2.65	74.26	-0.44
	Min, Max	43.316, 830.96	-848.64, 774.384	38.012, 137.904	-223.652, 49.504	47.736, 548.964	-20.332, 464.984
Week 36	n	39	39	41	41	42	41
	Mean (SD)	76.00 (15.49)	-19.15 (141.1)	69.71 (12.15)	-8.43 (38.06)	77.39 (44.05)	2.59 (40.29)
	Median	76.91	3.54	67.18	-2.65	71.60	-1.77
	Min, Max	49.504, 102.544	-874.276, 41.548	49.504, 97.24	-234.26, 15.912	42.432, 335.92	-32.708, 243.1

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Creatinine (µmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	40	45	45	40	39
	Mean (SD)	79.76 (18.36)	-15.67 (138.3)	85.83 (86.55)	7.88 (96.00)	72.36 (14.88)	-2.15 (10.43)
	Median	83.10	3.09	72.49	-1.77	73.37	-3.54
	Min, Max	48.62, 124.644	-861.9, 52.156	45.968, 646.204	-222.768, 594.048	40.664, 108.732	-25.636, 23.868

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Glucose (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	5.91 (1.62)		5.63 (1.48)		5.58 (0.88)	
	Median	5.38		5.16		5.25	
	Min, Max	3.885, 11.267		3.33, 12.21		4.274, 8.436	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Glucose (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	50	50	45	45
	Mean (SD)	5.92 (2.23)	0.03 (1.82)	5.71 (1.19)	0.03 (0.84)	5.91 (1.53)	0.31 (1.41)
	Median	5.38	-0.06	5.33	0.11	5.72	0.06
	Min, Max	3.996, 18.87	-4.163, 7.714	4.218, 9.269	-3.663, 2.165	3.996, 10.712	-2.331, 4.329
Week 24	n	41	41	45	45	41	41
	Mean (SD)	6.17 (2.03)	0.40 (1.85)	5.81 (1.26)	0.08 (1.21)	5.82 (1.33)	0.19 (1.19)
	Median	5.50	0.22	5.44	0.11	5.61	0.11
	Min, Max	3.885, 12.654	-4.884, 6.937	4.163, 10.712	-4.329, 2.997	3.608, 11.25	-2.081, 4.035

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Glucose (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	39	39	39	39
	Mean (SD)	6.37 (2.51)	0.51 (1.94)	5.85 (1.85)	0.32 (1.06)	6.02 (1.53)	0.41 (1.42)
	Median	5.52	0.28	5.16	0.05	5.66	0.33
	Min, Max	4.385, 19.481	-4.329, 8.325	4.218, 13.542	-1.554, 4.218	3.663, 10.828	-1.443, 3.663
Week 46	n	40	40	44	44	40	40
	Mean (SD)	6.13 (2.28)	0.41 (1.62)	5.98 (2.17)	0.43 (1.17)	5.90 (1.41)	0.30 (1.43)
	Median	5.52	0.06	5.25	0.11	5.72	0.25
	Min, Max	4.107, 16.761	-3.497, 5.605	4.385, 15.651	-0.943, 5.272	4.285, 13.098	-2.42, 5.883

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	25.91 (23.33)		31.09 (39.80)		23.11 (10.37)	
	Median	17.00		20.00		21.00	
	Min, Max	8, 118		8, 266		9, 52	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	24.21 (17.41)	-2.14 (14.65)	33.24 (36.90)	1.69 (48.58)	23.87 (12.43)	0.80 (7.51)
	Median	18.00	-1.00	21.00	1.00	21.00	2.00
	Min, Max	7, 93	-73, 25	7, 248	-239, 234	9, 63	-21, 20

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	22.67 (13.16)	-4.00 (14.05)	29.53 (20.94)	-2.02 (38.40)	25.32 (16.36)	1.63 (17.24)
	Median	18.00	0.00	23.00	1.00	23.00	1.00
	Min, Max	9, 64	-57, 9	8, 109	-243, 45	8, 112	-23, 97
Week 36	n	39	39	41	41	42	42
	Mean (SD)	22.56 (13.95)	-2.69 (11.11)	28.39 (26.53)	-4.05 (44.76)	24.24 (11.48)	0.76 (10.53)
	Median	17.00	0.00	21.00	1.00	22.50	1.50
	Min, Max	7, 64	-54, 10	7, 145	-245, 103	8, 61	-22, 35

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	40
	Mean (SD)	23.73 (13.39)	-2.88 (15.64)	31.64 (31.49)	-1.60 (43.82)	25.25 (11.01)	1.63 (10.56)
	Median	19.00	1.00	19.00	1.00	23.00	1.00
	Min, Max	8, 66	-62, 18	8, 178	-247, 67	10, 54	-23, 26

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: HDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		45	
	Mean (SD)	1.07 (0.30)		1.09 (0.31)		0.98 (0.30)	
	Median	1.06		1.04		0.98	
	Min, Max	0.363, 1.787		0.518, 2.072		0.389, 1.735	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: HDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	44
	Mean (SD)	1.06 (0.23)	-0.01 (0.24)	0.99 (0.30)	-0.10 (0.24)	0.95 (0.26)	-0.01 (0.22)
	Median	1.04	0.00	0.96	-0.08	0.91	-0.01
	Min, Max	0.622, 1.528	-0.492, 0.751	0.44, 1.761	-1.088, 0.259	0.466, 1.658	-0.466, 0.855
Week 24	n	42	42	47	47	41	40
	Mean (SD)	1.01 (0.30)	-0.05 (0.25)	1.05 (0.27)	-0.04 (0.23)	0.96 (0.24)	0.00 (0.27)
	Median	0.97	-0.04	1.01	-0.05	0.93	-0.03
	Min, Max	0.492, 1.709	-0.57, 0.544	0.311, 1.917	-0.57, 0.751	0.596, 1.632	-0.829, 1.036

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: HDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	41	41	42	41
	Mean (SD)	1.03 (0.28)	-0.03 (0.22)	1.05 (0.29)	-0.03 (0.21)	0.91 (0.25)	-0.04 (0.29)
	Median	0.96	-0.03	1.01	0.00	0.83	-0.03
	Min, Max	0.518, 1.684	-0.648, 0.518	0.337, 1.994	-0.725, 0.285	0.518, 1.606	-0.959, 0.907
Week 46	n	41	41	45	45	40	39
	Mean (SD)	1.02 (0.31)	-0.04 (0.25)	1.08 (0.26)	0.01 (0.29)	0.95 (0.27)	-0.02 (0.27)
	Median	0.98	-0.05	1.06	-0.05	0.92	-0.05
	Min, Max	0.544, 1.761	-0.726, 0.595	0.596, 1.761	-0.492, 1.14	0.414, 1.476	-0.855, 0.959

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Potassium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	4.33 (0.37)		4.38 (0.43)		4.32 (0.33)	
	Median	4.30		4.40		4.30	
	Min, Max	3.8, 5.2		3.6, 5.8		3.7, 5	
Week 12	n	42	42	51	51	44	44
	Mean (SD)	4.35 (0.36)	0.04 (0.33)	4.23 (0.33)	-0.18 (0.46)	4.28 (0.35)	-0.06 (0.34)
	Median	4.35	0.10	4.20	-0.10	4.30	-0.10
	Min, Max	3.4, 5.2	-0.7, 0.6	3.5, 5.1	-1.2, 0.8	3.7, 5.1	-0.7, 0.7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Potassium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	41	41	47	47	41	41
	Mean (SD)	4.22 (0.39)	-0.10 (0.36)	4.23 (0.39)	-0.18 (0.51)	4.31 (0.43)	-0.02 (0.52)
	Median	4.30	-0.10	4.20	-0.20	4.30	0.00
	Min, Max	3.4, 5.5	-1.2, 0.7	3.2, 5.4	-2.1, 0.7	3.8, 5.9	-0.8, 1.9
Week 36	n	39	39	41	41	42	42
	Mean (SD)	4.25 (0.38)	-0.08 (0.43)	4.28 (0.37)	-0.08 (0.46)	4.29 (0.35)	-0.04 (0.47)
	Median	4.20	-0.10	4.20	-0.10	4.25	-0.05
	Min, Max	3.4, 5.5	-1, 0.9	3.4, 5.1	-1.2, 1.5	3.5, 5.4	-1.3, 1.3

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Potassium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	40	45	45	40	40
	Mean (SD)	4.27 (0.37)	-0.06 (0.44)	4.35 (0.37)	0.01 (0.47)	4.28 (0.40)	-0.03 (0.51)
	Median	4.30	-0.10	4.30	0.00	4.20	0.00
	Min, Max	3.6, 5.2	-0.9, 0.9	3.8, 5.6	-0.9, 1.6	3.7, 5.2	-1, 0.9

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Lactate Dehydrogenase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	183.44 (46.55)		180.51 (38.90)		184.59 (39.94)	
	Median	179.00		176.00		177.50	
	Min, Max	116, 392		30, 278		124, 295	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Lactate Dehydrogenase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	45
	Mean (SD)	190.23 (52.08)	6.23 (46.74)	189.16 (33.47)	8.10 (46.01)	190.69 (56.63)	5.98 (52.17)
	Median	191.00	0.00	184.00	9.00	178.00	0.00
	Min, Max	120, 427	-166, 178	131, 296	-131, 136	93, 458	-71, 273
Week 24	n	42	42	47	47	41	41
	Mean (SD)	186.62 (41.92)	2.40 (50.18)	201.36 (83.85)	20.98 (90.78)	194.17 (42.84)	5.90 (38.31)
	Median	180.50	3.50	188.00	6.00	192.00	1.00
	Min, Max	125, 312	-212, 125	133, 692	-105, 541	127, 331	-70, 139

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Lactate Dehydrogenase (U/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	39	39	41	41	42	42
	Mean (SD)	187.00 (42.36)	2.49 (47.02)	187.98 (33.38)	2.83 (34.69)	192.67 (41.31)	4.76 (39.28)
	Median	183.00	-2.00	186.00	1.00	190.00	1.50
	Min, Max	111, 336	-208, 128	137, 299	-107, 94	114, 268	-82, 107
Week 46	n	41	41	45	45	40	40
	Mean (SD)	183.80 (40.56)	-1.17 (36.74)	191.87 (45.62)	8.00 (47.30)	195.58 (47.34)	6.43 (39.58)
	Median	182.00	-1.00	185.00	3.00	188.00	3.00
	Min, Max	113, 289	-139, 70	118, 352	-120, 137	113, 324	-61, 157

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		45	
	Mean (SD)	2.69 (0.84)		2.58 (0.83)		2.67 (0.71)	
	Median	2.39		2.58		2.55	
	Min, Max	1.45, 5.486		1.036, 5.004		1.02, 4.17	
Week 12	n	43	43	51	51	45	44
	Mean (SD)	2.75 (0.78)	0.06 (0.58)	2.62 (0.86)	0.05 (0.77)	2.95 (0.98)	0.22 (0.59)
	Median	2.65	0.13	2.49	0.02	2.74	0.09
	Min, Max	1.259, 4.413	-1.761, 1.083	0.518, 5.398	-2.46, 2.041	1.254, 5.465	-0.611, 1.704

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	40
	Mean (SD)	2.83 (0.85)	0.13 (0.63)	2.70 (0.92)	0.12 (0.75)	2.83 (0.79)	0.12 (0.68)
	Median	2.70	0.20	2.57	0.17	2.85	-0.01
	Min, Max	1.15, 5.641	-1.865, 1.233	0.518, 5.465	-3.367, 1.295	1.45, 5.076	-0.984, 2.175
Week 36	n	38	38	41	41	42	41
	Mean (SD)	2.78 (0.82)	0.08 (0.71)	2.62 (0.79)	0.05 (0.85)	2.64 (0.72)	-0.09 (0.58)
	Median	2.50	0.18	2.41	0.13	2.69	-0.10
	Min, Max	1.652, 5.315	-2.486, 1.585	0.943, 5.035	-2.331, 2.471	1.425, 4.533	-1.45, 1.518

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	39
	Mean (SD)	2.61 (0.65)	-0.11 (0.79)	2.67 (0.79)	0.07 (0.80)	2.84 (0.89)	0.08 (0.77)
	Median	2.62	0.01	2.52	0.18	2.77	0.00
	Min, Max	0.793, 4.268	-2.823, 1.233	1.207, 4.792	-2.678, 1.425	1.528, 4.74	-1.471, 2.269

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Sodium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	140.29 (2.76)		139.53 (3.17)		140.26 (2.68)	
	Median	140.00		140.00		140.00	
	Min, Max	134, 150		128, 146		136, 147	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Sodium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	45
	Mean (SD)	139.58 (2.76)	-0.58 (3.08)	139.63 (2.88)	0.02 (3.73)	139.20 (3.47)	-0.98 (3.42)
	Median	140.00	-1.00	139.00	0.00	140.00	0.00
	Min, Max	132, 144	-8, 7	130, 152	-7, 11	122, 145	-18, 4
Week 24	n	41	41	47	47	40	40
	Mean (SD)	139.10 (3.34)	-1.17 (4.46)	139.68 (2.10)	-0.30 (2.98)	139.45 (2.87)	-0.83 (3.12)
	Median	140.00	-1.00	140.00	0.00	140.00	-1.00
	Min, Max	126, 143	-20, 7	137, 145	-6, 7	131, 145	-8, 6

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Sodium (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	41	41	42	42
	Mean (SD)	139.18 (2.36)	-0.82 (3.19)	139.27 (2.20)	-0.51 (2.97)	139.29 (2.33)	-0.98 (3.04)
	Median	139.00	-0.50	140.00	0.00	139.00	-1.00
	Min, Max	133, 144	-9, 4	135, 143	-6, 7	136, 145	-7, 5
Week 46	n	40	40	44	44	40	40
	Mean (SD)	139.05 (3.75)	-1.00 (4.04)	138.86 (2.29)	-0.66 (3.46)	139.20 (2.46)	-1.05 (3.03)
	Median	139.00	-1.00	139.00	-1.00	139.00	-1.00
	Min, Max	125, 146	-15, 9	133, 143	-8, 9	133, 145	-10, 4

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Protein (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	73.57 (4.25)		73.59 (4.86)		71.89 (5.43)	
	Median	73.70		73.50		72.05	
	Min, Max	61.4, 81.8		60.2, 89.9		59, 81.9	
Week 12	n	43	43	51	51	45	45
	Mean (SD)	71.89 (4.37)	-1.63 (4.45)	73.32 (4.10)	-0.13 (4.27)	72.45 (5.09)	0.27 (4.09)
	Median	72.30	-0.80	72.80	0.10	72.00	0.60
	Min, Max	62.1, 80.5	-13.3, 6.8	64.6, 83.1	-8.5, 10	54.4, 86.4	-8.5, 8.5

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Protein (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	71.45 (5.77)	-1.96 (5.80)	74.19 (4.74)	0.88 (5.54)	73.35 (5.75)	1.61 (7.00)
	Median	72.45	-2.05	73.40	-0.20	73.80	2.90
	Min, Max	55, 79.6	-17, 8.1	64.8, 88.7	-7.7, 26	62.4, 84.4	-14.3, 17.5
Week 36	n	39	39	41	41	42	42
	Mean (SD)	72.46 (4.13)	-0.89 (4.69)	72.94 (4.11)	-0.14 (4.84)	71.38 (4.30)	-0.40 (5.78)
	Median	72.70	-0.60	72.40	-0.70	71.35	-0.65
	Min, Max	63.3, 81.5	-12.4, 8.7	66.4, 85.9	-8.5, 16.4	63.2, 78.5	-12.9, 15.7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Protein (g/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	45	45	40	40
	Mean (SD)	72.16 (4.43)	-1.24 (5.29)	72.78 (3.64)	-0.52 (5.20)	72.61 (6.01)	0.99 (6.04)
	Median	72.30	-1.10	72.80	-0.70	72.25	0.55
	Min, Max	64.4, 87.2	-12.4, 12.2	65.8, 81.9	-17.8, 13.2	57.3, 84.5	-9.1, 18.7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Triglycerides (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		45	
	Mean (SD)	1.61 (1.17)		1.76 (1.11)		1.89 (1.36)	
	Median	1.20		1.37		1.40	
	Min, Max	0.384, 6.509		0.554, 6.023		0.463, 7.04	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Triglycerides (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	45	44
	Mean (SD)	1.65 (1.24)	0.03 (1.05)	1.99 (1.25)	0.24 (0.98)	1.86 (1.16)	-0.04 (0.89)
	Median	1.18	0.03	1.68	0.17	1.68	0.10
	Min, Max	0.486, 6.633	-2.837, 3.797	0.52, 6.735	-1.48, 5.198	0.362, 7.526	-3.232, 1.853
Week 24	n	42	42	47	47	41	40
	Mean (SD)	1.73 (1.24)	0.10 (0.77)	1.74 (1.11)	-0.05 (0.81)	1.89 (1.11)	-0.05 (0.92)
	Median	1.31	0.06	1.51	0.07	1.71	0.02
	Min, Max	0.429, 7.017	-2.419, 2.08	0.531, 7.029	-1.887, 1.955	0.373, 5.503	-2.339, 3.028

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Triglycerides (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	38	38	41	41	42	41
	Mean (SD)	1.85 (1.33)	0.21 (0.75)	1.75 (1.19)	-0.08 (0.91)	2.09 (1.48)	0.18 (1.39)
	Median	1.40	0.09	1.31	-0.07	1.54	0.02
	Min, Max	0.429, 6.95	-1.854, 1.854	0.542, 6.057	-1.819, 2.362	0.373, 6.622	-2.633, 5.616
Week 46	n	41	41	45	45	40	39
	Mean (SD)	1.86 (1.11)	0.25 (0.99)	1.65 (1.25)	-0.21 (0.86)	1.95 (1.16)	0.10 (1.14)
	Median	1.61	0.21	1.42	-0.08	1.72	0.01
	Min, Max	0.486, 5.707	-2.792, 2.249	0.61, 8.645	-2.475, 2.622	0.52, 5.221	-2.327, 3.186

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Urea Nitrogen (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	3.19 (1.96)		2.85 (1.06)		2.82 (1.47)	
	Median	2.64		2.68		2.55	
	Min, Max	1.035, 11.424		1.25, 7.104		0.893, 11.067	
Week 12	n	43	43	51	51	44	44
	Mean (SD)	2.95 (2.04)	-0.14 (1.45)	2.55 (0.78)	-0.32 (0.95)	2.90 (1.78)	0.05 (0.80)
	Median	2.57	-0.18	2.46	-0.14	2.62	0.07
	Min, Max	1.285, 14.994	-7.354, 3.57	1.071, 4.141	-4.712, 1.749	1.428, 13.209	-1.606, 2.142

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Urea Nitrogen (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	47	47	41	41
	Mean (SD)	3.25 (2.93)	0.14 (2.85)	2.66 (1.00)	-0.23 (1.18)	3.02 (1.99)	0.23 (1.69)
	Median	2.68	0.00	2.46	0.00	2.54	0.00
	Min, Max	1, 18.707	-7.747, 15.708	0.75, 5.891	-4.962, 1.571	1.071, 11.424	-2.177, 8.211
Week 36	n	39	39	41	41	42	42
	Mean (SD)	2.90 (2.30)	-0.22 (1.81)	2.49 (0.87)	-0.31 (1.08)	3.01 (2.14)	0.22 (1.21)
	Median	2.57	-0.29	2.32	-0.18	2.50	-0.02
	Min, Max	1, 16.065	-8.247, 4.641	0.964, 5.355	-4.605, 1.071	1.321, 14.637	-1.999, 3.677

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: Urea Nitrogen (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	40	40	45	45	40	40
	Mean (SD)	2.83 (2.42)	-0.30 (1.84)	2.80 (1.49)	-0.03 (1.53)	3.07 (2.61)	0.22 (1.55)
	Median	2.57	-0.39	2.46	-0.04	2.46	-0.07
	Min, Max	0.75, 16.779	-8.318, 5.355	1.107, 10.353	-4.641, 7.533	1.392, 18.207	-1.927, 7.14

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: VLDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	41		50		42	
	Mean (SD)	0.62 (0.29)		0.70 (0.30)		0.73 (0.36)	
	Median	0.52		0.63		0.60	
	Min, Max	0.176, 1.336		0.254, 1.487		0.212, 1.481	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: VLDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	38	36	45	45	41	40
	Mean (SD)	0.61 (0.29)	0.01 (0.26)	0.75 (0.30)	0.07 (0.26)	0.76 (0.30)	0.03 (0.29)
	Median	0.52	0.02	0.72	0.08	0.75	0.07
	Min, Max	0.223, 1.432	-0.694, 0.839	0.238, 1.388	-0.679, 0.549	0.166, 1.311	-0.818, 0.85
Week 24	n	38	37	45	44	37	36
	Mean (SD)	0.68 (0.32)	0.06 (0.28)	0.72 (0.33)	0.01 (0.34)	0.75 (0.32)	0.01 (0.32)
	Median	0.59	0.03	0.69	0.03	0.76	0.01
	Min, Max	0.197, 1.368	-0.533, 0.788	0.243, 1.549	-0.793, 0.896	0.171, 1.44	-0.767, 0.627

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: VLDL Cholesterol (mmol/L)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 36	n	33	32	37	36	33	32
	Mean (SD)	0.69 (0.33)	0.10 (0.30)	0.66 (0.33)	-0.04 (0.32)	0.68 (0.36)	-0.02 (0.38)
	Median	0.62	0.04	0.54	-0.03	0.64	-0.01
	Min, Max	0.197, 1.549	-0.347, 0.849	0.249, 1.435	-0.715, 0.663	0.171, 1.533	-1.005, 0.772
Week 46	n	37	35	44	42	34	33
	Mean (SD)	0.76 (0.34)	0.17 (0.32)	0.68 (0.30)	-0.07 (0.28)	0.73 (0.28)	-0.01 (0.28)
	Median	0.73	0.10	0.65	-0.02	0.67	0.01
	Min, Max	0.223, 1.435	-0.492, 1	0.28, 1.409	-0.735, 0.673	0.238, 1.254	-0.761, 0.497

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Albumin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	45.13 (3.35)	
	Median	45.00	
	Min, Max	34.7, 53.6	
Week 12	n	139	139
	Mean (SD)	44.84 (3.00)	-0.29 (3.07)
	Median	45.10	0.10
	Min, Max	37.9, 52.5	-11, 8.1

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Albumin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	45.01 (3.64)	0.04 (3.52)
	Median	45.50	0.10
	Min, Max	30.8, 51.5	-13.5, 8.4
Week 36	n	122	122
	Mean (SD)	45.14 (2.96)	0.19 (3.41)
	Median	45.25	0.00
	Min, Max	36.8, 53.9	-8.6, 8.2

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Albumin (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	126
	Mean (SD)	45.32 (3.42)	0.30 (3.34)
	Median	45.55	-0.15
	Min, Max	35.8, 56.4	-8.6, 10.3

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alkaline Phosphatase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	83.66 (25.68)	
	Median	80.00	
	Min, Max	40, 190	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alkaline Phosphatase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	138	138
	Mean (SD)	85.46 (25.38)	1.46 (19.43)
	Median	81.50	1.00
	Min, Max	42, 176	-130, 72
Week 24	n	129	129
	Mean (SD)	86.11 (28.11)	1.96 (21.59)
	Median	81.00	3.00
	Min, Max	37, 188	-119, 88

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alkaline Phosphatase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	121	121
	Mean (SD)	84.55 (25.56)	0.57 (21.40)
	Median	82.00	1.00
	Min, Max	26, 185	-114, 74
Week 46	n	125	125
	Mean (SD)	82.75 (23.17)	-1.63 (23.93)
	Median	79.00	0.00
	Min, Max	36, 183	-115, 50

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alanine Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	24.80 (17.06)	
	Median	19.00	
	Min, Max	7, 87	
Week 12	n	139	139
	Mean (SD)	26.60 (16.90)	1.47 (15.77)
	Median	22.00	2.00
	Min, Max	8, 93	-72, 60

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alanine Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	26.35 (17.68)	0.98 (19.46)
	Median	21.00	1.00
	Min, Max	5, 130	-64, 110
Week 36	n	122	122
	Mean (SD)	26.06 (16.14)	0.81 (16.28)
	Median	22.00	1.50
	Min, Max	7, 93	-56, 54

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Alanine Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	126
	Mean (SD)	25.42 (15.43)	0.16 (17.45)
	Median	21.50	0.50
	Min, Max	6, 74	-63, 47

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Aspartate Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	22.71 (9.22)	
	Median	20.00	
	Min, Max	8.1, 51	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Aspartate Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	139
	Mean (SD)	23.83 (9.88)	1.06 (10.03)
	Median	21.00	1.00
	Min, Max	10, 69	-27, 34
Week 24	n	130	130
	Mean (SD)	23.11 (9.17)	0.31 (10.67)
	Median	21.00	1.00
	Min, Max	11, 69	-31, 53

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Aspartate Aminotransferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	122	122
	Mean (SD)	23.04 (8.82)	0.30 (10.32)
	Median	21.00	1.00
	Min, Max	10, 56	-29, 36
Week 46	n	126	126
	Mean (SD)	23.31 (9.92)	0.59 (10.86)
	Median	21.50	0.00
	Min, Max	9, 72	-25, 42

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bicarbonate (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	23.58 (3.16)	
	Median	24.00	
	Min, Max	10, 30	
Week 12	n	139	139
	Mean (SD)	23.14 (3.60)	-0.50 (4.28)
	Median	23.00	-1.00
	Min, Max	14, 33	-12, 11

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bicarbonate (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	23.38 (3.11)	-0.28 (4.06)
	Median	24.00	0.00
	Min, Max	13, 29	-11, 9
Week 36	n	122	122
	Mean (SD)	23.47 (3.39)	-0.20 (4.51)
	Median	24.00	0.00
	Min, Max	14, 33	-12, 13

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bicarbonate (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	126
	Mean (SD)	22.82 (3.01)	-0.80 (3.79)
	Median	23.00	0.00
	Min, Max	12, 30	-12, 11

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bilirubin (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	7.79 (5.58)	
	Median	6.50	
	Min, Max	0.15, 37.107	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bilirubin (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	139
	Mean (SD)	7.80 (5.08)	0.07 (3.54)
	Median	6.67	0.00
	Min, Max	1.71, 35.226	-15.561, 11.97
Week 24	n	130	130
	Mean (SD)	7.98 (4.79)	0.30 (4.16)
	Median	6.84	0.34
	Min, Max	1.71, 30.951	-18.126, 14.022

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Bilirubin (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	122	122
	Mean (SD)	7.85 (5.79)	0.37 (4.12)
	Median	6.50	0.43
	Min, Max	2.565, 52.497	-15.39, 27.018
Week 46	n	126	126
	Mean (SD)	8.67 (5.63)	1.11 (4.36)
	Median	7.01	0.34
	Min, Max	2.565, 35.568	-11.286, 26.163

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Calcium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	2.30 (0.12)	
	Median	2.30	
	Min, Max	1.75, 2.725	
Week 12	n	138	138
	Mean (SD)	2.30 (0.10)	-0.00 (0.11)
	Median	2.30	0.00
	Min, Max	1.8, 2.575	-0.375, 0.4

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Calcium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	129	129
	Mean (SD)	2.29 (0.14)	-0.01 (0.15)
	Median	2.30	0.00
	Min, Max	1.725, 2.625	-0.55, 0.45
Week 36	n	120	120
	Mean (SD)	2.28 (0.13)	-0.02 (0.13)
	Median	2.28	-0.02
	Min, Max	1.65, 2.6	-0.325, 0.275

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Calcium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	125	125
	Mean (SD)	2.28 (0.15)	-0.02 (0.15)
	Median	2.30	-0.02
	Min, Max	1.575, 2.575	-0.575, 0.3

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	4.48 (0.93)	
	Median	4.35	
	Min, Max	2.461, 7.382	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	138
	Mean (SD)	4.57 (1.02)	0.09 (0.80)
	Median	4.40	0.13
	Min, Max	2.15, 8.107	-3.108, 4.947
Week 24	n	130	129
	Mean (SD)	4.58 (0.96)	0.09 (0.76)
	Median	4.49	0.13
	Min, Max	2.124, 7.148	-4.014, 2.331

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	121	120
	Mean (SD)	4.49 (0.95)	-0.01 (0.83)
	Median	4.35	0.00
	Min, Max	2.331, 7.615	-3.237, 3.237
Week 46	n	125	124
	Mean (SD)	4.53 (0.91)	0.01 (0.82)
	Median	4.53	0.03
	Min, Max	2.331, 7.382	-3.237, 2.202

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Chloride (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	103.61 (3.15)	
	Median	103.50	
	Min, Max	96, 114	
Week 12	n	139	139
	Mean (SD)	103.16 (2.89)	-0.47 (3.29)
	Median	103.00	0.00
	Min, Max	93, 114	-9, 8

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Chloride (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	129	129
	Mean (SD)	102.87 (3.07)	-0.87 (3.76)
	Median	103.00	-1.00
	Min, Max	94, 114	-17, 11
Week 36	n	122	122
	Mean (SD)	102.89 (2.57)	-0.78 (3.33)
	Median	103.00	0.00
	Min, Max	94, 110	-12, 6

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Chloride (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	125	125
	Mean (SD)	102.65 (3.37)	-0.90 (3.95)
	Median	103.00	-1.00
	Min, Max	82, 109	-20, 8

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatine Kinase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	147.22 (123.9)	
	Median	115.00	
	Min, Max	1.17, 1246	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatine Kinase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	139
	Mean (SD)	144.97 (96.97)	4.55 (77.04)
	Median	118.00	2.00
	Min, Max	1.45, 528	-234, 342
Week 24	n	130	130
	Mean (SD)	148.78 (93.03)	8.33 (81.29)
	Median	126.50	2.00
	Min, Max	40, 546	-262, 300

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatine Kinase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	122	122
	Mean (SD)	164.37 (139.3)	20.83 (120.2)
	Median	130.00	4.50
	Min, Max	30, 1245	-216, 1004
Week 46	n	126	126
	Mean (SD)	196.62 (366.7)	54.85 (353.2)
	Median	136.50	10.50
	Min, Max	32, 4076	-241, 3832

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatinine (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	82.76 (76.56)	
	Median	72.49	
	Min, Max	42.432, 923.78	
Week 12	n	138	137
	Mean (SD)	75.00 (15.53)	-6.58 (75.96)
	Median	74.70	0.88
	Min, Max	45.084, 130.832	-848.64, 39.78

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatinine (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	129
	Mean (SD)	85.61 (79.73)	3.32 (112.3)
	Median	75.14	0.88
	Min, Max	38.012, 830.96	-848.64, 774.384
Week 36	n	122	121
	Mean (SD)	74.36 (28.16)	-8.15 (86.08)
	Median	70.72	0.00
	Min, Max	42.432, 335.92	-874.276, 243.1

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Creatinine (µmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	125	124
	Mean (SD)	79.57 (53.52)	-2.87 (97.43)
	Median	74.26	-1.77
	Min, Max	40.664, 646.204	-861.9, 594.048

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Glucose (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	5.70 (1.37)	
	Median	5.27	
	Min, Max	3.33, 12.21	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Glucose (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	138	138
	Mean (SD)	5.84 (1.67)	0.12 (1.39)
	Median	5.45	0.03
	Min, Max	3.996, 18.87	-4.163, 7.714
Week 24	n	127	127
	Mean (SD)	5.93 (1.57)	0.22 (1.44)
	Median	5.50	0.11
	Min, Max	3.608, 12.654	-4.884, 6.937

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Glucose (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	116	116
	Mean (SD)	6.08 (2.00)	0.41 (1.50)
	Median	5.55	0.19
	Min, Max	3.663, 19.481	-4.329, 8.325
Week 46	n	124	124
	Mean (SD)	6.00 (1.99)	0.38 (1.40)
	Median	5.44	0.11
	Min, Max	4.107, 16.761	-3.497, 5.883

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	26.92 (28.08)	
	Median	20.00	
	Min, Max	8, 266	
Week 12	n	139	139
	Mean (SD)	27.41 (25.59)	0.22 (30.68)
	Median	20.00	1.00
	Min, Max	7, 248	-239, 234

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	25.98 (17.40)	-1.51 (26.19)
	Median	21.50	1.00
	Min, Max	8, 112	-243, 97
Week 36	n	122	122
	Mean (SD)	25.10 (18.56)	-1.96 (27.25)
	Median	21.00	1.00
	Min, Max	7, 145	-245, 103

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Gamma Glutamyl Transferase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	126
	Mean (SD)	27.04 (21.37)	-0.99 (28.15)
	Median	21.00	1.00
	Min, Max	8, 178	-247, 67

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: HDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	1.05 (0.30)	
	Median	1.04	
	Min, Max	0.363, 2.072	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: HDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	138
	Mean (SD)	1.00 (0.27)	-0.04 (0.23)
	Median	0.96	-0.04
	Min, Max	0.44, 1.761	-1.088, 0.855
Week 24	n	130	129
	Mean (SD)	1.01 (0.27)	-0.03 (0.25)
	Median	0.96	-0.05
	Min, Max	0.311, 1.917	-0.829, 1.036

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: HDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	121	120
	Mean (SD)	1.00 (0.28)	-0.03 (0.24)
	Median	0.96	-0.03
	Min, Max	0.337, 1.994	-0.959, 0.907
Week 46	n	126	125
	Mean (SD)	1.02 (0.28)	-0.02 (0.27)
	Median	0.98	-0.05
	Min, Max	0.414, 1.761	-0.855, 1.14

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Potassium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	4.35 (0.38)	
	Median	4.30	
	Min, Max	3.6, 5.8	
Week 12	n	137	137
	Mean (SD)	4.28 (0.35)	-0.07 (0.39)
	Median	4.30	0.00
	Min, Max	3.4, 5.2	-1.2, 0.8

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Potassium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	129	129
	Mean (SD)	4.26 (0.40)	-0.10 (0.47)
	Median	4.30	-0.10
	Min, Max	3.2, 5.9	-2.1, 1.9
Week 36	n	122	122
	Mean (SD)	4.27 (0.36)	-0.06 (0.45)
	Median	4.20	-0.10
	Min, Max	3.4, 5.5	-1.3, 1.5

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Potassium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	125	125
	Mean (SD)	4.30 (0.38)	-0.02 (0.47)
	Median	4.30	0.00
	Min, Max	3.6, 5.6	-1, 1.6

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Lactate Dehydrogenase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	182.73 (41.50)	
	Median	177.00	
	Min, Max	30, 392	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Lactate Dehydrogenase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	139
	Mean (SD)	189.99 (47.48)	6.83 (47.97)
	Median	184.00	4.00
	Min, Max	93, 458	-166, 273
Week 24	n	130	130
	Mean (SD)	194.33 (60.60)	10.22 (65.28)
	Median	187.00	3.50
	Min, Max	125, 692	-212, 541

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Lactate Dehydrogenase (U/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	122	122
	Mean (SD)	189.28 (38.94)	3.39 (40.20)
	Median	186.00	1.00
	Min, Max	111, 336	-208, 128
Week 46	n	126	126
	Mean (SD)	190.42 (44.51)	4.52 (41.53)
	Median	184.00	1.00
	Min, Max	113, 352	-139, 157

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: LDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	2.65 (0.79)	
	Median	2.53	
	Min, Max	1.02, 5.486	
Week 12	n	139	138
	Mean (SD)	2.77 (0.88)	0.11 (0.66)
	Median	2.61	0.09
	Min, Max	0.518, 5.465	-2.46, 2.041

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: LDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	129
	Mean (SD)	2.78 (0.85)	0.13 (0.69)
	Median	2.74	0.11
	Min, Max	0.518, 5.641	-3.367, 2.175
Week 36	n	121	120
	Mean (SD)	2.68 (0.78)	0.01 (0.72)
	Median	2.54	0.03
	Min, Max	0.943, 5.315	-2.486, 2.471

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: LDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	125
	Mean (SD)	2.71 (0.78)	0.01 (0.79)
	Median	2.66	0.05
	Min, Max	0.793, 4.792	-2.823, 2.269

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Sodium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	140.00 (2.89)	
	Median	140.00	
	Min, Max	128, 150	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Sodium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	139
	Mean (SD)	139.47 (3.03)	-0.49 (3.44)
	Median	140.00	0.00
	Min, Max	122, 152	-18, 11
Week 24	n	128	128
	Mean (SD)	139.42 (2.77)	-0.74 (3.55)
	Median	140.00	-1.00
	Min, Max	126, 145	-20, 7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Sodium (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	121	121
	Mean (SD)	139.25 (2.28)	-0.77 (3.04)
	Median	139.00	-1.00
	Min, Max	133, 145	-9, 7
Week 46	n	124	124
	Mean (SD)	139.03 (2.87)	-0.90 (3.51)
	Median	139.00	-1.00
	Min, Max	125, 146	-15, 9

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Protein (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	73.04 (4.91)	
	Median	73.50	
	Min, Max	59, 89.9	
Week 12	n	139	139
	Mean (SD)	72.59 (4.53)	-0.47 (4.31)
	Median	72.60	-0.40
	Min, Max	54.4, 86.4	-13.3, 10

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Protein (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	73.04 (5.50)	0.19 (6.26)
	Median	73.30	-0.35
	Min, Max	55, 88.7	-17, 26
Week 36	n	122	122
	Mean (SD)	72.25 (4.20)	-0.47 (5.11)
	Median	72.40	-0.65
	Min, Max	63.2, 85.9	-12.9, 16.4

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Protein (g/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	126	126
	Mean (SD)	72.53 (4.72)	-0.28 (5.54)
	Median	72.45	-0.75
	Min, Max	57.3, 87.2	-17.8, 18.7

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Triglycerides (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	143	
	Mean (SD)	1.75 (1.21)	
	Median	1.31	
	Min, Max	0.384, 7.04	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Triglycerides (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	139	138
	Mean (SD)	1.84 (1.22)	0.09 (0.97)
	Median	1.53	0.10
	Min, Max	0.362, 7.526	-3.232, 5.198
Week 24	n	130	129
	Mean (SD)	1.78 (1.15)	0.00 (0.83)
	Median	1.57	0.04
	Min, Max	0.373, 7.029	-2.419, 3.028

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Triglycerides (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	121	120
	Mean (SD)	1.90 (1.34)	0.10 (1.06)
	Median	1.45	0.02
	Min, Max	0.373, 6.95	-2.633, 5.616
Week 46	n	126	125
	Mean (SD)	1.81 (1.17)	0.04 (1.01)
	Median	1.56	0.03
	Min, Max	0.486, 8.645	-2.792, 3.186

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Urea Nitrogen (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	2.95 (1.51)	
	Median	2.64	
	Min, Max	0.893, 11.424	
Week 12	n	138	138
	Mean (SD)	2.79 (1.59)	-0.15 (1.09)
	Median	2.52	-0.04
	Min, Max	1.071, 14.994	-7.354, 3.57

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Urea Nitrogen (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	130	130
	Mean (SD)	2.97 (2.09)	0.03 (2.00)
	Median	2.54	0.00
	Min, Max	0.75, 18.707	-7.747, 15.708
Week 36	n	122	122
	Mean (SD)	2.80 (1.87)	-0.10 (1.40)
	Median	2.48	-0.13
	Min, Max	0.964, 16.065	-8.247, 4.641

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: Urea Nitrogen (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	125	125
	Mean (SD)	2.90 (2.19)	-0.04 (1.64)
	Median	2.50	-0.14
	Min, Max	0.75, 18.207	-8.318, 7.533

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: VLDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	133	
	Mean (SD)	0.68 (0.32)	
	Median	0.59	
	Min, Max	0.176, 1.487	

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: VLDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	124	121
	Mean (SD)	0.71 (0.30)	0.04 (0.27)
	Median	0.65	0.05
	Min, Max	0.166, 1.432	-0.818, 0.85
Week 24	n	120	117
	Mean (SD)	0.72 (0.32)	0.02 (0.31)
	Median	0.69	0.03
	Min, Max	0.171, 1.549	-0.793, 0.896

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.2c
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population - Overall

Test: VLDL Cholesterol (mmol/L)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 36	n	103	100
	Mean (SD)	0.68 (0.33)	0.01 (0.34)
	Median	0.60	-0.01
	Min, Max	0.171, 1.549	-1.005, 0.849
Week 46	n	115	110
	Mean (SD)	0.72 (0.31)	0.03 (0.31)
	Median	0.68	0.02
	Min, Max	0.223, 1.435	-0.761, 1

Source: Listing 16.2.8.2
Glucose = Fasting Glucose or Random Glucose
N - Total number of subjects in the Safety Population, n - Number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.3c
Laboratory hematology : Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Eosinophils (10/L)	Week 12	>= 1.5	2 (1.4)
	Week 36	>= 1.5	1 (0.7)
Hematocrit (fraction of 1)	Week 12	<=0.85 x LLN	4 (2.8)
	Week 24	<=0.85 x LLN	5 (3.5)
	Week 36	<=0.85 x LLN	3 (2.1)
	Week 46	<=0.85 x LLN	5 (3.5)
Hemoglobin (g/L)	Week 12	<=0.85 x LLN	3 (2.1)

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.3c
Laboratory hematology : Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Hemoglobin (g/L)	Week 24	<=0.85 x LLN	5 (3.5)
	Week 36	<=0.85 x LLN	6 (4.2)
	Week 46	<=0.85 x LLN	6 (4.2)
Leukocytes (10/L)	Week 24	<= 3.0	1 (0.7)
	Week 36	<= 3.0	2 (1.4)
Neutrophils (10/L)	Week 24	=< 1.0	2 (1.4)
	Week 36	=< 1.0	1 (0.7)

Source: Listing 16.2.8.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Bicarbonate (mmol/L)	Week 12	<= 18	12 (8.3)
	Week 24	<= 18	7 (4.9)
	Week 36	<= 18	11 (7.6)
	Week 46	<= 18	7 (4.9)
	Week 12	>=33	1 (0.7)
	Week 36	>=33	1 (0.7)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Bilirubin (umol/L)	Week 12	>= 34	1 (0.7)
	Week 36	>= 34	1 (0.7)
	Week 46	>= 34	1 (0.7)
Calcium (mmol/L)	Week 24	<= 1.9	2 (1.4)
	Week 46	<= 1.9	4 (2.8)
Chloride (mmol/L)	Week 46	<= 90	1 (0.7)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Chloride (mmol/L)	Week 12	>= 113	1 (0.7)
	Week 24	>= 113	1 (0.7)
Cholesterol (mmol/L)	Week 12	>= 7.25	2 (1.4)
Creatinine (umol/L)	Week 24	>= 177	2 (1.4)
	Week 36	>= 177	1 (0.7)
	Week 46	>= 177	1 (0.7)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Glucose (mmol/L)	Week 24	>= 11.1	2 (1.4)
	Week 46	>= 11.1	3 (2.1)
LDL Cholesterol (mmol/L)	Week 12	>= 4.1	8 (5.6)
	Week 24	>= 4.1	5 (3.5)
	Week 36	>= 4.1	3 (2.1)
	Week 46	>= 4.1	6 (4.2)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Lactate Dehydrogenase (U/L)	Week 24	>= 500	1 (0.7)
Sodium (mmol/L)	Week 12	<= 127	1 (0.7)
	Week 24	<= 127	1 (0.7)
	Week 46	<= 127	1 (0.7)
	Week 12	>= 152	1 (0.7)
Triglycerides (mmol/L)	Week 12	>= 4.5	2 (1.4)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.2.4c
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings
Safety Population - Overall

Test (Unit)	Visit	Notable Criteria	Evenamide (N=144) n(%)
Triglycerides (mmol/L)	Week 24	>= 4.5	1 (0.7)
	Week 36	>= 4.5	4 (2.8)
	Week 46	>= 4.5	3 (2.1)

Source: Listing 16.2.8.2
N - Total number of subjects in the Safety Population, n - number of subjects with available data.Percentages are calculated by considering Male/Female count overall (Evenamide: 103/41) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Body Mass Index(kg/m2)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	24.8 (5.0)		25.0 (4.7)		25.3 (4.9)	
	Median	24.3		25.0		24.5	
	Min, Max	16, 37		17, 35		16, 38	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	25.0 (5.0)	0.1 (0.7)	25.2 (4.8)	0.2 (0.6)	25.5 (4.9)	0.2 (0.6)
	Median	24.9	0.1	25.2	0.1	24.5	0.1
	Min, Max	16, 37	-3, 2	17, 35	-2, 2	16, 38	-1, 3

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Body Mass Index(kg/m2)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	25.3 (4.8)	0.2 (0.7)	25.2 (4.6)	0.3 (0.7)	25.5 (4.9)	0.2 (0.8)
	Median	25.7	0.1	25.2	0.2	24.9	0.1
	Min, Max	17, 37	-3, 2	17, 35	-1, 3	16, 38	-2, 3
Week 18	n	43	43	50	50	45	45
	Mean (SD)	25.4 (4.8)	0.2 (1.0)	25.0 (4.6)	0.2 (0.9)	25.5 (5.0)	0.3 (0.9)
	Median	25.5	0.1	24.5	0.2	24.8	0.1
	Min, Max	17, 37	-4, 4	17, 35	-4, 3	16, 38	-2, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Body Mass Index(kg/m2)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	25.3 (4.7)	0.1 (1.2)	25.2 (4.5)	0.2 (1.0)	25.9 (5.1)	0.3 (1.0)
	Median	24.8	0.0	24.8	0.1	24.8	0.3
	Min, Max	17, 37	-6, 3	18, 35	-4, 3	16, 38	-2, 3
Week 36	n	40	40	41	41	42	42
	Mean (SD)	25.1 (4.4)	0.0 (1.5)	25.2 (4.3)	0.4 (1.1)	26.0 (4.9)	0.4 (0.9)
	Median	24.9	0.1	25.3	0.2	25.0	0.3
	Min, Max	18, 35	-8, 3	18, 35	-2, 4	16, 38	-2, 3

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Body Mass Index(kg/m2)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	25.0 (4.5)	0.1 (1.6)	25.6 (4.7)	0.6 (1.4)	26.2 (4.9)	0.4 (0.9)
	Median	24.9	0.2	26.0	0.4	24.7	0.4
	Min, Max	17, 36	-8, 4	17, 35	-3, 6	16, 38	-2, 3
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	23.8 (4.8)	-0.8 (3.5)	25.7 (4.8)	1.1 (1.9)	27.1 (4.3)	0.7 (1.3)
	Median	24.0	0.4	26.3	1.1	27.6	0.4
	Min, Max	17, 35	-14, 1	16, 35	-3, 6	19, 33	-2, 3

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Respiratory Rate(Breaths/minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	18.3 (1.4)		17.9 (2.3)		18.7 (3.6)	
	Median	18.0		18.0		19.0	
	Min, Max	15, 21		11, 21		10, 30	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	18.2 (1.9)	0.0 (1.2)	18.2 (2.4)	0.2 (1.2)	18.2 (3.1)	-0.5 (1.6)
	Median	18.0	0.0	18.0	0.0	18.0	0.0
	Min, Max	13, 22	-2, 4	11, 22	-1, 4	12, 28	-4, 2

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Respiratory Rate(Breaths/minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	18.5 (1.9)	0.3 (1.4)	18.5 (2.3)	0.5 (1.5)	18.1 (3.1)	-0.6 (2.2)
	Median	19.0	0.0	19.0	1.0	18.0	0.0
	Min, Max	13, 22	-3, 4	12, 22	-3, 4	12, 26	-11, 2
Week 18	n	43	43	50	50	45	45
	Mean (SD)	18.5 (1.9)	0.3 (1.6)	18.4 (2.5)	0.5 (1.7)	18.5 (3.1)	-0.2 (2.1)
	Median	18.0	0.0	18.0	1.0	19.0	0.0
	Min, Max	15, 22	-3, 4	12, 22	-3, 4	12, 25	-10, 2

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Respiratory Rate(Breaths/minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	18.6 (1.8)	0.4 (1.5)	18.4 (2.5)	0.4 (1.6)	18.5 (3.5)	-0.1 (2.1)
	Median	18.0	0.0	18.5	0.5	19.0	0.0
	Min, Max	15, 22	-3, 4	12, 22	-3, 4	10, 28	-9, 4
Week 36	n	40	40	41	41	42	42
	Mean (SD)	19.1 (1.7)	0.8 (1.6)	18.9 (1.9)	0.7 (1.8)	18.5 (3.4)	-0.1 (2.1)
	Median	19.0	1.0	19.0	1.0	19.0	0.0
	Min, Max	16, 22	-4, 4	12, 22	-3, 4	10, 26	-7, 6

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Respiratory Rate(Breaths/minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	19.2 (1.3)	0.9 (1.7)	19.0 (2.6)	0.9 (1.9)	18.2 (3.6)	-0.5 (2.3)
	Median	19.0	1.0	20.0	1.0	19.0	0.0
	Min, Max	16, 22	-3, 4	12, 26	-3, 6	12, 28	-7, 7
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	18.7 (1.3)	0.3 (2.4)	19.3 (2.6)	0.5 (3.0)	19.2 (3.9)	-2.3 (2.9)
	Median	19.0	0.0	18.0	1.0	19.5	-2.0
	Min, Max	16, 20	-4, 4	16, 28	-3, 8	13, 28	-8, 3

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	76.6 (8.6)		77.0 (8.7)		79.8 (10.1)	
	Median	79.0		79.0		78.0	
	Min, Max	52, 97		57, 93		61, 99	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	77.8 (8.3)	0.9 (6.8)	77.4 (8.5)	0.4 (7.6)	79.9 (10.4)	0.1 (9.6)
	Median	78.0	1.5	78.0	0.0	80.0	1.5
	Min, Max	59, 94	-13, 18	54, 96	-17, 18	59, 103	-33, 15

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
Programmer:AS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	77.3 (8.0)	0.4 (8.1)	77.5 (8.7)	0.8 (8.3)	79.3 (10.2)	-0.5 (11.4)
	Median	78.0	0.0	79.0	0.0	79.0	2.0
	Min, Max	52, 92	-21, 17	58, 92	-19, 21	60, 100	-27, 21
Week 18	n	43	43	50	50	45	45
	Mean (SD)	76.8 (8.6)	0.0 (8.9)	79.1 (8.6)	2.4 (9.7)	79.8 (9.5)	-0.3 (8.7)
	Median	78.0	-1.0	78.0	2.0	80.0	2.0
	Min, Max	57, 90	-17, 18	59, 100	-23, 28	60, 98	-23, 17

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	79.0 (8.5)	2.3 (8.1)	79.4 (7.2)	2.4 (10.1)	78.3 (8.7)	-1.5 (9.0)
	Median	80.0	2.5	79.5	-0.5	79.0	-2.0
	Min, Max	60, 98	-21, 19	62, 98	-14, 24	60, 92	-17, 17
Week 36	n	40	40	41	41	42	42
	Mean (SD)	79.4 (7.3)	2.8 (9.0)	78.7 (7.6)	1.9 (8.6)	79.4 (8.4)	0.0 (10.4)
	Median	80.0	3.5	78.0	0.0	78.5	2.0
	Min, Max	63, 96	-17, 19	62, 95	-16, 23	62, 99	-23, 26

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	78.6 (10.3)	1.9 (11.8)	78.6 (8.6)	2.0 (9.0)	81.3 (8.3)	2.3 (9.6)
	Median	78.0	2.0	78.5	1.0	80.0	3.0
	Min, Max	56, 102	-17, 31	56, 102	-16, 22	63, 98	-18, 22
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	78.8 (8.1)	0.4 (6.8)	78.7 (5.9)	1.1 (10.7)	81.5 (9.1)	1.2 (9.5)
	Median	78.0	2.0	78.0	-2.0	82.0	0.5
	Min, Max	58, 92	-16, 13	68, 90	-12, 23	65, 97	-18, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	80.1 (8.8)		81.2 (9.2)		84.0 (9.9)	
	Median	81.0		82.0		85.5	
	Min, Max	57, 96		59, 98		59, 97	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	82.2 (8.6)	1.9 (6.6)	82.4 (9.3)	1.1 (6.7)	85.1 (11.1)	1.1 (9.9)
	Median	82.0	2.5	84.0	2.0	85.0	1.0
	Min, Max	62, 98	-11, 19	56, 98	-15, 18	56, 103	-29, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	82.4 (8.7)	2.0 (9.2)	83.5 (9.3)	2.5 (8.9)	83.4 (9.4)	-0.6 (8.2)
	Median	84.0	1.0	85.0	1.0	82.5	1.5
	Min, Max	58, 99	-15, 30	61, 100	-17, 26	61, 100	-19, 13
Week 18	n	43	43	50	50	45	45
	Mean (SD)	82.8 (8.4)	2.4 (8.2)	83.5 (8.8)	2.7 (10.0)	84.6 (9.5)	0.2 (8.0)
	Median	85.0	1.0	83.5	2.0	84.0	2.0
	Min, Max	67, 97	-13, 17	60, 101	-21, 31	60, 99	-23, 12

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	84.6 (8.5)	4.2 (8.0)	83.8 (7.3)	2.6 (10.9)	82.0 (8.1)	-2.5 (8.4)
	Median	84.0	5.0	84.0	1.5	83.0	-2.0
	Min, Max	69, 106	-11, 21	59, 96	-21, 29	61, 97	-18, 16
Week 36	n	40	40	41	41	42	42
	Mean (SD)	85.3 (6.4)	5.1 (8.6)	83.1 (7.2)	2.2 (7.6)	83.2 (8.0)	-0.7 (9.7)
	Median	85.0	4.5	82.0	2.0	82.0	1.0
	Min, Max	72, 100	-7, 32	64, 100	-11, 22	63, 100	-18, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	83.9 (10.1)	3.5 (9.9)	82.4 (9.0)	1.4 (10.3)	84.9 (8.4)	1.7 (10.4)
	Median	84.0	4.0	82.0	0.0	84.0	2.0
	Min, Max	61, 105	-17, 29	62, 105	-19, 33	64, 100	-23, 19
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	83.6 (9.8)	1.0 (9.7)	82.6 (6.3)	1.1 (10.7)	82.3 (9.4)	-0.7 (9.8)
	Median	85.0	0.0	82.0	0.0	80.5	1.0
	Min, Max	61, 105	-18, 23	70, 92	-13, 30	68, 99	-17, 15

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	78.8 (9.1)		79.8 (8.6)		82.9 (9.9)	
	Median	81.0		81.0		82.5	
	Min, Max	57, 97		58, 99		60, 99	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	80.8 (9.2)	1.7 (6.6)	81.4 (10.1)	1.6 (7.5)	83.2 (10.5)	0.3 (9.6)
	Median	82.0	1.0	84.0	1.0	84.0	-0.5
	Min, Max	62, 96	-11, 16	53, 99	-17, 19	60, 103	-29, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	80.6 (9.5)	1.5 (8.7)	81.3 (8.6)	1.9 (8.5)	82.4 (9.3)	-0.5 (7.7)
	Median	82.0	0.0	82.0	1.0	82.0	0.5
	Min, Max	61, 103	-15, 25	64, 98	-13, 23	63, 100	-18, 14
Week 18	n	43	43	50	50	45	45
	Mean (SD)	81.0 (9.8)	2.0 (7.7)	82.7 (8.5)	3.4 (9.3)	83.3 (9.4)	0.2 (7.3)
	Median	82.0	2.0	82.0	2.5	82.0	1.0
	Min, Max	60, 96	-18, 16	64, 100	-17, 29	67, 100	-16, 13

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	82.4 (8.8)	3.4 (8.6)	83.5 (7.1)	4.0 (10.6)	81.3 (8.3)	-1.9 (7.7)
	Median	83.5	6.0	84.0	3.0	82.0	-2.0
	Min, Max	64, 102	-20, 20	68, 99	-23, 26	63, 97	-18, 17
Week 36	n	40	40	41	41	42	42
	Mean (SD)	84.3 (8.5)	5.5 (8.8)	81.8 (8.1)	2.7 (7.6)	81.5 (8.5)	-1.1 (9.1)
	Median	84.0	4.5	82.0	3.0	80.0	-1.5
	Min, Max	68, 104	-10, 36	60, 99	-12, 20	62, 98	-19, 17

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	81.9 (10.6)	2.9 (10.3)	81.3 (8.8)	1.6 (10.1)	82.5 (7.4)	0.3 (9.1)
	Median	82.0	3.0	81.0	0.5	82.0	1.0
	Min, Max	58, 104	-18, 28	66, 100	-17, 31	66, 96	-21, 18
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	82.0 (8.5)	0.5 (8.6)	80.4 (6.1)	-0.7 (9.3)	82.0 (10.1)	-1.4 (8.3)
	Median	81.0	1.0	79.0	-4.0	81.5	-2.0
	Min, Max	61, 97	-17, 22	68, 90	-13, 21	63, 96	-16, 13

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	118.3 (6.0)		119.6 (7.5)		120.4 (6.2)	
	Median	120.0		120.0		121.0	
	Min, Max	101, 130		93, 141		105, 135	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	118.9 (6.7)	0.7 (4.2)	119.1 (7.7)	-0.5 (5.7)	120.7 (8.4)	0.3 (8.1)
	Median	120.0	0.0	120.0	0.0	120.5	-1.0
	Min, Max	101, 132	-8, 13	99, 139	-16, 12	100, 147	-21, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	119.2 (5.8)	1.0 (6.3)	119.6 (7.2)	-0.2 (6.3)	119.4 (8.0)	-0.9 (8.3)
	Median	120.0	0.0	120.0	0.0	120.0	0.0
	Min, Max	100, 135	-12, 17	100, 133	-13, 19	100, 133	-24, 17
Week 18	n	43	43	50	50	45	45
	Mean (SD)	119.4 (5.3)	1.1 (4.4)	119.3 (7.3)	-0.5 (6.0)	119.9 (7.1)	-0.5 (7.3)
	Median	120.0	1.0	120.0	-1.0	120.0	0.0
	Min, Max	100, 130	-12, 13	100, 147	-13, 13	100, 137	-19, 15

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	118.7 (6.2)	0.5 (5.2)	119.0 (7.0)	-0.9 (7.3)	120.8 (6.7)	-0.4 (8.0)
	Median	120.0	0.0	120.0	0.0	122.0	0.0
	Min, Max	102, 130	-8, 19	100, 134	-37, 17	100, 132	-20, 17
Week 36	n	40	40	41	41	42	42
	Mean (SD)	122.0 (4.4)	3.4 (5.6)	119.1 (5.7)	-1.4 (5.6)	121.0 (6.9)	-0.1 (8.7)
	Median	122.0	2.5	120.0	-1.0	122.0	-0.5
	Min, Max	109, 130	-6, 19	104, 130	-31, 8	102, 135	-25, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	120.7 (6.5)	2.4 (6.2)	119.7 (5.9)	0.2 (8.8)	120.2 (7.3)	-0.6 (9.4)
	Median	122.0	2.0	121.5	0.5	121.0	0.0
	Min, Max	96, 135	-11, 19	103, 130	-33, 17	100, 134	-26, 19
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	120.2 (7.5)	0.2 (5.9)	118.3 (5.2)	-1.5 (8.6)	122.5 (11.0)	3.4 (9.2)
	Median	121.0	-2.0	120.0	-3.0	119.0	4.0
	Min, Max	100, 132	-7, 13	108, 128	-11, 28	112, 144	-7, 19

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	118.3 (5.1)		118.6 (7.1)		119.6 (6.3)	
	Median	119.0		119.0		119.5	
	Min, Max	104, 129		91, 135		102, 132	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	118.3 (6.0)	0.1 (5.2)	118.0 (6.7)	-0.7 (5.5)	120.9 (8.7)	1.3 (8.3)
	Median	118.0	0.0	118.0	-1.0	120.0	0.0
	Min, Max	99, 128	-8, 14	92, 136	-16, 18	102, 148	-20, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	118.7 (6.5)	0.4 (5.7)	118.5 (8.1)	-0.3 (5.6)	119.2 (8.7)	-0.4 (8.4)
	Median	118.0	1.0	118.0	0.0	120.0	-0.5
	Min, Max	100, 134	-14, 15	93, 136	-15, 16	100, 136	-27, 18
Week 18	n	43	43	50	50	45	45
	Mean (SD)	119.2 (6.2)	0.9 (5.0)	119.0 (7.5)	0.2 (5.3)	118.8 (7.9)	-0.8 (7.4)
	Median	118.0	0.0	119.0	0.0	119.0	0.0
	Min, Max	104, 134	-8, 15	95, 142	-9, 16	90, 132	-18, 14

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	118.9 (6.1)	0.7 (6.2)	118.7 (8.0)	0.0 (6.7)	119.6 (6.6)	-0.9 (7.1)
	Median	119.5	1.0	120.0	0.0	120.0	-1.0
	Min, Max	102, 128	-13, 17	100, 138	-33, 15	104, 131	-15, 18
Week 36	n	40	40	41	41	42	42
	Mean (SD)	122.2 (6.6)	3.8 (5.6)	119.1 (5.9)	-0.0 (6.2)	120.5 (6.8)	0.1 (8.2)
	Median	122.0	3.0	120.0	0.0	120.0	0.5
	Min, Max	104, 138	-12, 17	106, 130	-19, 24	102, 138	-25, 17

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	120.2 (7.0)	2.1 (5.6)	119.4 (5.7)	1.2 (6.5)	119.8 (7.9)	-0.4 (9.4)
	Median	120.0	2.0	120.0	0.5	120.0	-1.0
	Min, Max	101, 136	-9, 17	100, 133	-20, 21	98, 140	-34, 19
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	118.0 (6.7)	-0.4 (4.1)	116.3 (4.3)	-0.3 (6.9)	122.0 (9.6)	3.4 (8.0)
	Median	118.0	-2.0	117.0	-1.0	119.0	2.5
	Min, Max	106, 130	-5, 11	110, 126	-7, 27	111, 141	-7, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
Programmer:AS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	116.1 (6.0)		117.2 (7.3)		117.2 (6.6)	
	Median	118.0		119.0		118.0	
	Min, Max	101, 130		92, 135		100, 129	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	116.2 (6.7)	0.1 (4.8)	116.7 (6.2)	-0.5 (4.4)	119.2 (7.5)	2.0 (7.6)
	Median	117.0	0.0	116.0	0.0	119.0	0.0
	Min, Max	100, 133	-8, 20	100, 130	-11, 8	100, 144	-18, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	116.9 (6.7)	0.9 (5.7)	117.2 (7.0)	0.1 (6.0)	116.6 (7.0)	-0.6 (8.8)
	Median	116.0	0.0	118.0	0.0	118.0	-0.5
	Min, Max	102, 136	-8, 17	100, 132	-15, 16	101, 130	-22, 23
Week 18	n	43	43	50	50	45	45
	Mean (SD)	117.6 (5.5)	1.6 (4.6)	117.2 (7.3)	0.5 (6.0)	117.6 (7.2)	0.4 (7.6)
	Median	120.0	1.0	118.0	1.0	119.0	0.0
	Min, Max	105, 128	-8, 13	98, 145	-16, 17	98, 136	-16, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	117.6 (6.4)	1.7 (6.0)	116.3 (7.1)	-0.3 (5.6)	117.7 (5.8)	-0.5 (7.6)
	Median	119.0	2.0	118.0	0.0	118.0	-1.0
	Min, Max	104, 134	-13, 19	100, 132	-26, 10	100, 135	-18, 17
Week 36	n	40	40	41	41	42	42
	Mean (SD)	120.0 (6.2)	4.3 (6.9)	115.8 (5.7)	-0.9 (5.3)	119.2 (7.6)	1.1 (8.8)
	Median	120.0	3.5	116.0	-1.0	120.0	1.0
	Min, Max	106, 137	-10, 19	104, 127	-14, 10	94, 138	-26, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	118.0 (7.0)	2.3 (7.3)	116.9 (5.7)	0.1 (7.1)	118.0 (7.4)	0.1 (9.5)
	Median	120.0	1.0	118.0	0.5	118.0	0.0
	Min, Max	98, 132	-19, 23	102, 129	-19, 16	99, 138	-30, 21
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	116.6 (7.3)	0.2 (6.1)	114.8 (5.4)	-0.1 (7.4)	121.6 (10.0)	5.8 (9.1)
	Median	117.0	0.0	114.0	-2.0	118.0	3.0
	Min, Max	104, 130	-13, 10	104, 124	-11, 27	110, 142	-6, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	77.6 (3.9)		79.2 (4.7)		79.5 (5.4)	
	Median	79.0		79.0		80.0	
	Min, Max	67, 83		67, 93		65, 93	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	77.6 (5.1)	0.0 (4.5)	78.9 (4.9)	-0.3 (5.0)	80.0 (6.3)	0.5 (6.4)
	Median	80.0	0.0	80.0	0.0	80.0	-0.5
	Min, Max	61, 88	-13, 9	62, 93	-14, 11	69, 98	-10, 22

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	78.8 (3.9)	1.3 (3.9)	78.2 (4.4)	-1.1 (3.4)	79.9 (4.9)	0.4 (5.9)
	Median	80.0	1.0	80.0	-1.0	80.0	0.0
	Min, Max	70, 86	-9, 11	65, 92	-9, 6	70, 93	-14, 14
Week 18	n	43	43	50	50	45	45
	Mean (SD)	77.7 (4.9)	0.2 (3.9)	78.9 (5.3)	-0.4 (3.5)	80.6 (4.9)	0.7 (6.5)
	Median	78.0	-1.0	80.0	0.0	80.0	0.0
	Min, Max	63, 88	-7, 12	66, 102	-8, 9	67, 94	-10, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	78.3 (5.5)	0.8 (4.4)	77.6 (4.6)	-2.0 (4.9)	81.1 (5.4)	1.1 (5.3)
	Median	80.0	0.0	78.0	-1.0	82.0	1.0
	Min, Max	56, 91	-11, 12	66, 88	-17, 10	72, 94	-9, 18
Week 36	n	40	40	41	41	42	42
	Mean (SD)	80.6 (4.0)	2.9 (5.1)	78.5 (4.9)	-1.1 (4.5)	80.2 (5.9)	0.2 (6.4)
	Median	80.0	2.0	80.0	-1.0	80.0	0.0
	Min, Max	68, 90	-6, 16	61, 86	-17, 6	68, 94	-15, 18

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	80.4 (4.3)	2.9 (4.4)	78.9 (5.5)	0.1 (6.4)	80.3 (4.9)	0.4 (5.7)
	Median	82.0	3.0	80.0	0.0	80.0	0.0
	Min, Max	70, 89	-5, 14	61, 94	-22, 15	70, 98	-11, 13
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	77.1 (3.9)	-1.0 (4.8)	78.0 (4.5)	-0.7 (5.5)	82.4 (8.8)	2.2 (7.3)
	Median	78.0	-1.0	78.0	0.0	80.0	2.0
	Min, Max	70, 87	-11, 10	69, 88	-11, 13	73, 104	-8, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	78.3 (3.4)		78.9 (4.9)		79.7 (4.9)	
	Median	79.0		79.0		79.0	
	Min, Max	72, 86		71, 92		71, 90	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	77.8 (5.4)	-0.5 (4.5)	78.9 (5.9)	-0.1 (5.1)	80.2 (6.1)	0.5 (4.5)
	Median	78.0	-1.0	78.0	0.0	80.0	0.0
	Min, Max	63, 94	-12, 12	64, 93	-13, 16	70, 94	-8, 13

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	79.6 (5.8)	1.4 (5.1)	78.3 (5.6)	-0.6 (4.1)	80.3 (5.7)	0.6 (5.1)
	Median	78.0	1.0	78.0	-1.0	78.0	0.5
	Min, Max	70, 103	-7, 21	67, 95	-8, 10	68, 92	-11, 13
Week 18	n	43	43	50	50	45	45
	Mean (SD)	79.2 (4.4)	1.0 (3.7)	79.4 (4.7)	0.6 (3.8)	80.8 (5.4)	1.0 (5.4)
	Median	78.0	1.0	80.0	0.0	80.0	1.0
	Min, Max	66, 86	-8, 11	65, 100	-8, 9	70, 94	-10, 19

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	79.5 (4.5)	1.3 (3.7)	79.0 (4.7)	0.0 (4.8)	81.3 (5.1)	1.3 (5.1)
	Median	78.5	1.0	78.0	-1.0	82.0	1.0
	Min, Max	68, 92	-6, 10	70, 88	-17, 15	70, 94	-10, 17
Week 36	n	40	40	41	41	42	42
	Mean (SD)	82.6 (5.6)	4.5 (6.3)	79.2 (4.9)	0.5 (4.5)	80.4 (6.2)	0.4 (5.5)
	Median	80.5	3.0	78.0	0.0	80.0	0.0
	Min, Max	74, 101	-5, 24	69, 90	-16, 13	65, 93	-12, 12

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	80.8 (4.8)	2.7 (5.5)	79.3 (5.1)	0.5 (5.6)	79.9 (6.2)	0.2 (6.1)
	Median	80.0	1.0	80.0	0.0	80.0	0.0
	Min, Max	72, 92	-6, 19	69, 94	-21, 17	64, 100	-14, 18
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	76.5 (5.5)	-0.9 (6.0)	76.6 (3.5)	-0.8 (4.4)	80.6 (7.5)	1.6 (5.0)
	Median	76.0	-1.0	76.0	-1.0	79.0	2.5
	Min, Max	70, 94	-10, 21	70, 83	-9, 10	73, 97	-7, 8

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	76.8 (4.0)		77.8 (4.6)		78.3 (4.7)	
	Median	78.0		79.0		78.0	
	Min, Max	70, 85		69, 90		70, 89	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	77.2 (5.5)	0.5 (4.7)	78.1 (5.7)	0.3 (4.9)	79.5 (4.8)	1.3 (5.1)
	Median	77.0	0.0	78.0	0.0	80.0	1.0
	Min, Max	69, 99	-9, 19	65, 94	-11, 12	70, 89	-10, 14

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	78.7 (5.2)	2.1 (4.9)	77.5 (5.0)	-0.3 (4.1)	79.2 (5.9)	1.0 (5.4)
	Median	80.0	1.0	78.0	-1.0	80.0	2.0
	Min, Max	70, 94	-7, 17	67, 90	-12, 13	68, 94	-11, 14
Week 18	n	43	43	50	50	45	45
	Mean (SD)	77.8 (4.3)	1.1 (4.1)	78.4 (5.2)	0.7 (4.0)	80.3 (6.2)	1.9 (5.7)
	Median	78.0	1.0	78.0	1.0	80.0	1.0
	Min, Max	69, 89	-8, 11	68, 101	-7, 11	70, 97	-6, 22

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	79.0 (6.1)	2.4 (5.0)	76.7 (4.9)	-1.1 (4.5)	80.0 (5.1)	1.1 (4.6)
	Median	80.0	1.0	77.0	-1.0	80.0	1.0
	Min, Max	65, 99	-9, 19	67, 86	-15, 11	70, 98	-10, 13
Week 36	n	40	40	41	41	42	42
	Mean (SD)	80.7 (5.1)	4.4 (6.0)	77.4 (4.5)	-0.0 (4.4)	79.0 (6.7)	0.3 (6.0)
	Median	80.0	3.0	78.0	1.0	78.0	0.0
	Min, Max	70, 96	-10, 20	70, 90	-14, 7	67, 99	-10, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population
Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	79.2 (4.8)	2.8 (5.2)	78.1 (5.4)	0.5 (5.8)	78.7 (6.1)	0.1 (6.4)
	Median	80.0	1.0	78.0	0.0	78.0	1.0
	Min, Max	70, 92	-8, 15	67, 90	-19, 17	62, 98	-16, 16
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	75.7 (5.9)	-0.7 (6.2)	75.3 (3.6)	-0.5 (4.5)	79.3 (7.7)	1.8 (5.4)
	Median	74.0	-1.0	74.0	-1.0	77.5	3.0
	Min, Max	69, 97	-7, 23	70, 83	-9, 8	70, 94	-7, 10

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Temperature(C)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	36.6 (0.2)		36.7 (0.3)		36.6 (0.3)	
	Median	36.7		36.7		36.7	
	Min, Max	36, 37		35, 37		36, 37	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	36.7 (0.3)	0.1 (0.3)	36.7 (0.3)	0.1 (0.3)	36.7 (0.3)	0.0 (0.3)
	Median	36.8	0.0	36.8	0.1	36.8	0.0
	Min, Max	36, 37	-1, 1	36, 37	-1, 1	36, 37	-1, 1

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
Programmer:AS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Temperature(C)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	36.7 (0.3)	0.1 (0.3)	36.7 (0.3)	0.1 (0.2)	36.7 (0.3)	0.0 (0.4)
	Median	36.8	0.1	36.8	0.0	36.8	0.0
	Min, Max	36, 37	-1, 1	36, 37	-1, 1	36, 37	-1, 1
Week 18	n	43	43	50	50	45	45
	Mean (SD)	36.7 (0.3)	0.1 (0.3)	36.8 (0.2)	0.1 (0.3)	36.7 (0.3)	0.1 (0.3)
	Median	36.8	0.1	36.8	0.1	36.8	0.0
	Min, Max	36, 37	-1, 1	36, 37	-0, 1	36, 37	-0, 1

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Temperature(C)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	36.8 (0.4)	0.1 (0.5)	36.8 (0.2)	0.1 (0.3)	36.7 (0.2)	-0.0 (0.3)
	Median	36.8	0.1	36.8	0.1	36.8	-0.0
	Min, Max	36, 39	-0, 3	36, 37	-0, 2	36, 37	-1, 1
Week 36	n	40	40	41	41	42	42
	Mean (SD)	36.7 (0.3)	0.1 (0.3)	36.7 (0.2)	0.0 (0.2)	36.6 (0.3)	-0.0 (0.3)
	Median	36.8	0.1	36.8	0.0	36.7	-0.0
	Min, Max	36, 37	-1, 1	36, 37	-0, 1	36, 37	-1, 1

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Temperature(C)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	36.7 (0.3)	0.0 (0.3)	36.7 (0.3)	0.0 (0.3)	36.7 (0.3)	0.0 (0.4)
	Median	36.8	0.1	36.7	0.0	36.7	0.0
	Min, Max	36, 37	-1, 1	36, 37	-1, 2	36, 37	-1, 1
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	36.7 (0.2)	0.0 (0.2)	36.7 (0.2)	0.1 (0.3)	36.6 (0.3)	0.0 (0.5)
	Median	36.7	0.0	36.8	0.0	36.6	-0.1
	Min, Max	36, 37	-0, 0	36, 37	-0, 1	36, 37	-0, 1

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Waist Circumference(cm)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	93.0 (11.8)		90.9 (11.9)		89.7 (11.0)	
	Median	92.0		89.5		90.0	
	Min, Max	69, 115		62, 115		64, 114	
Week 46	n	41	41	46	46	41	41
	Mean (SD)	92.7 (12.3)	-0.1 (3.3)	91.4 (12.8)	0.5 (3.4)	92.1 (12.9)	1.4 (5.1)
	Median	92.3	0.0	91.0	0.0	91.4	0.0
	Min, Max	69, 115	-14, 4	62, 122	-12, 13	64, 130	-9, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Weight(kg)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		53		46	
	Mean (SD)	67.2 (15.4)		67.4 (12.6)		67.5 (13.4)	
	Median	66.9		66.2		65.0	
	Min, Max	42, 120		45, 91		42, 96	
Week 6	n	44	44	53	53	46	46
	Mean (SD)	67.6 (15.4)	0.2 (1.7)	67.8 (12.7)	0.4 (1.5)	68.0 (13.5)	0.5 (1.6)
	Median	67.1	0.2	67.3	0.4	65.1	0.3
	Min, Max	41, 120	-8, 4	45, 92	-6, 4	42, 104	-2, 9

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
Programmer:AS
Date of Extraction:18DEC2023 Final- 18JAN2024:10:58

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Weight(kg)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 12	n	43	43	51	51	46	46
	Mean (SD)	68.4 (15.1)	0.5 (1.8)	67.8 (12.6)	0.7 (1.7)	68.0 (13.8)	0.6 (2.4)
	Median	67.0	0.2	67.4	0.4	66.2	0.4
	Min, Max	42, 120	-8, 5	42, 92	-3, 6	42, 106	-5, 11
Week 18	n	43	43	50	50	45	45
	Mean (SD)	68.5 (15.0)	0.6 (2.5)	67.6 (12.7)	0.4 (2.6)	68.2 (14.0)	0.7 (2.6)
	Median	67.2	0.3	65.3	0.5	65.8	0.3
	Min, Max	42, 120	-11, 8	42, 92	-12, 7	42, 107	-6, 11

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Weight(kg)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 24	n	42	42	48	48	41	41
	Mean (SD)	68.4 (15.3)	0.4 (3.0)	68.1 (12.6)	0.5 (2.7)	69.1 (14.5)	0.9 (2.7)
	Median	67.0	0.1	66.1	0.4	67.3	0.7
	Min, Max	42, 120	-14, 8	43, 92	-12, 8	42, 107	-6, 11
Week 36	n	40	40	41	41	42	42
	Mean (SD)	67.2 (13.2)	0.1 (3.7)	68.2 (12.1)	1.1 (2.8)	69.2 (14.0)	1.0 (2.4)
	Median	67.0	0.3	67.4	0.5	67.8	0.9
	Min, Max	43, 104	-19, 9	43, 93	-4, 12	42, 104	-5, 8

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1
Summary of Change from Baseline in Vital Signs Parameters
Safety Population

Test:Weight(kg)

		Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Week 46	n	41	41	46	46	41	41
	Mean (SD)	67.1 (13.3)	0.3 (4.1)	68.9 (12.3)	1.5 (4.1)	69.8 (13.8)	1.2 (2.6)
	Median	67.3	0.5	68.4	1.0	67.5	1.0
	Min, Max	44, 103	-21, 12	45, 93	-9, 19	42, 103	-6, 10
Safety follow-up-015 - Day 7	n	21	21	23	23	12	12
	Mean (SD)	66.1 (12.7)	-2.6 (11.0)	68.7 (11.9)	3.1 (5.5)	73.5 (15.0)	1.9 (4.0)
	Median	66.2	0.8	68.0	2.7	72.9	1.1
	Min, Max	44, 85	-46, 3	49, 93	-10, 19	50, 104	-5, 10

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1.sas
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Body Mass Index(kg/m2)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	25.0 (4.81)	
	Median	24.5	
	Min, Max	16, 38	
Week 6	n	143	143
	Mean (SD)	25.2 (4.84)	0.2 (0.60)
	Median	24.7	0.1
	Min, Max	16, 38	-3, 3

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Body Mass Index(kg/m2)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	25.3 (4.73)	0.2 (0.75)
	Median	25.1	0.1
	Min, Max	16, 38	-3, 3
Week 18	n	138	138
	Mean (SD)	25.3 (4.78)	0.2 (0.96)
	Median	24.9	0.1
	Min, Max	16, 38	-4, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Body Mass Index(kg/m2)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	25.5 (4.75)	0.2 (1.03)
	Median	24.8	0.1
	Min, Max	16, 38	-6, 3
Week 36	n	123	123
	Mean (SD)	25.4 (4.54)	0.3 (1.15)
	Median	25.0	0.2
	Min, Max	16, 38	-8, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Body Mass Index(kg/m2)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	25.6 (4.70)	0.4 (1.35)
	Median	25.1	0.3
	Min, Max	16, 38	-8, 6
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	25.3 (4.80)	0.3 (2.67)
	Median	25.4	0.5
	Min, Max	16, 35	-14, 6

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Respiratory Rate(Breaths/minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	18.3 (2.59)	
	Median	18.0	
	Min, Max	10, 30	
Week 6	n	143	143
	Mean (SD)	18.2 (2.52)	-0.1 (1.37)
	Median	18.0	0.0
	Min, Max	11, 28	-4, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Respiratory Rate(Breaths/minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	18.4 (2.49)	0.1 (1.79)
	Median	19.0	0.0
	Min, Max	12, 26	-11, 4
Week 18	n	138	138
	Mean (SD)	18.5 (2.53)	0.2 (1.84)
	Median	19.0	0.0
	Min, Max	12, 25	-10, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Respiratory Rate(Breaths/minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	18.5 (2.65)	0.2 (1.73)
	Median	19.0	0.0
	Min, Max	10, 28	-9, 4
Week 36	n	123	123
	Mean (SD)	18.8 (2.46)	0.4 (1.88)
	Median	19.0	1.0
	Min, Max	10, 26	-7, 6

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Respiratory Rate(Breaths/minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	18.8 (2.65)	0.5 (2.08)
	Median	19.0	1.0
	Min, Max	12, 28	-7, 7
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	19.1 (2.53)	-0.2 (2.93)
	Median	19.0	0.0
	Min, Max	13, 28	-8, 8

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	77.8 (9.15)	
	Median	79.0	
	Min, Max	52, 99	
Week 6	n	143	143
	Mean (SD)	78.3 (9.11)	0.4 (8.03)
	Median	78.0	1.0
	Min, Max	54, 103	-33, 18

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	78.0 (9.00)	0.3 (9.31)
	Median	79.0	0.0
	Min, Max	52, 100	-27, 21
Week 18	n	138	138
	Mean (SD)	78.6 (8.92)	0.8 (9.15)
	Median	78.0	1.0
	Min, Max	57, 100	-23, 28

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
Programmer:AS
Date of Extraction:18DEC2023 Final- 18JAN2024:11:07

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	78.9 (8.07)	1.1 (9.27)
	Median	80.0	0.0
	Min, Max	60, 98	-21, 24
Week 36	n	123	123
	Mean (SD)	79.2 (7.74)	1.5 (9.36)
	Median	78.0	2.0
	Min, Max	62, 99	-23, 26

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	79.5 (9.11)	2.1 (10.07)
	Median	79.5	2.0
	Min, Max	56, 102	-18, 31
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	79.3 (7.46)	0.9 (8.97)
	Median	78.0	1.0
	Min, Max	58, 97	-18, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
Programmer:AS
Date of Extraction:18DEC2023 Final- 18JAN2024:11:07

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	81.8 (9.38)	
	Median	82.0	
	Min, Max	57, 98	
Week 6	n	143	143
	Mean (SD)	83.2 (9.72)	1.3 (7.80)
	Median	84.0	2.0
	Min, Max	56, 103	-29, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	83.1 (9.07)	1.3 (8.83)
	Median	84.0	1.0
	Min, Max	58, 100	-19, 30
Week 18	n	138	138
	Mean (SD)	83.6 (8.87)	1.8 (8.83)
	Median	84.0	2.0
	Min, Max	60, 101	-23, 31

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	83.5 (7.96)	1.5 (9.63)
	Median	84.0	1.0
	Min, Max	59, 106	-21, 29
Week 36	n	123	123
	Mean (SD)	83.8 (7.26)	2.1 (8.96)
	Median	84.0	2.0
	Min, Max	63, 100	-18, 32

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	83.7 (9.18)	2.2 (10.16)
	Median	84.0	1.5
	Min, Max	61, 105	-23, 33
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	82.9 (8.28)	0.7 (9.98)
	Median	81.5	0.0
	Min, Max	61, 105	-18, 30

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	80.5 (9.30)	
	Median	81.0	
	Min, Max	57, 99	
Week 6	n	143	143
	Mean (SD)	81.8 (9.94)	1.2 (7.96)
	Median	83.0	1.0
	Min, Max	53, 103	-29, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	81.4 (9.07)	1.0 (8.33)
	Median	82.0	1.0
	Min, Max	61, 103	-18, 25
Week 18	n	138	138
	Mean (SD)	82.4 (9.16)	1.9 (8.25)
	Median	82.0	1.5
	Min, Max	60, 100	-18, 29

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	82.5 (8.05)	2.0 (9.44)
	Median	84.0	2.0
	Min, Max	63, 102	-23, 26
Week 36	n	123	123
	Mean (SD)	82.5 (8.40)	2.3 (8.85)
	Median	82.0	3.0
	Min, Max	60, 104	-19, 36

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Pulse Rate(bpm) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	81.9 (8.95)	1.6 (9.85)
	Median	82.0	1.0
	Min, Max	58, 104	-21, 31
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	81.4 (7.87)	-0.4 (8.71)
	Median	80.0	-1.0
	Min, Max	61, 97	-17, 22

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	119.5 (6.66)	
	Median	120.0	
	Min, Max	93, 141	
Week 6	n	143	143
	Mean (SD)	119.6 (7.64)	0.1 (6.18)
	Median	120.0	0.0
	Min, Max	99, 147	-21, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	119.4 (7.07)	-0.1 (6.98)
	Median	120.0	0.0
	Min, Max	100, 135	-24, 19
Week 18	n	138	138
	Mean (SD)	119.5 (6.62)	0.0 (6.01)
	Median	120.0	0.0
	Min, Max	100, 147	-19, 15

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	119.5 (6.65)	-0.3 (6.94)
	Median	120.0	0.0
	Min, Max	100, 134	-37, 19
Week 36	n	123	123
	Mean (SD)	120.7 (5.86)	0.6 (7.04)
	Median	121.0	0.0
	Min, Max	102, 135	-31, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
Programmer:AS
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	120.2 (6.54)	0.6 (8.29)
	Median	122.0	1.0
	Min, Max	96, 135	-33, 19
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	119.9 (7.61)	0.2 (7.88)
	Median	120.0	-3.0
	Min, Max	100, 144	-11, 28

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	118.8 (6.26)	
	Median	119.0	
	Min, Max	91, 135	
Week 6	n	143	143
	Mean (SD)	119.0 (7.28)	0.2 (6.46)
	Median	118.0	-1.0
	Min, Max	92, 148	-20, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	118.8 (7.79)	-0.1 (6.63)
	Median	118.0	0.0
	Min, Max	93, 136	-27, 18
Week 18	n	138	138
	Mean (SD)	119.0 (7.20)	0.1 (5.98)
	Median	118.5	0.0
	Min, Max	90, 142	-18, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	119.0 (6.96)	-0.1 (6.67)
	Median	120.0	0.0
	Min, Max	100, 138	-33, 18
Week 36	n	123	123
	Mean (SD)	120.6 (6.52)	1.3 (6.95)
	Median	120.0	1.0
	Min, Max	102, 138	-25, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
Programmer:AS
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Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	119.8 (6.82)	1.0 (7.33)
	Median	120.0	1.0
	Min, Max	98, 140	-34, 21
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	118.1 (6.85)	0.4 (6.38)
	Median	118.0	-1.0
	Min, Max	106, 141	-7, 27

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	116.9 (6.69)	
	Median	118.0	
	Min, Max	92, 135	
Week 6	n	143	143
	Mean (SD)	117.3 (6.85)	0.5 (5.77)
	Median	118.0	0.0
	Min, Max	100, 144	-18, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	116.9 (6.87)	0.1 (6.96)
	Median	118.0	0.0
	Min, Max	100, 136	-22, 23
Week 18	n	138	138
	Mean (SD)	117.4 (6.71)	0.8 (6.20)
	Median	118.5	1.0
	Min, Max	98, 145	-16, 17

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	117.1 (6.50)	0.3 (6.43)
	Median	118.0	0.0
	Min, Max	100, 135	-26, 19
Week 36	n	123	123
	Mean (SD)	118.3 (6.74)	1.5 (7.43)
	Median	118.0	1.0
	Min, Max	94, 138	-26, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Systolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	117.6 (6.65)	0.8 (8.00)
	Median	118.0	1.0
	Min, Max	98, 138	-30, 23
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	116.9 (7.58)	1.3 (7.60)
	Median	116.5	0.0
	Min, Max	104, 142	-13, 27

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	78.8 (4.73)	
	Median	79.0	
	Min, Max	65, 93	
Week 6	n	143	143
	Mean (SD)	78.8 (5.50)	0.1 (5.32)
	Median	80.0	0.0
	Min, Max	61, 98	-14, 22

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	78.9 (4.45)	0.1 (4.59)
	Median	80.0	0.0
	Min, Max	65, 93	-14, 14
Week 18	n	138	138
	Mean (SD)	79.1 (5.12)	0.1 (4.74)
	Median	80.0	0.0
	Min, Max	63, 102	-10, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	78.9 (5.33)	-0.1 (5.06)
	Median	80.0	0.0
	Min, Max	56, 94	-17, 18
Week 36	n	123	123
	Mean (SD)	79.8 (5.08)	0.7 (5.61)
	Median	80.0	0.0
	Min, Max	61, 94	-17, 18

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Supine(5 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	79.9 (4.93)	1.1 (5.69)
	Median	80.0	1.0
	Min, Max	61, 98	-22, 15
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	78.6 (5.77)	-0.2 (5.69)
	Median	78.0	0.0
	Min, Max	69, 104	-11, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	79.0 (4.49)	
	Median	79.0	
	Min, Max	71, 92	
Week 6	n	143	143
	Mean (SD)	79.0 (5.85)	0.0 (4.72)
	Median	78.0	0.0
	Min, Max	63, 94	-13, 16

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	79.4 (5.71)	0.4 (4.79)
	Median	78.0	0.0
	Min, Max	67, 103	-11, 21
Week 18	n	138	138
	Mean (SD)	79.8 (4.88)	0.8 (4.34)
	Median	80.0	1.0
	Min, Max	65, 100	-10, 19

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	79.9 (4.82)	0.8 (4.58)
	Median	80.0	0.0
	Min, Max	68, 94	-17, 17
Week 36	n	123	123
	Mean (SD)	80.7 (5.69)	1.8 (5.77)
	Median	80.0	1.0
	Min, Max	65, 101	-16, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(1 minute)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	80.0 (5.37)	1.1 (5.80)
	Median	80.0	1.0
	Min, Max	64, 100	-21, 19
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	77.4 (5.48)	-0.3 (5.19)
	Median	78.0	-1.0
	Min, Max	70, 97	-10, 21

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	77.6 (4.48)	
	Median	78.0	
	Min, Max	69, 90	
Week 6	n	143	143
	Mean (SD)	78.3 (5.41)	0.7 (4.90)
	Median	79.0	0.0
	Min, Max	65, 99	-11, 19

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	78.4 (5.39)	0.8 (4.90)
	Median	80.0	0.5
	Min, Max	67, 94	-12, 17
Week 18	n	138	138
	Mean (SD)	78.8 (5.34)	1.2 (4.63)
	Median	79.0	1.0
	Min, Max	68, 101	-8, 22

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	78.5 (5.52)	0.7 (4.90)
	Median	80.0	0.0
	Min, Max	65, 99	-15, 19
Week 36	n	123	123
	Mean (SD)	79.0 (5.66)	1.5 (5.83)
	Median	78.0	1.0
	Min, Max	67, 99	-14, 24

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall
Test:Diastolic Blood Pressure(mmHg) Standing(3 minutes)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	78.6 (5.42)	1.1 (5.88)
	Median	78.0	1.0
	Min, Max	62, 98	-19, 17
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	76.3 (5.67)	-0.1 (5.40)
	Median	74.5	-0.5
	Min, Max	69, 97	-9, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADVS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.3.1c.sas
Programmer:AS
Date of Extraction:18DEC2023 Final- 18JAN2024:11:07

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Temperature(C)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	18.3 (2.59)	
	Median	18.0	
	Min, Max	10, 30	
Week 6	n	143	143
	Mean (SD)	18.2 (2.52)	-0.1 (1.37)
	Median	18.0	0.0
	Min, Max	11, 28	-4, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Temperature(C)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	18.4 (2.49)	0.1 (1.79)
	Median	19.0	0.0
	Min, Max	12, 26	-11, 4
Week 18	n	138	138
	Mean (SD)	18.5 (2.53)	0.2 (1.84)
	Median	19.0	0.0
	Min, Max	12, 25	-10, 4

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Temperature(C)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	18.5 (2.65)	0.2 (1.73)
	Median	19.0	0.0
	Min, Max	10, 28	-9, 4
Week 36	n	123	123
	Mean (SD)	18.8 (2.46)	0.4 (1.88)
	Median	19.0	1.0
	Min, Max	10, 26	-7, 6

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Temperature(C)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	18.8 (2.65)	0.5 (2.08)
	Median	19.0	1.0
	Min, Max	12, 28	-7, 7
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	19.1 (2.53)	-0.2 (2.93)
	Median	19.0	0.0
	Min, Max	13, 28	-8, 8

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Waist Circumference(cm)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	91.2 (11.60)	
	Median	90.3	
	Min, Max	62, 115	
Week 46	n	128	128
	Mean (SD)	92.1 (12.57)	0.6 (3.99)
	Median	91.8	0.0
	Min, Max	62, 130	-14, 23

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Weight(kg)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	144	
	Mean (SD)	67.4 (13.70)	
	Median	65.8	
	Min, Max	42, 120	
Week 6	n	143	143
	Mean (SD)	67.8 (13.76)	0.4 (1.61)
	Median	66.4	0.3
	Min, Max	41, 120	-8, 9

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Weight(kg)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 12	n	140	140
	Mean (SD)	68.1 (13.69)	0.6 (1.97)
	Median	67.0	0.4
	Min, Max	42, 120	-8, 11
Week 18	n	138	138
	Mean (SD)	68.1 (13.79)	0.6 (2.56)
	Median	66.7	0.4
	Min, Max	42, 120	-12, 11

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Weight(kg)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 24	n	131	131
	Mean (SD)	68.5 (13.98)	0.6 (2.77)
	Median	67.0	0.4
	Min, Max	42, 120	-14, 11
Week 36	n	123	123
	Mean (SD)	68.2 (13.02)	0.7 (3.01)
	Median	67.3	0.5
	Min, Max	42, 104	-19, 12

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.1c
Summary of Change from Baseline in Vital Signs Parameters
Safety Population - Overall

Test:Weight(kg)

		Evenamide (N=144)	
Visit	Statistic	Observed	Change from Baseline
Week 46	n	128	128
	Mean (SD)	68.6 (13.06)	1.0 (3.69)
	Median	67.5	0.8
	Min, Max	42, 103	-21, 19
Safety follow-up-015 - Day 7	n	56	56
	Mean (SD)	68.7 (12.95)	0.7 (8.13)
	Median	67.8	1.6
	Min, Max	44, 104	-46, 19

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.2c
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population - Overall

Vital Signs	Visit	Criteria	Evenamide (N=144) n(%)
Respiratory Rate (breaths/min)	Week 24	>25	1 (0.7)
	Week 36	>25	1 (0.7)
	Week 46	>25	2 (1.4)
	Safety follow-up-015 - Day 7	>25	2 (1.4)
Temperature (C)	Week 24	Value >= 38.3 and >= 1.1 increase from baseline	1 (0.7)

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.2c
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population - Overall

Vital Signs	Visit	Criteria	Evenamide (N=144) n(%)
Weight (kg)	Week 6	>= 7% decrease from Baseline	2 (1.4)
	Week 6	>=7% increase from Baseline	1 (0.7)
	Week 12	>= 7% decrease from Baseline	3 (2.1)
	Week 12	>=7% increase from Baseline	7 (4.9)
	Week 18	>= 7% decrease from Baseline	4 (2.8)

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.2c
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population - Overall

Vital Signs	Visit	Criteria	Evenamide (N=144) n(%)
Weight (kg)	Week 18	>=7% increase from Baseline	6 (4.2)
	Week 24	>= 7% decrease from Baseline	3 (2.1)
	Week 24	>=7% increase from Baseline	7 (4.9)
	Week 36	>= 7% decrease from Baseline	2 (1.4)
	Week 36	>=7% increase from Baseline	8 (5.6)

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.3.2c
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population - Overall

Vital Signs	Visit	Criteria	Evenamide (N=144) n(%)
Weight (kg)	Week 46	>= 7% decrease from Baseline	3 (2.1)
	Week 46	>=7% increase from Baseline	11 (7.6)
	Safety follow-up-015 - Day 7	>= 7% decrease from Baseline	3 (2.1)
	Safety follow-up-015 - Day 7	>=7% increase from Baseline	7 (4.9)

Source: Listing 16.2.9
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.4
Physical Examination: Treatment Emergent Abnormalities
Safety Population

Result	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
No Subject meets these Criteria			

Source: Listing 16.2.10

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Screening	n	45		52		44	
		Mean (SD)	80.8 (13.74)		79.3 (13.41)		77.2 (12.62)	
		Median	81.0		79.0		76.5	
		Min, Max	59, 115		50, 107		56, 103	
	Baseline	n	45		52		45	
		Mean (SD)	78.2 (12.32)		75.8 (10.63)		77.4 (13.41)	
		Median	76.7		74.0		76.3	
		Min, Max	54, 115		53, 102		54, 102	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	81.3 (12.99)	2.7 (10.42)	78.4 (13.50)	2.8 (10.54)	77.6 (16.25)	0.6 (12.53)
		Median	78.0	2.5	78.0	2.3	76.0	1.8
		Min, Max	58, 112	-23, 30	48, 116	-25, 28	48, 137	-24, 51
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	79.9 (12.01)	1.0 (8.58)	78.5 (13.37)	3.1 (11.34)	78.3 (12.28)	0.3 (10.81)
		Median	82.0	0.0	76.0	2.3	78.0	1.0
		Min, Max	53, 112	-22, 19	53, 103	-20, 28	54, 107	-22, 21

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	80.4 (14.60)	1.6 (15.02)	79.6 (13.01)	4.4 (11.41)	79.6 (13.17)	1.4 (11.93)
		Median	79.0	3.3	77.0	4.2	78.0	1.0
		Min, Max	53, 116	-24, 32	59, 112	-26, 32	59, 111	-24, 31
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	80.6 (14.69)	1.9 (11.75)	81.8 (13.16)	6.2 (14.18)	78.8 (12.80)	1.0 (10.83)
		Median	80.0	2.5	78.5	5.3	78.0	0.2
		Min, Max	59, 116	-25, 33	52, 107	-21, 37	55, 101	-27, 37

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	80.8 (14.08)	2.9 (12.09)	78.3 (12.37)	3.2 (10.09)	80.2 (12.37)	4.1 (15.04)
		Median	82.5	2.0	78.0	1.7	78.5	3.7
		Min, Max	58, 123	-19, 48	53, 102	-19, 24	60, 106	-28, 50
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	80.4 (16.44)	2.3 (14.56)	77.7 (15.64)	2.3 (16.00)	81.4 (14.25)	4.2 (15.63)
		Median	79.0	1.3	71.0	1.0	80.0	1.8
		Min, Max	54, 123	-32, 44	56, 112	-29, 40	54, 122	-38, 50

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	151.2 (20.15)		149.6 (18.44)		155.7 (21.92)	
		Median	143.0		150.0		156.5	
		Min, Max	123, 197		113, 193		113, 241	
	Baseline	n	45		52		45	
		Mean (SD)	152.4 (20.00)		148.3 (17.34)		153.5 (16.24)	
		Median	144.7		148.5		154.0	
		Min, Max	121, 194		118, 181		109, 188	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 6	n	44	44	53	52	44	43
		Mean (SD)	151.7 (22.05)	-1.1 (12.01)	149.4 (18.89)	0.8 (14.34)	155.7 (27.75)	2.3 (20.98)
		Median	146.0	-1.2	149.0	0.3	153.0	-0.3
		Min, Max	116, 198	-35, 35	110, 189	-38, 58	115, 245	-42, 89
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	152.8 (19.12)	-0.0 (8.60)	151.5 (20.46)	3.8 (14.75)	156.8 (23.35)	3.3 (18.02)
		Median	151.0	0.3	147.0	3.0	155.0	0.7
		Min, Max	121, 195	-18, 17	113, 208	-35, 40	114, 235	-37, 79

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	152.0 (20.82)	-0.8 (14.71)	148.0 (19.13)	-0.1 (15.40)	156.2 (22.11)	2.7 (17.52)
		Median	148.0	-1.3	147.0	-0.7	156.0	0.7
		Min, Max	123, 204	-40, 51	116, 185	-39, 52	115, 242	-36, 86
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	154.3 (18.93)	1.3 (9.22)	145.1 (15.75)	-2.2 (11.98)	156.5 (21.40)	3.8 (16.48)
		Median	150.0	1.8	145.0	-2.7	156.0	0.5
		Min, Max	128, 207	-22, 18	107, 180	-26, 31	107, 235	-16, 79

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	151.2 (22.11)	-1.8 (13.30)	149.7 (18.41)	2.0 (11.29)	153.7 (20.99)	1.3 (16.53)
		Median	144.5	-1.3	150.0	1.7	154.0	-1.0
		Min, Max	121, 201	-48, 17	113, 185	-19, 28	116, 235	-24, 79
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	153.3 (20.84)	-0.1 (12.32)	150.2 (19.54)	0.9 (13.17)	157.7 (20.00)	3.7 (17.14)
		Median	147.0	3.3	149.0	2.2	160.0	2.0
		Min, Max	127, 206	-39, 17	113, 194	-32, 40	111, 234	-27, 78

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	86.8 (7.61)		90.4 (10.88)		87.7 (7.89)	
		Median	85.0		88.5		87.0	
		Min, Max	73, 103		78, 143		73, 107	
	Baseline	n	45		52		45	
		Mean (SD)	87.8 (6.80)		90.4 (10.98)		88.5 (5.71)	
		Median	87.0		87.5		87.7	
		Min, Max	71, 105		75, 151		78, 102	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	86.1 (7.63)	-1.3 (5.86)	90.3 (11.43)	0.1 (5.65)	88.5 (8.09)	0.4 (7.55)
		Median	85.0	-1.2	89.0	0.0	89.0	0.0
		Min, Max	71, 104	-13, 15	75, 153	-10, 14	67, 105	-13, 18
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	86.3 (7.52)	-1.5 (5.85)	89.3 (10.66)	-0.8 (7.33)	88.5 (8.17)	0.3 (7.04)
		Median	85.0	-1.3	88.0	-2.0	88.0	1.0
		Min, Max	71, 105	-14, 11	74, 142	-13, 21	68, 107	-16, 17

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	87.5 (7.38)	-0.2 (6.15)	89.0 (11.58)	-1.2 (5.66)	87.7 (8.24)	-0.5 (7.18)
		Median	87.0	0.3	87.0	-1.0	87.0	-1.7
		Min, Max	74, 105	-16, 11	75, 153	-17, 12	75, 111	-14, 19
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	85.8 (7.18)	-2.0 (5.33)	90.8 (10.63)	0.7 (6.80)	89.6 (7.27)	1.5 (6.13)
		Median	84.5	-2.0	90.0	0.3	91.0	1.0
		Min, Max	71, 103	-15, 12	73, 132	-19, 13	73, 105	-12, 15

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	85.6 (7.58)	-1.9 (5.87)	92.7 (12.10)	1.9 (6.41)	87.6 (8.35)	-0.2 (8.02)
		Median	83.0	-1.3	92.0	1.7	86.5	0.7
		Min, Max	74, 108	-14, 8	74, 149	-18, 16	73, 106	-14, 24
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	87.7 (6.52)	-0.0 (6.79)	89.5 (10.10)	-0.9 (6.28)	84.9 (7.52)	-3.4 (5.62)
		Median	87.0	0.0	88.0	-0.5	84.0	-3.8
		Min, Max	76, 107	-24, 14	73, 130	-21, 12	72, 105	-15, 9

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	359.2 (32.01)		355.8 (26.80)		361.8 (27.98)	
		Median	361.0		355.5		360.5	
		Min, Max	292, 447		313, 441		313, 423	
	Baseline	n	45		52		45	
		Mean (SD)	360.8 (26.15)		361.1 (24.71)		362.9 (30.67)	
		Median	357.7		359.7		361.0	
		Min, Max	298, 421		315, 423		314, 451	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	358.7 (28.21)	-1.6 (22.66)	358.7 (32.04)	-2.8 (22.57)	361.4 (28.28)	-2.0 (23.38)
		Median	358.0	-0.5	356.0	-1.3	357.0	3.3
		Min, Max	293, 412	-62, 49	294, 445	-42, 52	312, 435	-61, 36
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	359.7 (27.53)	0.3 (23.75)	359.4 (28.95)	-1.7 (21.64)	363.0 (26.83)	1.5 (23.21)
		Median	351.0	-4.0	355.0	-2.0	355.0	2.2
		Min, Max	321, 432	-49, 51	305, 421	-39, 49	321, 425	-51, 53

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	357.3 (26.52)	-2.1 (27.65)	357.6 (25.38)	-3.4 (24.19)	360.1 (28.25)	-2.3 (27.19)
		Median	361.0	-5.0	356.0	-5.8	355.0	0.3
		Min, Max	293, 414	-48, 59	313, 422	-56, 58	297, 435	-80, 56
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	358.7 (27.15)	-1.2 (22.85)	355.3 (22.23)	-5.7 (25.75)	358.8 (27.68)	-4.3 (26.66)
		Median	359.0	-1.2	354.5	1.7	351.0	0.2
		Min, Max	297, 410	-56, 47	317, 415	-76, 47	313, 418	-99, 43

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	355.4 (28.79)	-5.5 (22.12)	360.3 (29.30)	-1.3 (24.05)	357.0 (25.42)	-9.6 (26.01)
		Median	355.5	-5.8	365.0	-2.0	353.0	-5.0
		Min, Max	283, 408	-75, 38	301, 413	-53, 49	323, 408	-89, 46
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	358.8 (30.66)	-2.2 (22.57)	362.1 (29.98)	-0.2 (32.58)	353.5 (28.75)	-11.2 (33.66)
		Median	361.0	-7.3	364.0	1.2	351.0	-4.5
		Min, Max	289, 418	-57, 57	309, 427	-89, 73	283, 428	-94, 62

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	413.3 (23.44)		405.7 (27.26)		407.2 (19.32)	
		Median	412.0		404.0		407.0	
		Min, Max	362, 465		338, 471		359, 455	
	Baseline	n	45		52		45	
		Mean (SD)	408.8 (20.18)		403.8 (23.87)		407.8 (15.96)	
		Median	407.3		403.0		409.0	
		Min, Max	371, 455		338, 479		372, 440	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	414.2 (21.19)	4.9 (17.55)	406.3 (24.13)	3.0 (17.61)	406.3 (22.66)	-1.3 (14.64)
		Median	415.0	7.0	404.0	4.3	405.0	-2.5
		Min, Max	367, 460	-42, 41	361, 464	-35, 32	345, 472	-33, 53
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	412.0 (22.91)	3.0 (14.52)	407.8 (24.14)	5.2 (16.12)	411.3 (18.18)	3.7 (17.36)
		Median	410.0	-0.7	406.0	3.7	410.0	4.8
		Min, Max	367, 472	-26, 40	360, 482	-30, 47	375, 453	-28, 45

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	409.9 (21.45)	0.9 (19.71)	409.2 (26.89)	7.4 (17.34)	411.0 (16.55)	1.7 (13.57)
		Median	408.0	-1.0	407.0	8.3	410.0	0.0
		Min, Max	363, 454	-36, 61	357, 495	-34, 46	378, 441	-26, 31
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	412.0 (21.98)	3.0 (17.17)	412.7 (24.55)	9.7 (22.54)	407.7 (15.96)	-1.5 (12.99)
		Median	407.0	5.2	413.5	11.0	408.0	-2.0
		Min, Max	362, 466	-34, 43	361, 484	-34, 58	372, 435	-26, 25

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	408.9 (21.70)	0.5 (20.16)	408.2 (20.50)	6.0 (16.97)	409.8 (17.57)	1.0 (19.55)
		Median	410.0	0.2	409.0	6.7	408.0	-2.0
		Min, Max	359, 458	-41, 37	355, 474	-33, 55	372, 443	-36, 47
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	410.1 (23.97)	1.2 (20.80)	408.0 (23.87)	4.3 (18.85)	407.6 (22.02)	-2.1 (19.45)
		Median	409.0	-0.3	411.0	3.3	409.0	1.8
		Min, Max	365, 475	-62, 45	349, 465	-37, 48	356, 467	-46, 33

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	394.0 (22.46)		388.1 (22.09)		391.1 (17.71)	
		Median	387.0		386.0		391.5	
		Min, Max	350, 459		338, 442		355, 426	
	Baseline	n	45		52		45	
		Mean (SD)	391.8 (17.68)		388.8 (20.67)		391.9 (16.02)	
		Median	391.7		388.8		388.3	
		Min, Max	360, 428		336, 447		368, 436	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	394.5 (19.50)	2.6 (15.57)	389.5 (22.72)	0.8 (15.53)	390.3 (16.40)	-1.7 (12.45)
		Median	395.0	3.5	388.0	1.3	387.0	-1.8
		Min, Max	359, 440	-46, 30	347, 457	-33, 31	358, 434	-36, 29
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	393.4 (20.50)	2.0 (15.61)	390.7 (20.97)	2.7 (12.98)	394.2 (16.39)	3.0 (14.73)
		Median	393.0	-0.7	392.0	1.3	393.0	3.2
		Min, Max	359, 458	-32, 41	349, 448	-26, 33	366, 440	-36, 40

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

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Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	391.2 (16.63)	-0.2 (15.51)	391.0 (21.55)	3.5 (14.82)	393.1 (16.02)	0.4 (14.29)
		Median	390.0	0.0	387.0	3.7	389.0	-3.7
		Min, Max	358, 426	-25, 42	350, 458	-27, 49	365, 437	-41, 30
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	393.1 (17.74)	1.5 (13.92)	392.3 (18.39)	4.0 (17.43)	390.3 (14.74)	-2.5 (14.29)
		Median	393.0	0.8	393.5	8.3	389.0	-0.7
		Min, Max	359, 431	-23, 38	350, 439	-33, 38	358, 427	-38, 21

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	390.0 (19.89)	-1.6 (16.22)	391.4 (19.43)	3.4 (15.72)	391.2 (15.33)	-2.7 (13.44)
		Median	390.0	-2.7	391.0	0.7	391.5	-5.0
		Min, Max	356, 441	-37, 30	348, 443	-32, 40	357, 422	-37, 30
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	391.9 (19.96)	-0.0 (13.64)	391.7 (19.69)	2.5 (16.49)	388.4 (19.59)	-5.3 (19.29)
		Median	387.0	-2.0	389.0	4.7	387.0	-2.2
		Min, Max	364, 452	-32, 37	343, 435	-30, 37	351, 454	-62, 28

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Screening	n	45		52		44	
		Mean (SD)	763.0 (128.32)		779.9 (138.85)		797.3 (128.34)	
		Median	740.0		760.0		785.5	
		Min, Max	521, 1010		560, 1193		581, 1067	
	Baseline	n	45		52		45	
		Mean (SD)	787.5 (123.28)		807.7 (114.64)		799.9 (142.83)	
		Median	784.7		813.7		787.3	
		Min, Max	523, 1104		586, 1128		586, 1105	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
Programmer:SH
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Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 6	n	44	44	53	52	45	44
		Mean (SD)	756.3 (118.07)	-26.6 (96.71)	787.7 (136.59)	-23.5 (103.47)	805.2 (165.46)	2.3 (116.63)
		Median	769.5	-22.8	770.0	-21.0	793.0	-18.3
		Min, Max	537, 1041	-253, 181	518, 1241	-243, 284	437, 1241	-268, 228
	Week 12	n	43	43	51	50	45	44
		Mean (SD)	769.1 (120.25)	-11.1 (86.75)	786.6 (134.41)	-25.8 (113.02)	785.6 (125.16)	-8.7 (116.53)
		Median	736.0	-4.3	789.0	-17.0	767.0	-8.8
		Min, Max	533, 1131	-224, 224	581, 1131	-300, 205	563, 1120	-239, 276

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
Programmer:SH
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Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 18	n	43	43	49	48	43	43
		Mean (SD)	771.3 (145.78)	-8.9 (145.37)	773.3 (122.92)	-42.0 (120.96)	773.7 (123.49)	-17.4 (121.70)
		Median	755.0	-32.7	784.0	-34.2	771.0	-6.7
		Min, Max	515, 1129	-265, 253	535, 1017	-347, 265	539, 1011	-301, 292
	Week 24	n	42	42	48	47	41	40
		Mean (SD)	768.9 (134.91)	-13.6 (116.23)	751.3 (123.44)	-58.3 (140.53)	782.4 (135.26)	-12.5 (117.29)
		Median	754.0	-21.8	761.0	-48.3	767.0	-9.5
		Min, Max	517, 1019	-274, 276	559, 1145	-362, 282	593, 1099	-434, 255

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
Programmer:SH
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Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Parameter	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 36	n	40	40	41	41	38	37
		Mean (SD)	763.0 (127.94)	-25.6 (112.42)	785.7 (130.78)	-30.2 (109.68)	765.7 (119.40)	-46.5 (152.04)
		Median	727.0	-22.5	772.0	-18.3	762.5	-34.7
		Min, Max	487, 1027	-344, 239	587, 1128	-261, 202	567, 1004	-510, 267
	Week 46/Early Withdrawal	n	41	41	43	42	37	36
		Mean (SD)	776.6 (152.16)	-10.8 (138.60)	802.4 (150.80)	-10.0 (161.17)	760.2 (135.84)	-39.9 (149.54)
		Median	758.0	-24.0	843.0	-10.3	747.0	-18.8
		Min, Max	489, 1121	-322, 425	536, 1071	-409, 356	493, 1111	-457, 418

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
Programmer:SH
Date of Extraction:18DEC2023 Final - 18JAN2024:11:47

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Screening	n	141	
		Mean (SD)	79.1 (13.26)	
		Median	78.0	
		Min, Max	50, 115	
	Baseline	n	142	
		Mean (SD)	77.1 (12.06)	
		Median	76.3	
		Min, Max	53, 115	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 6	n	142	140
		Mean (SD)	79.0 (14.26)	2.1 (11.14)
		Median	78.0	2.2
		Min, Max	48, 137	-25, 51
	Week 12	n	139	137
		Mean (SD)	78.8 (12.54)	1.6 (10.37)
		Median	80.0	1.0
		Min, Max	53, 112	-22, 28

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 18	n	135	134
		Mean (SD)	79.9 (13.49)	2.5 (12.81)
		Median	78.0	2.7
		Min, Max	53, 116	-26, 32
	Week 24	n	131	129
		Mean (SD)	80.5 (13.52)	3.2 (12.56)
		Median	78.0	2.7
		Min, Max	52, 116	-27, 37

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Week 36	n	119	118
		Mean (SD)	79.8 (12.91)	3.4 (12.38)
		Median	79.0	2.3
		Min, Max	53, 123	-28, 50
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	79.7 (15.46)	2.9 (15.30)
		Median	79.0	1.7
		Min, Max	54, 123	-38, 50

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Screening	n	141	
		Mean (SD)	152.0 (20.14)	
		Median	150.0	
		Min, Max	113, 241	
	Baseline	n	142	
		Mean (SD)	151.2 (17.92)	
		Median	149.5	
		Min, Max	109, 194	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 6	n	141	139
		Mean (SD)	152.1 (22.92)	0.7 (16.02)
		Median	150.0	-0.3
		Min, Max	110, 245	-42, 89
	Week 12	n	139	137
		Mean (SD)	153.6 (21.02)	2.5 (14.38)
		Median	152.0	1.0
		Min, Max	113, 235	-37, 79

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	151.9 (20.77)	0.6 (15.85)
		Median	149.0	-0.5
		Min, Max	115, 242	-40, 86
	Week 24	n	131	129
		Mean (SD)	151.6 (19.22)	0.8 (12.95)
		Median	150.0	-0.3
		Min, Max	107, 235	-26, 79

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
PR Interval, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	151.5 (20.43)	0.5 (13.76)
		Median	151.0	-0.3
		Min, Max	113, 235	-48, 79
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	153.6 (20.19)	1.4 (14.19)
		Median	153.0	2.7
		Min, Max	111, 234	-39, 78

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Screening	n	141	
		Mean (SD)	88.4 (9.11)	
		Median	87.0	
		Min, Max	73, 143	
	Baseline	n	142	
		Mean (SD)	89.0 (8.34)	
		Median	87.3	
		Min, Max	71, 151	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 6	n	142	140
		Mean (SD)	88.5 (9.45)	-0.3 (6.37)
		Median	88.0	-0.3
		Min, Max	67, 153	-13, 18
	Week 12	n	139	137
		Mean (SD)	88.1 (9.02)	-0.7 (6.79)
		Median	87.0	-1.3
		Min, Max	68, 142	-16, 21

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	88.1 (9.32)	-0.7 (6.30)
		Median	87.0	-1.0
		Min, Max	74, 153	-17, 19
	Week 24	n	131	129
		Mean (SD)	88.8 (8.83)	0.1 (6.27)
		Median	87.0	-1.0
		Min, Max	71, 132	-19, 15

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QRS Duration, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	88.7 (9.98)	-0.1 (6.91)
		Median	87.0	0.0
		Min, Max	73, 149	-18, 24
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	87.5 (8.38)	-1.4 (6.37)
		Median	86.0	-1.3
		Min, Max	72, 130	-24, 14

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Screening	n	141	
		Mean (SD)	358.8 (28.81)	
		Median	358.0	
		Min, Max	292, 447	
	Baseline	n	142	
		Mean (SD)	361.6 (26.99)	
		Median	359.3	
		Min, Max	298, 451	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 6	n	142	140
		Mean (SD)	359.6 (29.53)	-2.2 (22.69)
		Median	356.0	0.2
		Min, Max	293, 445	-62, 52
	Week 12	n	139	137
		Mean (SD)	360.6 (27.69)	-0.0 (22.69)
		Median	355.0	-1.7
		Min, Max	305, 432	-51, 53

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	358.3 (26.51)	-2.6 (26.12)
		Median	357.0	-3.3
		Min, Max	293, 435	-80, 59
	Week 24	n	131	129
		Mean (SD)	357.5 (25.49)	-3.8 (25.01)
		Median	355.0	-0.3
		Min, Max	297, 418	-99, 47

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QT Interval, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	357.6 (27.78)	-5.3 (24.10)
		Median	359.0	-3.8
		Min, Max	283, 413	-89, 49
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	358.4 (29.80)	-4.2 (29.99)
		Median	358.0	-2.3
		Min, Max	283, 428	-94, 73

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Screening	n	141	
		Mean (SD)	408.6 (23.85)	
		Median	407.0	
		Min, Max	338, 471	
	Baseline	n	142	
		Mean (SD)	406.6 (20.44)	
		Median	408.0	
		Min, Max	338, 479	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 6	n	142	140
		Mean (SD)	408.7 (22.92)	2.2 (16.79)
		Median	407.5	0.8
		Min, Max	345, 472	-42, 53
	Week 12	n	139	137
		Mean (SD)	410.2 (21.90)	4.0 (15.97)
		Median	408.0	3.3
		Min, Max	360, 482	-30, 47

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	410.0 (22.13)	3.5 (17.20)
		Median	408.0	3.7
		Min, Max	357, 495	-36, 61
	Week 24	n	131	129
		Mean (SD)	410.9 (21.29)	4.0 (18.71)
		Median	411.0	4.0
		Min, Max	361, 484	-34, 58

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcB Interval, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	408.9 (19.88)	2.6 (18.91)
		Median	409.0	3.8
		Min, Max	355, 474	-41, 55
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	408.6 (23.19)	1.3 (19.72)
		Median	409.0	1.7
		Min, Max	349, 475	-62, 48

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Screening	n	141	
		Mean (SD)	390.9 (20.95)	
		Median	389.0	
		Min, Max	338, 459	
	Baseline	n	142	
		Mean (SD)	390.7 (18.28)	
		Median	388.8	
		Min, Max	336, 447	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 6	n	142	140
		Mean (SD)	391.3 (19.88)	0.6 (14.64)
		Median	389.0	1.3
		Min, Max	347, 457	-46, 31
	Week 12	n	139	137
		Mean (SD)	392.7 (19.37)	2.6 (14.31)
		Median	393.0	1.0
		Min, Max	349, 458	-36, 41

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	391.7 (18.28)	1.3 (14.86)
		Median	389.0	2.2
		Min, Max	350, 458	-41, 49
	Week 24	n	131	129
		Mean (SD)	391.9 (17.02)	1.2 (15.52)
		Median	393.0	1.3
		Min, Max	350, 439	-38, 38

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
QTcF Interval, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	390.8 (18.24)	-0.2 (15.33)
		Median	391.0	-1.2
		Min, Max	348, 443	-37, 40
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	390.8 (19.65)	-0.7 (16.67)
		Median	389.0	-0.3
		Min, Max	343, 454	-62, 37

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Screening	n	141	
		Mean (SD)	779.9 (132.08)	
		Median	769.0	
		Min, Max	521, 1193	
	Baseline	n	142	
		Mean (SD)	798.8 (126.22)	
		Median	785.7	
		Min, Max	523, 1128	

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 6	n	142	140
		Mean (SD)	783.5 (141.64)	-16.3 (105.79)
		Median	773.0	-20.3
		Min, Max	437, 1241	-268, 284
	Week 12	n	139	137
		Mean (SD)	780.8 (126.51)	-15.7 (106.21)
		Median	755.0	-7.3
		Min, Max	533, 1131	-300, 276

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 18	n	135	134
		Mean (SD)	772.8 (129.82)	-23.5 (129.33)
		Median	773.0	-29.7
		Min, Max	515, 1129	-347, 292
	Week 24	n	131	129
		Mean (SD)	766.7 (130.56)	-29.6 (126.86)
		Median	765.0	-29.7
		Min, Max	517, 1145	-434, 282

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.1c
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population- Overall

			Evenamide (N=144)	
Parameter	Visit	Statistic	Observed	Change from Baseline
RR Interval, Aggregate(ms)	Week 36	n	119	118
		Mean (SD)	771.7 (125.63)	-33.8 (124.57)
		Median	763.0	-22.8
		Min, Max	487, 1128	-510, 267
	Week 46/Early Withdrawal	n	121	119
		Mean (SD)	780.7 (146.68)	-19.3 (149.52)
		Median	761.0	-19.3
		Min, Max	489, 1121	-457, 425

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.2
Electrocardiogram (ECG): Treatment Emergent Abnormalities as Assessed by Central Reader
Safety Population

Result	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)	Total (N=144) n(%)
Abnormal	8 (17.8)	6 (11.3)	10 (21.7)	24 (16.7)

Source: Listing 16.2.11.2
N - Total number of subjects in the Safety population, n - number of subjects with abnormal ECG. Subjects with abnormal post-baseline findings at more than one assessment will be counted only once. Percentages are based on the total number of subjects in each group (N) under Safety population.

Table 14.3.5.3
Electrocardiogram (ECG): Treatment Emergent Abnormalities as Assessed by Investigator
Safety Population

Result	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)	Total (N=144) n(%)
Abnormal NCS	8 (17.8)	12 (22.6)	11 (23.9)	31 (21.5)
Abnormal CS	0	0	0	0

Source: Listing 16.2.11.1
N - Total number of subjects in the Safety population, n - number of subjects in the specified category. Percentages are based on the total number of subjects in each group (N) under Safety population.
CS = Clinically Significant, NCS = Not Clinically Significant.
Subjects with abnormal post-baseline findings at more than one assessment will be counted only once.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
PR Interval, Aggregate(ms)	Week 6	Absolute Value	> 200 msec	2 (1.4)
		Change From Baseline value	More than 25% change from baseline	3 (2.1)
	Week 12	Absolute Value	> 200 msec	2 (1.4)
		Change From Baseline value	More than 25% change from baseline	5 (3.5)
	Week 18	Absolute Value	> 200 msec	2 (1.4)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
PR Interval, Aggregate(ms)	Week 18	Change From Baseline value	More than 25% change from baseline	4 (2.8)
	Week 24	Absolute Value	> 200 msec	2 (1.4)
		Change From Baseline value	More than 25% change from baseline	2 (1.4)
	Week 36	Absolute Value	> 200 msec	2 (1.4)
		Change From Baseline value	More than 25% change from baseline	1 (0.7)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
PR Interval, Aggregate(ms)	Week 46/Early Withdrawal	Absolute Value	> 200 msec	2 (1.4)
		Change From Baseline value	More than 25% change from baseline	2 (1.4)
QRS Duration, Aggregate(ms)	Week 18	Absolute Value	> 110 msec	1 (0.7)
	Week 36	Change From Baseline value	More than 25% change from baseline	1 (0.7)
QTcB Interval, Aggregate(ms)	Week 6	Change From Baseline value	> 30 msec AND <= 60 msec	5 (3.5)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
QTcB Interval, Aggregate(ms)	Week 6	Absolute Value	> 450 msec AND <= 480 msec	3 (2.1)
	Week 12	Change From Baseline value	> 30 msec AND <= 60 msec	9 (6.3)
		Absolute Value	> 450 msec AND <= 480 msec	2 (1.4)
	Week 18	Change From Baseline value	> 30 msec AND <= 60 msec	8 (5.6)
		Absolute Value	> 450 msec AND <= 480 msec	3 (2.1)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
QTcB Interval, Aggregate(ms)	Week 18	Change From Baseline value	> 60 msec	1 (0.7)
	Week 24	Change From Baseline value	> 30 msec AND <= 60 msec	9 (6.3)
		Absolute Value	> 450 msec AND <= 480 msec	3 (2.1)
		Absolute Value	> 480 msec AND <= 500 msec	1 (0.7)
	Week 36	Change From Baseline value	> 30 msec AND <= 60 msec	8 (5.6)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
QTcB Interval, Aggregate(ms)	Week 36	Absolute Value	> 450 msec AND <= 480 msec	1 (0.7)
	Week 46/Early Withdrawal	Change From Baseline value	> 30 msec AND <= 60 msec	9 (6.3)
		Absolute Value	> 450 msec AND <= 480 msec	3 (2.1)
QTcF Interval, Aggregate(ms)	Week 6	Change From Baseline value	> 30 msec AND <= 60 msec	1 (0.7)
		Absolute Value	> 450 msec AND <= 480 msec	1 (0.7)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
QTcF Interval, Aggregate(ms)	Week 12	Change From Baseline value	> 30 msec AND <= 60 msec	5 (3.5)
		Absolute Value	> 450 msec AND <= 480 msec	1 (0.7)
	Week 18	Change From Baseline value	> 30 msec AND <= 60 msec	4 (2.8)
		Absolute Value	> 450 msec AND <= 480 msec	1 (0.7)
	Week 24	Change From Baseline value	> 30 msec AND <= 60 msec	7 (4.9)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.5.4c
Electrocardiogram (ECG) Parameters Categorical Analysis
Safety Population - Overall

Parameter	Visit	Criteria	Category	Total (N=144) n(%)
QTcF Interval, Aggregate(ms)	Week 36	Change From Baseline value	> 30 msec AND <= 60 msec	3 (2.1)
	Week 46/Early Withdrawal	Change From Baseline value	> 30 msec AND <= 60 msec	2 (1.4)
		Absolute Value	> 450 msec AND <= 480 msec	2 (1.4)

Source: Listing 16.2.11.3
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.6
Neurological Examination: Treatment Emergent Abnormalities
Safety Population

Result	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Abnormal, NCS	0(0.0)	0(0.0)	1(2.2)	1(0.7)
Abnormal, CS	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.12
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population. CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any neurological system are counted only once.

Table 14.3.7
Standard Eye Examination: Treatment Emergent Abnormalities
Safety Population

Result	Evenamide 7.5 mg BID (N=45) n (%)	Evenamide 15 mg BID (N=53) n (%)	Evenamide 30 mg BID (N=46) n (%)	Total (N=144) n (%)
Abnormal, NCS	2(4.4)	2(3.8)	1(2.2)	5(3.5)
Abnormal, CS	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.13
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population. CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any body system is counted only once

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Rigidity:Upper Limbs	Baseline	No rigidity	44(97.8)	53(100.0)	45(97.8)
			Minimal	1(2.2)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Upper Limbs	Week 12	No rigidity	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Upper Limbs	Week 24	No rigidity	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Upper Limbs	Week 36	No rigidity	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Upper Limbs	Week 46	No rigidity	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	Rigidity:Lower Limbs	Baseline	No rigidity	44(97.8)	53(100.0)	45(97.8)
			Minimal	1(2.2)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Lower Limbs	Week 12	No rigidity	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Lower Limbs	Week 24	No rigidity	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Lower Limbs	Week 36	No rigidity	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Lower Limbs	Week 46	No rigidity	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Rigidity:Neck	Baseline	No rigidity	44(97.8)	53(100.0)	45(97.8)
			Minimal	1(2.2)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Neck	Week 12	No rigidity	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Neck	Week 24	No rigidity	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Rigidity:Neck	Week 36	No rigidity	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Rigidity:Neck	Week 46	No rigidity	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	Tremor:Face/Jaw/Chin/Lips/Head	Baseline	No tremor	45(100.0)	52(98.1)	46(100.0)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 12	No tremor	42(93.3)	51(96.2)	46(100.0)
			Minimal	1(2.2)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 24	No tremor	42(93.3)	47(88.7)	41(89.1)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 36	No tremor	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 46	No tremor	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final - 18JAN2024:15:39

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Tremor:Upper Limbs/Hands	Baseline	No tremor	44(97.8)	52(98.1)	45(97.8)
			Minimal	1(2.2)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	1(2.2)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Upper Limbs/Hands	Week 12	No tremor	42(93.3)	51(96.2)	46(100.0)
			Minimal	1(2.2)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Upper Limbs/Hands	Week 24	No tremor	41(91.1)	47(88.7)	41(89.1)
			Minimal	1(2.2)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Upper Limbs/Hands	Week 36	No tremor	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Upper Limbs/Hands	Week 46	No tremor	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	Tremor:Lower Limbs/Feet	Baseline	No tremor	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Lower Limbs/Feet	Week 12	No tremor	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Lower Limbs/Feet	Week 24	No tremor	42(93.3)	47(88.7)	41(89.1)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tremor:Lower Limbs/Feet	Week 36	No tremor	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tremor:Lower Limbs/Feet	Week 46	No tremor	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Reduced Facial Expression/Speech	Baseline	Normal	43(95.6)	52(98.1)	43(93.5)
			Minimal	1(2.2)	1(1.9)	3(6.5)
			Mild	1(2.2)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Reduced Facial Expression/Speech	Week 12	Normal	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final - 18JAN2024:15:39

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Reduced Facial Expression/Speech	Week 24	Normal	42(93.3)	47(88.7)	41(89.1)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Reduced Facial Expression/Speech	Week 36	Normal	40(88.9)	41(77.4)	41(89.1)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Reduced Facial Expression/Speech	Week 46	Normal	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	Impaired Gait/Posture	Baseline	Normal	44(97.8)	53(100.0)	45(97.8)
			Minimal	1(2.2)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Impaired Gait/Posture	Week 12	Normal	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Impaired Gait/Posture	Week 24	Normal	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Impaired Gait/Posture	Week 36	Normal	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Impaired Gait/Posture	Week 46	Normal	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Postural/Instability	Baseline	No postural instability	45(100.0)	52(98.1)	46(100.0)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Postural/Instability	Week 12	No postural instability	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final - 18JAN2024:15:39

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Postural/Instability	Week 24	No postural instability	41(91.1)	48(90.6)	41(89.1)
			Minimal	1(2.2)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Postural/Instability	Week 36	No postural instability	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Postural/Instability	Week 46	No postural instability	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	Bradykinesia/Hypokinesia	Baseline	No slowness of movement	44(97.8)	52(98.1)	43(93.5)
			Minimal	1(2.2)	1(1.9)	3(6.5)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Bradykinesia/Hypokinesia	Week 12	No slowness of movement	43(95.6)	51(96.2)	45(97.8)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Bradykinesia/Hypokinesia	Week 24	No slowness of movement	42(93.3)	47(88.7)	41(89.1)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Bradykinesia/Hypokinesia	Week 36	No slowness of movement	40(88.9)	41(77.4)	41(89.1)
			Minimal	0(0.0)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Bradykinesia/Hypokinesia	Week 46	No slowness of movement	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Tables\Table 14.3.8.1.sas
Programmer:Ak
Date of Extraction:18Dec2023

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dystonia	Tongue	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tongue	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tongue	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tongue	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tongue	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dystonia	Jaw	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Jaw	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Jaw	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Jaw	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Jaw	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dystonia	Eyes/Face/Larnyx	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Eyes/Face/Larnyx	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Eyes/Face/Larnyx	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Eyes/Face/Larnyx	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Eyes/Face/Larnyx	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dystonia	Shoulders/Upper Limbs/Hands	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Shoulders/Upper Limbs/Hands	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Shoulders/Upper Limbs/Hands	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dystonia	Hips/Lower Limbs/Feet	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Hips/Lower Limbs/Feet	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Hips/Lower Limbs/Feet	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Hips/Lower Limbs/Feet	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Hips/Lower Limbs/Feet	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dystonia	Trunk/Neck	Baseline	None	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Trunk/Neck	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Trunk/Neck	Week 24	None	42(93.3)	47(88.7)	41(89.1)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Trunk/Neck	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Trunk/Neck	Week 46	None	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dyskinesia	Tongue	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tongue	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tongue	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Tongue	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Tongue	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dyskinesia	Jaw	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Jaw	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Jaw	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Jaw	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Jaw	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dyskinesia	Eyes/Face	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Eyes/Face	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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	Eyes/Face	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Eyes/Face	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Eyes/Face	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dyskinesia	Shoulders/Upper Limbs/Hands	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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	Shoulders/Upper Limbs/Hands	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

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	Shoulders/Upper Limbs/Hands	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dyskinesia	Hips/Lower Limbs/Feet	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Hips/Lower Limbs/Feet	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Hips/Lower Limbs/Feet	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Hips/Lower Limbs/Feet	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Hips/Lower Limbs/Feet	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Dyskinesia	Trunk/Neck	Baseline	Absent	45(100.0)	53(100.0)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Trunk/Neck	Week 12	Absent	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Trunk/Neck	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Trunk/Neck	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Trunk/Neck	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Akathisia	Subjective	Baseline	None	45(100.0)	52(98.1)	45(97.8)
			Minimal	0(0.0)	1(1.9)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Subjective	Week 12	None	43(95.6)	50(94.3)	46(100.0)
			Minimal	0(0.0)	1(1.9)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Subjective	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Subjective	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Subjective	Week 46	None	40(88.9)	46(86.8)	41(89.1)
			Minimal	1(2.2)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
Akathisia	Objective	Baseline	None	44(97.8)	53(100.0)	45(97.8)
			Minimal	1(2.2)	0(0.0)	1(2.2)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Objective	Week 12	None	43(95.6)	51(96.2)	46(100.0)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Objective	Week 24	None	42(93.3)	48(90.6)	41(89.1)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

Scale	Symptom/ Body Part	Visit	Rating	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
	Objective	Week 36	None	40(88.9)	41(77.4)	42(91.3)
			Minimal	0(0.0)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)
	Objective	Week 46	None	40(88.9)	46(86.8)	41(89.1)
			Minimal	1(2.2)	0(0.0)	0(0.0)
			Mild	0(0.0)	0(0.0)	0(0.0)
			Moderate	0(0.0)	0(0.0)	0(0.0)
			Severe	0(0.0)	0(0.0)	0(0.0)
			Extreme	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Parkinsonism	Rigidity:Upper Limbs	Baseline	No rigidity	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Upper Limbs	Week 12	No rigidity	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Upper Limbs	Week 24	No rigidity	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Upper Limbs	Week 36	No rigidity	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Upper Limbs	Week 46	No rigidity	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Parkinsonism	Rigidity:Lower Limbs	Baseline	No rigidity	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Lower Limbs	Week 12	No rigidity	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Lower Limbs	Week 24	No rigidity	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Lower Limbs	Week 36	No rigidity	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Lower Limbs	Week 46	No rigidity	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Parkinsonism	Rigidity:Neck	Baseline	No rigidity	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Neck	Week 12	No rigidity	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Neck	Week 24	No rigidity	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Rigidity:Neck	Week 36	No rigidity	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Rigidity:Neck	Week 46	No rigidity	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Parkinsonism	Tremor:Face/Jaw/Chin/Lips/Head	Baseline	No tremor	143(99.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 12	No tremor	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 24	No tremor	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 36	No tremor	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Face/Jaw/Chin/Lips/Head	Week 46	No tremor	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Parkinsonism	Tremor:Upper Limbs/Hands	Baseline	No tremor	141(97.9)
			Minimal	2(1.4)
			Mild	1(0.7)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Upper Limbs/Hands	Week 12	No tremor	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Upper Limbs/Hands	Week 24	No tremor	129(89.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Upper Limbs/Hands	Week 36	No tremor	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Upper Limbs/Hands	Week 46	No tremor	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Parkinsonism	Tremor:Lower Limbs/Feet	Baseline	No tremor	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Lower Limbs/Feet	Week 12	No tremor	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Lower Limbs/Feet	Week 24	No tremor	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tremor:Lower Limbs/Feet	Week 36	No tremor	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tremor:Lower Limbs/Feet	Week 46	No tremor	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Parkinsonism	Reduced Facial Expression/Speech	Baseline	Normal	138(95.8)
			Minimal	5(3.5)
			Mild	1(0.7)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Reduced Facial Expression/Speech	Week 12	Normal	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Reduced Facial Expression/Speech	Week 24	Normal	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Reduced Facial Expression/Speech	Week 36	Normal	122(84.7)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Reduced Facial Expression/Speech	Week 46	Normal	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Parkinsonism	Impaired Gait/Posture	Baseline	Normal	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Impaired Gait/Posture	Week 12	Normal	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Impaired Gait/Posture	Week 24	Normal	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Impaired Gait/Posture	Week 36	Normal	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Impaired Gait/Posture	Week 46	Normal	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Parkinsonism	Postural/Instability	Baseline	No postural instability	143(99.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Postural/Instability	Week 12	No postural instability	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Postural/Instability	Week 24	No postural instability	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Postural/Instability	Week 36	No postural instability	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Postural/Instability	Week 46	No postural instability	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Parkinsonism	Bradykinesia/Hypokinesia	Baseline	No slowness of movement	139(96.5)
			Minimal	5(3.5)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Bradykinesia/Hypokinesia	Week 12	No slowness of movement	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Bradykinesia/Hypokinesia	Week 24	No slowness of movement	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Bradykinesia/Hypokinesia	Week 36	No slowness of movement	122(84.7)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Bradykinesia/Hypokinesia	Week 46	No slowness of movement	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dystonia	Tongue	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tongue	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tongue	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tongue	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tongue	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dystonia	Jaw	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Jaw	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Jaw	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Jaw	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Jaw	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dystonia	Eyes/Face/Larnyx	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Eyes/Face/Larnyx	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Eyes/Face/Larnyx	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Eyes/Face/Larnyx	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Eyes/Face/Larnyx	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dystonia	Shoulders/Upper Limbs/Hands	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Shoulders/Upper Limbs/Hands	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Shoulders/Upper Limbs/Hands	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dystonia	Hips/Lower Limbs/Feet	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Hips/Lower Limbs/Feet	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Hips/Lower Limbs/Feet	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Hips/Lower Limbs/Feet	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Hips/Lower Limbs/Feet	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dystonia	Trunk/Neck	Baseline	None	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Trunk/Neck	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Trunk/Neck	Week 24	None	130(90.3)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Trunk/Neck	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Trunk/Neck	Week 46	None	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dyskinesia	Tongue	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tongue	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tongue	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Tongue	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Tongue	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dyskinesia	Jaw	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Jaw	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Jaw	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Jaw	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Jaw	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dyskinesia	Eyes/Face	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Eyes/Face	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Eyes/Face	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Eyes/Face	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Eyes/Face	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dyskinesia	Shoulders/Upper Limbs/Hands	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Shoulders/Upper Limbs/Hands	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Shoulders/Upper Limbs/Hands	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Shoulders/Upper Limbs/Hands	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Dyskinesia	Hips/Lower Limbs/Feet	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Hips/Lower Limbs/Feet	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Hips/Lower Limbs/Feet	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Hips/Lower Limbs/Feet	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Hips/Lower Limbs/Feet	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Dyskinesia	Trunk/Neck	Baseline	Absent	144(100.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
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Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Trunk/Neck	Week 12	Absent	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Trunk/Neck	Week 24	Absent	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

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Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Trunk/Neck	Week 36	Absent	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Trunk/Neck	Week 46	Absent	128(88.9)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
Akathisia	Subjective	Baseline	None	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Subjective	Week 12	None	139(96.5)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Subjective	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Subjective	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Subjective	Week 46	None	127(88.2)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
Akathisia	Objective	Baseline	None	142(98.6)
			Minimal	2(1.4)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Objective	Week 12	None	140(97.2)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Objective	Week 24	None	131(91.0)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.1c
Summary of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

Scale	Symptom/ Body Part	Visit	Rating	Evenamide (N=144) n(%)
	Objective	Week 36	None	123(85.4)
			Minimal	0(0.0)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)
	Objective	Week 46	None	127(88.2)
			Minimal	1(0.7)
			Mild	0(0.0)
			Moderate	0(0.0)
			Severe	0(0.0)
			Extreme	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Parkinsonism	Baseline	n	45		53		46	
		Mean (SD)	0.2 (0.94)		0.1 (0.35)		0.3 (0.74)	
		Median	0.0		0.0		0.0	
		Min,Max	0,6		0,2		0,3	
	Week 12	n	43	43	51	51	46	46
		Mean (SD)	0.0 (0.30)	-0.2 (0.69)	0.0 (0.00)	-0.1 (0.36)	0.1 (0.62)	-0.1 (0.45)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-4,0	0,0	-2,0	0,3	-2,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.0 (0.31)	-0.2 (0.70)	0.1 (0.72)	0.0 (0.83)	0.0 (0.00)	-0.2 (0.73)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-4,0	0,5	-2,5	0,0	-3,0
	Week 36	n	40	40	41	41	42	42
		Mean (SD)	0.0 (0.00)	-0.2 (1.00)	0.0 (0.00)	-0.1 (0.35)	0.0 (0.31)	-0.2 (0.73)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-6,0	0,0	-2,0	0,2	-3,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.0 (0.00)	-0.2 (0.99)	0.0 (0.00)	-0.1 (0.35)	0.0 (0.00)	-0.3 (0.78)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-6,0	0,0	-2,0	0,0	-3,0
Dystonia	Baseline	n	45		53		46	
		Mean (SD)	0.0 (0.00)		0.0 (0.00)		0.0 (0.00)	
		Median	0.0		0.0		0.0	
		Min,Max	0,0		0,0		0,0	

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 12	n	43	43	51	51	46	46
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.14)	0.0 (0.14)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,1	0,1	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 36	n	40	40	41	41	42	42
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Dyskinesia	Baseline	n	45		53		46	
		Mean (SD)	0.0 (0.00)		0.0 (0.00)		0.0 (0.00)	
		Median	0.0		0.0		0.0	
		Min,Max	0,0		0,0		0,0	
	Week 12	n	43	43	51	51	46	46
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0
	Week 36	n	40	40	41	41	42	42
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	0,0	0,0	0,0	0,0	0,0
Akathisia	Baseline	n	45		53		46	
		Mean (SD)	0.0 (0.15)		0.0 (0.14)		0.0 (0.21)	
		Median	0.0		0.0		0.0	
		Min,Max	0,1		0,1		0,1	

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 12	n	43	43	51	51	46	46
		Mean (SD)	0.0 (0.00)	-0.0 (0.15)	0.0 (0.14)	0.0 (0.20)	0.0 (0.00)	-0.0 (0.21)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-1,0	0,1	-1,1	0,0	-1,0
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.0 (0.00)	-0.0 (0.15)	0.0 (0.00)	-0.0 (0.14)	0.0 (0.00)	-0.0 (0.22)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-1,0	0,0	-1,0	0,0	-1,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 36	n	40	40	41	41	42	42
		Mean (SD)	0.0 (0.00)	-0.0 (0.16)	0.0 (0.00)	-0.0 (0.16)	0.0 (0.00)	-0.0 (0.22)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-1,0	0,0	-1,0	0,0	-1,0
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.0 (0.31)	0.0 (0.35)	0.0 (0.00)	-0.0 (0.15)	0.0 (0.00)	-0.0 (0.22)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-1,2	0,0	-1,0	0,0	-1,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Total Score	Baseline	n	45		53		46	
		Mean (SD)	0.2 (0.95)		0.1 (0.47)		0.3 (0.81)	
		Median	0.0		0.0		0.0	
		Min,Max	0,6		0,3		0,3	
	Week 12	n	43	43	51	51	46	46
		Mean (SD)	0.0 (0.30)	-0.2 (0.70)	0.0 (0.14)	-0.1 (0.46)	0.1 (0.62)	-0.2 (0.57)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-4,0	0,1	-3,0	0,3	-3,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 24	n	42	42	48	48	41	41
		Mean (SD)	0.0 (0.31)	-0.2 (0.71)	0.1 (0.73)	0.0 (0.90)	0.0 (0.00)	-0.3 (0.81)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-4,0	0,5	-3,5	0,0	-3,0
	Week 36	n	40	40	41	41	42	42
		Mean (SD)	0.0 (0.00)	-0.3 (1.01)	0.0 (0.00)	-0.1 (0.49)	0.0 (0.31)	-0.3 (0.81)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,0	-6,0	0,0	-3,0	0,2	-3,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population

			Evenamide 7.5 mg BID (N=45)		Evenamide 15 mg BID (N=53)		Evenamide 30 mg BID (N=46)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
	Week 46	n	41	41	46	46	41	41
		Mean (SD)	0.0 (0.31)	-0.2 (0.71)	0.0 (0.00)	-0.1 (0.48)	0.0 (0.00)	-0.3 (0.85)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,2	-4,0	0,0	-3,0	0,0	-3,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
Parkinsonism	Baseline	n	144	
		Mean (SD)	0.2 (0.71)	
		Median	0.0	
		Min,Max	0,6	
	Week 12	n	140	140
		Mean (SD)	0.1 (0.39)	-0.1 (0.51)
		Median	0.0	0.0
		Min,Max	0,3	-4,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 24	n	131	131
		Mean (SD)	0.1 (0.47)	-0.1 (0.76)
		Median	0.0	0.0
		Min,Max	0,5	-4,5
	Week 36	n	123	123
		Mean (SD)	0.0 (0.18)	-0.2 (0.74)
		Median	0.0	0.0
		Min,Max	0,2	-6,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 46	n	128	128
		Mean (SD)	0.0 (0.00)	-0.2 (0.74)
		Median	0.0	0.0
		Min,Max	0,0	-6,0
Dystonia	Baseline	n	144	
		Mean (SD)	0.0 (0.00)	
		Median	0.0	
		Min,Max	0,0	

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 12	n	140	140
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0
	Week 24	n	131	131
		Mean (SD)	0.0 (0.09)	0.0 (0.09)
		Median	0.0	0.0
		Min,Max	0,1	0,1

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 36	n	123	123
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0
	Week 46	n	128	128
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
Dyskinesia	Baseline	n	144	
		Mean (SD)	0.0 (0.00)	
		Median	0.0	
		Min,Max	0,0	
	Week 12	n	140	140
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 24	n	131	131
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0
	Week 36	n	123	123
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 46	n	128	128
		Mean (SD)	0.0 (0.00)	0.0 (0.00)
		Median	0.0	0.0
		Min,Max	0,0	0,0
Akathisia	Baseline	n	144	
		Mean (SD)	0.0 (0.16)	
		Median	0.0	
		Min,Max	0,1	

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 12	n	140	140
		Mean (SD)	0.0 (0.08)	-0.0 (0.19)
		Median	0.0	0.0
		Min,Max	0,1	-1,1
	Week 24	n	131	131
		Mean (SD)	0.0 (0.00)	-0.0 (0.17)
		Median	0.0	0.0
		Min,Max	0,0	-1,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 36	n	123	123
		Mean (SD)	0.0 (0.00)	-0.0 (0.18)
		Median	0.0	0.0
		Min,Max	0,0	-1,0
	Week 46	n	128	128
		Mean (SD)	0.0 (0.18)	-0.0 (0.25)
		Median	0.0	0.0
		Min,Max	0,2	-1,2

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
Total Score	Baseline	n	144	
		Mean (SD)	0.2 (0.76)	
		Median	0.0	
		Min,Max	0,6	
	Week 12	n	140	140
		Mean (SD)	0.1 (0.40)	-0.2 (0.57)
		Median	0.0	0.0
		Min,Max	0,3	-4,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 24	n	131	131
		Mean (SD)	0.1 (0.48)	-0.2 (0.82)
		Median	0.0	0.0
		Min,Max	0,5	-4,5
	Week 36	n	123	123
		Mean (SD)	0.0 (0.18)	-0.2 (0.79)
		Median	0.0	0.0
		Min,Max	0,2	-6,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.2c
Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A)
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistic	Observed	Change from Baseline
	Week 46	n	128	128
		Mean (SD)	0.0 (0.18)	-0.2 (0.69)
		Median	0.0	0.0
		Min,Max	0,2	-4,0

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data. SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.8.3
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population

Scale Category	Visit	CGI-S	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Baseline	Absent	43(95.6)	50(94.3)	42(91.3)
Parkinsonism		Minimal	2(4.4)	3(5.7)	4(8.7)
Dyskinesia		Absent	45(100.0)	53(100.0)	46(100.0)
Dystonia		Absent	45(100.0)	53(100.0)	46(100.0)
Akathisia		Absent	45(100.0)	53(100.0)	45(97.8)
Akathisia		Minimal	0(0.0)	0(0.0)	1(2.2)
Parkinsonism	Week 12	Absent	43(95.6)	50(94.3)	45(97.8)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.8.3.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final- 18JAN2024:15:44

Table 14.3.8.3
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population

Scale Category	Visit	CGI-S	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Parkinsonism	Week 12	Minimal	0(0.0)	1(1.9)	1(2.2)
Dyskinesia		Absent	43(95.6)	51(96.2)	46(100.0)
Dystonia		Absent	43(95.6)	51(96.2)	46(100.0)
Akathisia		Absent	43(95.6)	50(94.3)	46(100.0)
Akathisia		Minimal	0(0.0)	1(1.9)	0(0.0)
Parkinsonism	Week 24	Absent	41(91.1)	47(88.7)	40(87.0)
Parkinsonism		Minimal	1(2.2)	1(1.9)	1(2.2)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.8.3.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final- 18JAN2024:15:44

Table 14.3.8.3
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population

Scale Category	Visit	CGI-S	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dyskinesia	Week 24	Absent	42(93.3)	48(90.6)	41(89.1)
Dystonia		Absent	42(93.3)	47(88.7)	41(89.1)
Dystonia		Minimal	0(0.0)	1(1.9)	0(0.0)
Akathisia		Absent	42(93.3)	48(90.6)	41(89.1)
Parkinsonism	Week 36	Absent	40(88.9)	41(77.4)	41(89.1)
Parkinsonism		Minimal	0(0.0)	0(0.0)	1(2.2)
Dyskinesia		Absent	40(88.9)	41(77.4)	42(91.3)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.8.3.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final- 18JAN2024:15:44

Table 14.3.8.3
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population

Scale Category	Visit	CGI-S	Evenamide 7.5 mg BID (N=45) n(%)	Evenamide 15 mg BID (N=53) n(%)	Evenamide 30 mg BID (N=46) n(%)
Dystonia	Week 36	Absent	40(88.9)	41(77.4)	42(91.3)
Akathisia		Absent	40(88.9)	41(77.4)	42(91.3)
Parkinsonism	Week 46	Absent	41(91.1)	46(86.8)	41(89.1)
Dyskinesia		Absent	41(91.1)	46(86.8)	41(89.1)
Dystonia		Absent	41(91.1)	46(86.8)	41(89.1)
Akathisia		Absent	40(88.9)	46(86.8)	41(89.1)
Akathisia		Minimal	1(2.2)	0(0.0)	0(0.0)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Reference Datasets:ADSL,ADRS
Program Path:D:\Studies\study_015\CSR_015\development_programs\TFL_progs\Table\Table 14.3.8.3.sas
Programmer:Ak
Date of Extraction:18Dec2023 Final- 18JAN2024:15:44

Table 14.3.8.3c
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population - Overall

Scale Category	Visit	CGI-S	Evenamide (N=144) n(%)
Parkinsonism	Baseline	Absent	135(93.8)
Parkinsonism		Minimal	9(6.3)
Dyskinesia		Absent	144(100.0)
Dystonia		Absent	144(100.0)
Akathisia		Absent	143(99.3)
Akathisia		Minimal	1(0.7)
Parkinsonism	Week 12	Absent	138(95.8)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.8.3c
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population - Overall

Scale Category	Visit	CGI-S	Evenamide (N=144) n(%)
Parkinsonism	Week 12	Minimal	2(1.4)
Dyskinesia		Absent	140(97.2)
Dystonia		Absent	140(97.2)
Akathisia		Absent	139(96.5)
Akathisia		Minimal	1(0.7)
Parkinsonism	Week 24	Absent	128(88.9)
Parkinsonism		Minimal	3(2.1)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.8.3c
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population - Overall

Scale Category	Visit	CGI-S	Evenamide (N=144) n(%)
Dyskinesia	Week 24	Absent	131(91.0)
Dystonia		Absent	130(90.3)
Dystonia		Minimal	1(0.7)
Akathisia		Absent	131(91.0)
Parkinsonism	Week 36	Absent	122(84.7)
Parkinsonism		Minimal	1(0.7)
Dyskinesia		Absent	123(85.4)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.8.3c
ESRS-A: Summary of Clinical Global Impression of Movement Severity (CGI-S)
Safety Population - Overall

Scale Category	Visit	CGI-S	Evenamide (N=144) n(%)
Dystonia	Week 36	Absent	123(85.4)
Akathisia		Absent	123(85.4)
Parkinsonism	Week 46	Absent	128(88.9)
Dyskinesia		Absent	128(88.9)
Dystonia		Absent	128(88.9)
Akathisia		Absent	127(88.2)
Akathisia		Minimal	1(0.7)

Source: Listing 16.2.14
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Depression	Screening	n	144	
		Mean (SD)	0.2 (0.41)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.2 (0.40)	
		Median	0.0	
		Min, Max	0, 1	
	Week 24	n	131	131
		Mean (SD)	0.1 (0.32)	-0.1 (0.35)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Depression	Week 46	n	128	128
		Mean (SD)	0.1 (0.34)	-0.1 (0.36)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
Hopelessness	Screening	n	144	
		Mean (SD)	0.1 (0.32)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.1 (0.31)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Hopelessness	Week 24	n	131	131
		Mean (SD)	0.1 (0.29)	-0.0 (0.15)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
	Week 46	n	128	128
		Mean (SD)	0.1 (0.31)	-0.0 (0.23)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
Self Depreciation	Screening	n	144	
		Mean (SD)	0.1 (0.30)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Self Depreciation	Baseline	n	144	
		Mean (SD)	0.1 (0.30)	
		Median	0.0	
		Min, Max	0, 2	
	Week 24	n	131	131
		Mean (SD)	0.1 (0.27)	-0.0 (0.32)
		Median	0.0	0.0
		Min, Max	0, 2	-2, 2
	Week 46	n	128	128
		Mean (SD)	0.1 (0.23)	-0.0 (0.23)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Guilty Ideas of Reference	Screening	n	144	
		Mean (SD)	0.1 (0.24)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.0 (0.18)	
		Median	0.0	
		Min, Max	0, 1	
	Week 24	n	131	131
		Mean (SD)	0.0 (0.09)	-0.0 (0.12)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 0

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Guilty Ideas of Reference	Week 46	n	128	128
		Mean (SD)	0.0 (0.17)	-0.0 (0.15)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
Pathological Guilt	Screening	n	144	
		Mean (SD)	0.0 (0.18)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.0 (0.16)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Pathological Guilt	Week 24	n	131	131
		Mean (SD)	0.0 (0.09)	-0.0 (0.09)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 0
	Week 46	n	128	128
		Mean (SD)	0.0 (0.15)	-0.0 (0.09)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 0
Morning Depression	Screening	n	144	
		Mean (SD)	0.0 (0.22)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Morning Depression	Baseline	n	144	
		Mean (SD)	0.0 (0.20)	
		Median	0.0	
		Min, Max	0, 1	
	Week 24	n	131	131
		Mean (SD)	0.0 (0.00)	-0.0 (0.17)
		Median	0.0	0.0
		Min, Max	0, 0	-1, 0
	Week 46	n	128	128
		Mean (SD)	0.0 (0.09)	-0.0 (0.17)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 0

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Early Wakening	Screening	n	144	
		Mean (SD)	0.0 (0.20)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.0 (0.20)	
		Median	0.0	
		Min, Max	0, 1	
	Week 24	n	131	131
		Mean (SD)	0.0 (0.12)	-0.0 (0.23)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Early Wakening	Week 46	n	128	128
		Mean (SD)	0.0 (0.12)	-0.0 (0.23)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
Suicide	Screening	n	144	
		Mean (SD)	0.0 (0.08)	
		Median	0.0	
		Min, Max	0, 1	
	Baseline	n	144	
		Mean (SD)	0.0 (0.08)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Suicide	Week 24	n	131	131
		Mean (SD)	0.0 (0.09)	0.0 (0.00)
		Median	0.0	0.0
		Min, Max	0, 1	0, 0
	Week 46	n	128	128
		Mean (SD)	0.0 (0.09)	0.0 (0.00)
		Median	0.0	0.0
		Min, Max	0, 1	0, 0
Observed Depression	Screening	n	144	
		Mean (SD)	0.1 (0.27)	
		Median	0.0	
		Min, Max	0, 1	

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Observed Depression	Baseline	n	144	
		Mean (SD)	0.1 (0.23)	
		Median	0.0	
		Min, Max	0, 1	
	Week 24	n	131	131
		Mean (SD)	0.0 (0.19)	-0.0 (0.21)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1
	Week 46	n	128	128
		Mean (SD)	0.0 (0.15)	-0.0 (0.23)
		Median	0.0	0.0
		Min, Max	0, 1	-1, 1

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Total Score	Screening	n	144	
		Mean (SD)	0.7 (1.37)	
		Median	0.0	
		Min, Max	0, 6	
	Baseline	n	144	
		Mean (SD)	0.6 (1.31)	
		Median	0.0	
		Min, Max	0, 6	
	Week 24	n	131	131
		Mean (SD)	0.3 (0.90)	-0.2 (0.90)
		Median	0.0	0.0
		Min, Max	0, 4	-5, 3

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

Table 14.3.9c
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population - Overall

			Evenamide (N=144)	
Scale Category	Visit	Statistics	Observed	Change from Baseline
Total Score	Week 46	n	128	128
		Mean (SD)	0.4 (1.05)	-0.2 (0.98)
		Median	0.0	0.0
		Min, Max	0, 6	-5, 4

Source: Listing 16.2.15
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, Baseline: Pre-dose of 014, Post-Baseline intervals of 015 are of after Day 43 of 014 study dosing.

14.4 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

The Expanded Narratives of all the serious adverse events, including the death case, other significant adverse events leading to study discontinuation, and one case of pregnancy are described in this section. The brief narratives of all these cases are provided in Section 11.6.2.

Study: NW-3509/015/II/2019-401013

Study Number:	**NW-3509/015/II/2019**
Country of Origin:	**Sri Lanka**
Type of Narrative:	**Serious Adverse Event**
Subject Number:	**401013**
MFR Case ID	**2023NEW000002**
Treatment Group:	**Evenamide 30 mg bid**
Reported Term [Preferred Term]:	**Death [Death]**

This 31-year-old Asian male subject with chronic schizophrenia received the first dose of study medication (evenamide) in Study 014 on 29 Aug 2022 (Day 1); he completed the study on 12 Oct 2022 (Day 45) and entered in the extension Study 015 the same day. On 1 Mar 2023 (Day 185), the subject's family member informed the site that the subject had been found fallen inside the house. He was taken to the hospital, where they were informed that the subject was dead. The subject received the last dose on 01 Mar 2023 for a total of 185 days on evenamide 30 mg *bid*.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug.*

This 31-year-old Asian male subject with chronic schizophrenia received the first dose of study medication (evenamide) in Study 014 on 29 Aug 2022 (Day 1); he completed the study on 12 Oct 2022 (Day 45) and entered in the extension Study 015 the same day. The subject was continuing his medication olanzapine 20 mg/day.

At screening (09 Aug 2022) the subject's weight was 60 kg, his height was 160 cm with a body mass index of 23.8. Except for minor abnormalities in ALT, AST, lipid profile, and PRL all other laboratories, electrocardiogram (ECG), vital signs (VS), physical (PE) and neurological examination (NE) were normal. No substance use/ drug abuse or alcohol abuse were reported.

At baseline on 29 Aug 2022 (Day 0) the subject’s Positive and Negative Syndrome Scale (PANSS) total score was rated as 84 with Clinical Global Impression of Severity (CGI-S) of 5 (markedly ill). The findings in laboratory examinations were similar to those seen at the screening visit. The subject received the first dose of the study medication (evenamide) on the same day (Day 1). Post-dose safety evaluations were normal.

On 12 Oct 2022 (Day 45) the patient completed Study 014, showing a beneficial response to treatment: the PANSS total score was rated as 66 (-21% compared to baseline) with a Clinical Global Impressions of Change from baseline (CGI-C) of 3 (minimally improved). The CGI-S rating was unchanged (markedly ill). The findings in laboratory tests were substantially

unchanged from baseline; ECG, vital signs, physical and neurological examination were normal, and the subject elected to enter in the extension Study 015 and continue evenamide at the dose of 30 mg bid.

On 04 Jan 2023 (129 days on evenamide), the subject completed the planned study visit (Week 12) the findings in laboratory were substantially unchanged from baseline; ECG, vital signs, physical and neurological examination were normal. The subject showed a further improvement in symptoms based on PANSS total score of 62 (-26% compared to baseline), a CGI-C of 3 (minimally improved), and a CGI-S of 4 (moderately ill). The study medication was continued.

On 17 Feb 2023 (173 days on evenamide), the subject completed the planned study visit (Week 18) with ECG, vital signs (Systolic/diastolic blood pressure 100/72 mmHg, pulse rate of 65 bpm; no orthostatic changes after 1 and 3 min standing: systolic/diastolic blood pressure 90/78 mmHg, pulse rate of 65 bpm and 98/80 mmHg, pulse rate of 70 bpm respectively). No symptoms, discomfort or negative effects were reported.

On 1 Mar 2023 (Day 185) subject's family member informed the site that the subject fell on the ground in his house. He was taken to the hospital, where they were informed that the subject had died. The subject received the last dose on 01 Mar 2023 for a total of 185 days on evenamide 30 mg *bid*. There is no known cause of death.

The final autopsy report was received on 27 Oct 2023, and it stated that cause of death could not be ascertained (see below).

Medical History and Concomitant Medication:

The subject’s concurrent conditions included schizophrenia (since 14 Feb 2020), for which he received risperidone 4 mg daily up to 11 Aug 2020, when the dose was increased to 8 mg/day till 30 Dec 2020, and from that date the dose was further increased to 10 mg/day. From 17 Mar 2020 to 31 Dec 2020, he received adjunctive therapy with flupenthixol decanoate 40 mg qm. Risperidone 10 mg/day was continued up to 28 May 2022, when the therapy was changed to olanzapine 20 mg/day that was ongoing at the time of the event.

Other concomitant medication included trihexyphenidyl 2 mg/day for extrapyramidal symptoms from 28 May 2022.

Autopsy findings (post-mortem report dated 08 April 2023):

An autopsy was performed on 01 March 2023 by Judicial Medical Officer in the Colombo North Teaching Hospital Ragama. Overall, the autopsy did not detect significant remarkable findings. Notable findings included 25% narrowing of left anterior descending branch of the left coronary artery and narrowing of circumflex branch and normal right coronary artery. Several atherosclerotic plaques were present in the aorta. Bilateral congestions with mild pulmonary oedema were noted in the lungs. The liver was congested, dull in appearance and flabby in texture with fatty changes.

Autopsy findings (updated post-mortem report dated 26 October 2023):

Updated post-mortem report indicated that the blood sample sent to a Government Analyst for toxicology studies is negative. There is no apparent cause of death found after post-mortem, histological studies, and toxicology investigations. However, sudden cardiac events, such as cardiac arrhythmia, as a mechanism of death are impossible to determine at the autopsy examination, and therefore cannot be excluded.

Updated Investigator Assessment:

On 27 October 2023, based on an updated post-mortem report indicating the absence of any identifiable cause of death, the investigator considered the event of death as 'possibly related' to study medication (initially rated this event as not related).

Autopsy findings (updated post-mortem report dated 04 January 2024):

In the autopsy report version dated 26 October 2023 some information already reported in the autopsy dated 08 April 2023 was missed (e.g. "Notable findings included 25% narrowing of left anterior descending branch of the left coronary artery and narrowing of circumflex branch and normal right coronary artery. Several atherosclerotic plaques were present in the aorta. Bilateral congestions with mild pulmonary oedema were noted in the lungs. The liver was congested, dull in appearance and flabby in texture with fatty changes).

Updated post-mortem report was corrected from some typo errors (e.g. study medication name and date on drug trial).

Sponsor Assessment:

The corrected autopsy report indicating cardiac changes, but not enough for an identifiable cause of death, does not change the Sponsor's initial assessment that the SAE is unexpected, and not related to the study drug.

Pertinent Positives and Negatives:

Schizophrenia is associated with significantly increased mortality; studies estimate a reduction of 10-25 years in lifespan compared with the general population[1, 2]. These studies identified Sudden Unexpected Death (SUD) in 20% of the cases of mortality in patients with schizophrenia[3]. Epidemiologic studies in the US, indicated that the cardiac causes were two-fold higher, if patients had received First or Second-generation Antipsychotics in the last month of life, reflecting arrythmias as a potential cause of sudden death; however, these findings were rejected by the APA council on research that considered analyses of death certificates overestimates due to Sudden Cardiac Death (SCD)[4].

Retrospective reviews of 391 autopsy cases of patients with schizophrenia who died during a Five-year period in Maryland, US[5], identified the following distribution of deaths: race (48% white), gender bias (Male to female 1.5: 1), age (15.6% between the ages of 15 to 40). The majority of cases (64%) died of natural causes: cardiovascular diseases accounted for 79% for all deaths. No causes of death could be identified in 2.8% cases; these were young adults, predominantly with the age of 50 (average of 38 years).

This 31-year-old Asian male on olanzapine and trihexyphenidyl, did not report any adverse findings of vital signs, ECG, or laboratory variables when treated concomitantly with evenamide 30 mg bid for 185 days. The patient experienced improvement of his psychosis in Study 014 (20% improvement in "PANSS" and a rating of minimally improved on "CGI-C"). He elected to continue in the extension Study 015. During the extension study, he further improved on the rating of the PANSS compared to baseline by 26%; the CGI-S improved from markedly ill to moderately ill. On Day 185, the patient fell on the ground suddenly, and he was rushed to the hospital but was pronounced dead.

An autopsy was performed on 01 March 2023 by Judicial Medical Officer in the Colombo North Teaching Hospital Ragama (report dated 08 April 2023). The autopsy detected 25% narrowing of left anterior descending branch of the left coronary artery, and 25% narrowing of circumflex branch and normal right coronary artery. Several atherosclerotic plaques were present in the aorta. Bilateral congestions with mild pulmonary oedema were noted in the lungs.

The liver was congested, dull in appearance and flabby in texture with fatty changes. These findings may be suggestive of a contribution of cardiovascular dysfunction in the subject's death as reported in the literature.

Evenamide has been classified as a class 1b antiarrhythmic drug (Vaughan-Williams classification), therefore it is unlikely to produce cardiac disfunction, as suggested by the absence of any adverse ECG or laboratory findings in this patient. However, as a definitive cause could not be established, a contribution of evenamide could not be fully excluded.

References

1- Simpson JC et al. Mortality among patients with schizophrenia. Schizophrenia Bulletin, 1996; 22(3), 485–499.

2-Koponen H et al. Schizophrenia and sudden cardiac death: a review. Nord J Psychiatry, 2008; 62: 342−345.

3- Ifteni P et al. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr Res. 2014; 155 (1-3): 72-6

4- Murray-Thomas T et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. Cardiovasc Psychiatry Neurol. 2013; 2013: 247486

5-Sun D et al. Causes of Sudden Unexpected Death in Schizophrenia Patients: A Forensic Autopsy Population Study. The American Journal of Forensic Medicine and Pathology, 2019; 40 (4) 312-317, December

Subject Number: 30 Y Male **401013 ECG recording**

Visit	Days	ECG Date/Time	HR (change)	RR (change)	PR (change)	QRS (change)	QT (change)	QTcB (change)	QTcF (change)	Overall Interpretation
Screening	-21	09/08/2022 10:00	79	763	192	92	337	385	368	Normal
Baseline (Triplicate)		29/08/2022 09:15	83	721	175	88	325	382	362	Normal
		09:31	84	718	189	88	332	392	371	Normal
		09:43	86	701	188	84	336	401	378	Normal
Day 1 1 Hour Post Dose	1	29/08/2022 11:05	84 (0)	717 (4)	185 (1)	87 (0)	336 (5)	397 (5)	375 (5)	Normal
4 Hour Post Dose	1	14:05	79 (-5)	756 (43)	191 (7)	83 (-4)	328 (-3)	377 (-15)	360 (-10)	Normal
Day 8 1 Hour Post Dose	9	06/09/2022 10:03	93 (9)	648 (-65)	177 (-7)	86 (-1)	323 (-8)	401 (9)	373 (3)	Normal
4 Hour Post Dose	9	12:13	108 (24)	553 (-160)	193 (9)	77 (-10)	287 (-44)	386 (-6)	350 (-20)	Sinus Tachycardia Normal
Day 15	15	12/09/2022 10:18	88 (4)	678 (-35)	180 (-4)	74 (-13)	313 (-18)	380 (-12)	356 (-14)	Normal
Day 29	30	27/09/2022 10:52	82 (-2)	732 (19)	191 (7)	82 (-5)	333 (2)	389 (-3)	369 (-1)	Normal
Day 43/Baseline 015	45	12/10/2022 12:19	66 (-18)	915 (202)	187 (3)	91 (4)	335 (4)	350 (-42)	345 (-25)	Normal
Unscheduled Postdose	79	16/11/2022 09:15	96 (12)	626 (-87)	185 (1)	85 (-2)	332 (1)	420 (28)	388 (18)	Normal
Week 6 Postdose	79	16/11/2022 09:19	93 (9)	643 (-70)	185 (1)	78 (-9)	312 (-19)	389 (-3)	361 (-9)	Normal
Week 12 Postdose	129	04/01/2023 09:57	73 (-11)	821 (108)	195 (11)	90 (3)	355 (24)	392 (0)	379 (9)	Normal

Week 18 Postdose	173	17/02/2023 11:01	60 (-24)	1005 (292)	175 (-9)	81 (-6)	387 (56)	387 (-5)	387 (17)	Normal

Primary Lead=Lead II; all ECG Quality have been rated as Good Tracing.

Subject Number: 30 Y Male **401013 Vital signs**

Date	Days	Visit	Systolic BP[(a)] mmHg		Diastolic BP[(a)] mmHg		Pulse rate[(a)] bpm		Respiratory Rate [(a)] bpm	Weight [(a)] kg
			Supine	OC	Supine	OC	Supine	OC		
09/08/2022	-19	Screening	112 (7)	-2 / 1	75 (-4)	2 / 5	71 (-17)	9 / 17	22 (8)	60.7 (2.7)
29/08/2022	0	Baseline[(b)]	105	3 / -3	79	6 / -4	88	-1 / -5	14	58
	1	1 Hour Post Dose	110 (5)	3 / 4	75 (-4)	9 / 5	87 (-1)	3 / 7	16 (2)	
		4 Hour Post Dose	102 (-3)	-2 / -1	78 (-1)	-6 / -4	90 (2)	1 / 3	14 (0)	
06/09/2022	9	Day 8 Pre dose	105 (0)	-2 / 0	76 (-3)	3 / 7	90 (2)	6 / 2	16 (2)	59.7 (1.7)
		1 Hour Post Dose	110 (5)	-5 / -6	81 (2)	2 / 6	99 (11)	-3 / -5	18 (4)	
		4 Hour Post Dose	103 (-2)	-1 / -3	89 (10)	1 / 1	96 (8)	-1 / 0	17 (3)	
12/09/2022	15	Day 15 Pre dose	114 (9)	0 / -12	78 (-1)	7 / 6	85 (-3)	13 / 14	14 (0)	61 (3)
		1 Hour Post Dose	106 (1)	1 / 1	79 (0)	-3 / 1	95 (7)	2 / 4	14 (0)	
27/09/2022	30	Day 29 Pre dose	109 (4)	-3 / -8	78 (-1)	-3 / 6	79 (-9)	5 / 16	15 (1)	61.1 (3.1)
12/10/2022	45	Day 43/Baseline 015	111 (6)	2 / -1	73 (-6)	18 / 3	72 (-16)	10 / 18	14 (0)	61.7 (3.7)
16/11/2022	80	Week 6 Post Dose	110 (5)	-4 / -9	82 (3)	3 / 5	90 (2)	2 / 0	14 (0)	61.7 (3.7)
04/01/2023	129	Week 12 Post Dose	113 (8)	-1 / -5	80 (1)	7 / 4	63 (-25)	19 / 22	14 (0)	63.4 (5.4)
17/02/2023	173	Week 18 Post Dose	100 (-5)	-10 / -2	72 (-7)	6 / 8	65 (-23)	7 / 5	16 (2)	64.5 (6.5)

(a) in parenthesis change from baseline; (b) baseline value=average of 3 pre-dose readings; Supine (after 5 minutes rest), OC=orthostatic changes readings at 1 min / 3 min standing.

Laboratory: Clinical chemistry

Analyte	Normal range	Screening	Baseline	Day 8	Day 15	Day 29	Day 43	Day 127
Albumin	35-52 g/l	46.7	49.9	49.8	47.5	49.2	46.7	44.0
Total protein	64-83 g/l	76.1	76.4	78.8	74.6	76.9	75.6	68.7
Alkaline phosphatase (ALP)	40-130 U/L	79.0	76.0	82.0	74.0	74.0	78.0	69.0
ALT (SGPT)	0-45 U/L	58.0 H	54.0 H	69.0 H	69.0 H	74.0 H	82.0 H	72.0 H
AST (SGOT)	0-40 U/L	41.0	36.0	44.0 H	42.0 H	42.0 H	52.0 H	43.0 H
Gamma glutamyl transferase (GGT)	0-45 U/L	24.0	24.0	24.0	23.0	27.0	26.0	22.0
Total bilirubin	0.1-1.2 mg/dL	0.9	0.6	1.1	0.7	1.0	0.8	0.7
Lactate dehydrogenase (LDH)	135-250 U/L	191.0	194.0	193.0	192.0	191.0	211.0	246.0
Creatine kinase (CPK)	20-200 U/L	172.0	141.0	188.0	129.0	146.0	151.0	151.0
Blood urea nitrogen (BUN)	6-20 mg/dL	9.00	7.00	12.00	5.00 L	8.00	5.00 L	5.00 L
Creatinine	0.67-1.17 mg/dL	0.93	1.0	1.05	0.95	0.98	0.97	0.99
Bicarbonate	22-29 mmol/L	25.0	28.0	26.0	23.0	24.0	25.0	29.0 H
Calcium	8.6-10.2 mg/dL	9.7	9.5	9.8	9.6	9.6	9.4	8.8
Chloride	98-107 mmol/L	99.0	99.0	97.0 L	100.0	97.0 L	98.0	99.0
Potassium	3.5-5.1 mmol/L	4.3	3.6	3.5	3.7	4.0	4.2	3.7
Sodium	136-145 mmol/L	139.0	140.0	137.0	139.0	137.0	141.0	140.0
Fasting plasma glucose	70-100 mg/dL	77.0	75.0	78.0	77.0	76.0	79.0	80.0
Triglycerides	0-150 mg/dL	116.0	84.0	80.0	88.0	141.0	162.0 H	140.0
Total cholesterol	0-200 mg/dL	171.0	185.0	184.0	158.0	204.0 H	176.0	149.0
LDL cholesterol	0-130 mg/dL	107.0	123.0	126.0	96.0	133.0 H	106.0	84.0
HDL cholesterol	40-(blank) mg/dL	41.0	45.0	42.0	44.0	43.0	38.0 L	37.0 L
VLDL cholesterol	0-30 mg/dL	23.2	16.8	16.0	17.6	28.2	32.4 H	28.0

Laboratory: Haematology/Complete blood count (CBC)

Analyte	Normal range	Screening	Baseline	Day 8	Day 15	Day 29	Day 43	Day 127
Red blood cells (RBCs)	4.5-5.5 10^6/microL	4.95	5.13	5.55	5.03	5.48	5.26	5.17
White blood cells (WBCs)	4-10 10^3/microL	7.19	7.23	8.01	6.46	7.98	7.19	6.37
Haemoglobin (HB)	13-17 g/dL	15.7	16.1	16.9	16.1	16.6	16.4	16.1
Platelet Count / Thrombocytes	150-410 10^3/microL	263	199	288	243	260	232	222
Basophils (absolute)	0.02-0.1 10^3/microL	0.03	0.01	0.03	0.01 L	0.05	0 L	0.01
Eosinophils (absolute)	0.02-0.5 10^3/microL	0.34	0.4	0.4	0.3	0.34	0.37	0.46
Lymphocytes (absolute)	1-3 10^3/microL	2.8	2.66	2.76	2.27	2.91	2.88	2.61
Monocytes (absolute)	0.2-1 10^3/microL	0.63	0.54	0.59	0.47	0.61	0.57	0.52
Neutrophils (absolute)	2-7 10^3/microL	3.39	3.61	4.22	3.42	4.07	3.37	2.78

The flags L = lower or H = higher than the normal range.

Laboratory: Serology/ Hormones

Analyte	Normal range	Screening	Baseline	Day 43
Free thyroxine (FT4)	0.93-1.7 ng/dL	1.65		
Free triiodothyronine (FT3)	2-4.4 pg/mL	3.08		
Total antibody to hepatitis B core antigen (anti-HBc)		Negative		
Hepatitis B surface antibody (anti-HBs) (Quantitative)	0-9.9 mIU/mL	1.09		
Hepatitis B surface antigen (HBsAg)		Negative		
Hepatitis C (Antigen + Antibody)		Negative		
HIV I & II (Antigen+Antibody)		Negative		
Prolactin	4.04-15.2 ng/mL		19.95 H	9.86
TSH (Thyroid-Stimulating Hormone)	0.27-4.2 microIU/mL	4.61		

The flags L = lower or H = higher than the normal range

Study: NW-3509/015/II/2019-311006

Study Number:	**NW-3509/015/II/2019**
Country of Origin:	**India**
Type of Narrative:	**Serious Adverse Event**
Subject Number:	**311006**
MFR Case ID	**2022NEW000003**
Treatment Group:	**Evenamide 15 mg bid**
Reported Term [Preferred Term]:	**Dilutional hyponatremia [Hyponatraemia] and Acute symptomatic seizure [Seizure]**

This 35-year-old Asian male subject with chronic schizophrenia received the first dose of study medication (evenamide 7.5 mg *bid*) in Study 014 on 12 Apr 2021 (Day 1); he completed the study on 24 May 2021 (Day 43) and entered in the extension Study 015 on the same day. The subject received evenamide in the extension Study 015 for 385 days; due to the study medication supply disruption the subject received the last dose on 2 May 2022. Twenty-six days after the last dose of study medication (28 May 2022), the patient experienced a seizure, later diagnosed as due to dilutional hyponatremia.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug.*

This 35-year-old Asian male subject with chronic schizophrenia was randomized to receive evenamide. The first dose of study medication (15 mg of evenamide) was administered on 12 Apr 2021. The subject completed Study 014 on the 24 May 2021 (Day 43) and entered in Study 015 (46-week extension) on the same day. On 11 Apr 2022 the subject completed the planned 46-week treatment period (365 days on evenamide) and entered a further period (24-week) of treatment with evenamide. The subject was continuing his antipsychotic medications (haloperidol 5 mg bid).

On 02 May 2022 (385 days on evenamide), the subject received the last dose of study medication, due to unavailability of the investigational product at the study site (last 3 kits of study medication were dispensed on 11 Apr 2022). The haloperidol 5 mg bid was continued.

On 28 May 2022 (Day 411) 26 days after receiving the last dose of evenamide, the subject had an episode of tonic-clonic convulsions at 5:30 p.m., associated with a fall, along with one episode of vomiting and bed wetting. He also had a contused lacerated wound on the mandible. The patient was brought to hospital around 7:00 p.m. in a confused state (post ictal confusion). In the Emergency Room he was treated with antiepileptic medication brivaracetam at a dose of 100 mg i.v., followed by a dose of 50 mg i.v. bid for seizure, pantoprazole 40 mg bid qd, ondansetron 4 mg iv tid ceftriaxone/ sulbactam 1 mg iv bid. The subject regained his consciousness and was oriented by night.

The subject had attended a party (marriage ceremony) during which he consumed copious amounts of water for two days and was sleep deprived. Laboratory findings included severe hyponatremia (103.6 mmol/L normal range 135-155 mEq/L) and elevated Alanine transaminase (ALT) 139.7 IU/l (normal range 0-45 IU/L) (for these laboratory results, see Table-1). The ECG report had indicated possible myocardial ischemia changes (ST abnormality, possible transmural injury

(anterolateral) and T wave inversion); however, they were considered not clinically significant. Brain CT Scan and an electroencephalogram were normal. The hyponatremia was treated with 100 mL i.v. bolus of 3 percent saline.

On 29 May 2022 (Day 412), a neurologist examined the subject and concluded that the seizure was due to dilutional hyponatremia caused by excessive water intake. There was no prior history of seizure or hyponatremia in the subject. A single dose of oral 15 mg tolvaptan, for hyponatremia was administered. Subject vital signs were stable, and sodium levels improved to 128.9 mEq/L (normal range 135-155 mEq/L).

On 30 May 2022 (Day 413) the subject's vitals were stable, the electroencephalogram (EEG) was normal, ALT level was high at 213.7 IU/L (normal range 0-45 IU/L), and sodium level was 133.5 mEq/l (normal range 135-155 mEq/L). Brivaracetam was discontinued and ceftriaxone/sulbactam was replaced with cefoparazone/sulbactam.

On 31 May 2022, the laboratory results indicated that the sodium level was almost normalized 134.9 mEq/l (normal range 135-155 mEq/L), however the ALT indicated continued increase (232.4 IU/l normal range 0-45 IU/L); HCV Ab and Hbs Ag tests were negative, and no other significant hepatic laboratory findings were detected. An abdominal ultrasound (USG) indicated mild hydronephrosis, with three small calculi in the left kidney and cystitis.

Intravenous administration of cefoperazone/sulbactam, ondansetron and pantoprazole were discontinued. Oral pantoprazole at a dose of 40 mg bid and domperidone at a dose of 30 mg bid were initiated, as prophylaxis for acidity and vomiting.

The same day, the events of acute symptomatic seizure and dilutional hyponatremia were considered resolved and the subject was discharged as stable, oriented, and conscious. As the subject was off the study medication (evenamide) since 02 May 2022, there was no need for action to be taken with study medication.

Both the neurologist and investigator assessed the events of acute symptomatic seizure and dilutional hyponatremia as not related to evenamide that was last administered 26 days before the onset of the events. The seizure had been due to dilutional hyponatremia due to the subject's excessive water intake.

Medical History and Concomitant Medication:

The subject's concurrent conditions included schizophrenia (since 12 Jan 2015) and type 2 diabetes mellitus since 08 Dec 2021. The patient was receiving haloperidol since 24 Feb 2018 at the dose of 5 mg bid daily. Other concomitant medications included metformin 250 mg daily for diabetes mellitus type 2 and lorazepam 2 mg as needed for exacerbation of psychosis.

Treatment of events included: 100 mL iv bolus of 3 percent saline, brivaracetam 100 iv once, followed by a 50 mg iv bid for seizure, pantoprazole, ondansetron, ceftriaxone/sulbactam iv, vitamin C, ursodeoxycholic acid and oral silymarin, zinc amino acid, and vitamin suspension of Syrup Heptagon as prophylaxis for liver.

Investigator Assessment:

The investigator considered the SAE of acute symptomatic seizure and dilutional hyponatremia as moderate in intensity, with seriousness criteria of hospitalization, and as an important medical

event. The investigator considers the SAE as not related to the study drug evenamide, as the subject was off the IP for 26 days (due to unavailability of IMP on site), prior to the events.

Sponsor Assessment:

The Sponsor agrees with the investigator's causality assessment that this event is not related to the study medication (evenamide).

Pertinent Positives and Negatives:

A 35-year-old Asian male subject with history of chronic schizophrenia and type 2 diabetes mellitus, receiving haloperidol 5 mg at stable dose, received evenamide 15 mg *bid*. for more than one year up to 2 May 2022 (Day 385). On 28 May 2022 (Day 411), 26 days after the last dose of study medication, the patient experienced a seizure, later diagnosed as due to dilutional hyponatremia caused by excess water intake. Prior to the event, the subject attended a marriage party at home, was unsupervised, slept very little, and drank too much water for two days. Based on the evidence that evenamide half-life is approx. 1 hour, does not have accumulation, and the subject had been off the study medication (evenamide) for 26 days (since 02 May 2022) before the onset of the events, a temporal relationship between evenamide and the event can be excluded; therefore, the events are not related to evenamide. The events are possibly related to the excess water intake by the patient, that led to dilutional hyponatremia (common in patients with chronic schizophrenia), and to an acute symptomatic seizure.

Table 1 - Key laboratory data for Subject Number: 311006

Timepoints		**Sodium**	**ALT**	**AST**	**Bilirubin total**	**CPK**	**LDH**
Date	**Day**	**136-145 mmol/L**	**0-41 U/L**	**0-40 U/L**	**0-1.2 mg/dL**	**0-189 U/L**	**0-250 U/L**
22-Mar-21 (screening)	-21	140	24	28	0.24	**253 H**	227
12-Apr-21 (study day 1)	1	▼ 1st dose of study medication					
		139	20	22	0.16	**204 H**	232
19-Apr-21	8	**135 L**	20	22	0.2	**201 H**	251
26-Apr-21	15	**134 L**	20	23	0.45	**259 H**	227
10-May-21	29	137	24	26	0.17	**221 H**	226
24-May-21	43	**134 L**	37	35	0.39	**283 H**	248
16-Aug-21	127	139	28	27	0.19	**306 H**	249
11-Nov-21	214	**133 L**	22	25	0.33	**467 H**	250
29-Jan-22	293	**135 L**	27	26	0.28	**261 H**	225
11-Apr-22	365	**125 LN**	32	29	0.33	**273 H**	204
02-May-22	386	▽ last dose of study medication prior to the AE *					
28-May-22	412	**103.6 LN**	**139.7 HN**	.	.	.	.
29-May-22	413	**128.9 L**	**213.7 HN**	.	.	.	.
31-May-22	415	**133.5 L**	**232.4 HN**	.	.	.	.
06-Jun-22	421	**134.9 L**	**105 H**	**87.3 H**	.	.	.

Timepoints		Sodium	ALT	AST	Bilirubin total	CPK	LDH
Date	**Day**	**136-145 mmol/L**	**0-41 U/L**	**0-40 U/L**	**0-1.2 mg/dL**	**0-189 U/L**	**0-250 U/L**
15-Jun-22	430	.	**68 H**	37	.	.	.
		▼ re-start of study medication					
30-Jun-22	445	▽ last dose of study medication *					
05-Jul-22	450	**130 L**	24	24	0.4	189	224
13-Jul-22 (end of study visit)	458	136	16	21	0.15	**193 H**	185
*Legend: L=below lower limit; LN=below lower limit notable; H=above upper limit; HN=above upper limit notable. * due to unavailability of IP kits, IP was not dispensed.*							

Study NW-3509/015/II/2019-401003

Study Number:	**NW-3509/015/II/2019**
Country of Origin:	**Sri Lanka**
Type of Narrative:	**Adverse Drop-out**
Subject Number:	**401003**
MFR Case ID	**ADO_2021-000002**
Treatment Group:	**Evenamide (15 mg bid)**
Reported Term [Preferred Term]:	**Somnolence, increased sweating, reduced concentration [Somnolence, Hyperhidrosis, and Disturbance in attention]**

This 36-year-old Asian male subject from Sri Lanka received the first dose of study medication on 01 Apr 2021 (Day 1), and after 114 days on study medication, experienced somnolence that worsened on 11 Oct 2021 (Day 194), and on the same day the study medication was discontinued. The subject had also experienced hyperhidrosis and disturbance in attention on 09 Oct 2021 (Day 192). All the adverse events resolved without sequelae by 01 Nov 2021. The patient was withdrawn from the study on 13 Nov 2021 (Day 227).

Clinical Summary:

This was a 36-year-old Asian male subject who received the first dose of study medication on 01 Apr 2021 (Day 1). He completed Study 014 on 11 May 2021 and entered in the open-label extension Study 015, where he continued on evenamide 15 mg *bid*.

At screening, the subject weighed 70.2 Kg (height 166 cm, and his BMI was 25.5 kg/m2). Laboratory findings included slightly abnormal total cholesterol, triglycerides, VLDL, HDL, GGT, CPK, and lymphocytes. Dyslipidemia was captured as an adverse event and was considered not related to the study medication.

On 23 Jul 2021 (Day 114) the subject experienced somnolence of mild intensity. On 09 Oct 2021 (Day 192) the subject experienced increased sweating, and reduced concentration, both considered mild in intensity, and somnolence was still ongoing. On 11 Oct 2021 (Day 194) somnolence increased in intensity to moderate and for this reason the study medication was discontinued. By 01 Nov 2021 (Day 215) all the adverse events were resolved without sequelae. On 12 Nov 2021 (Day 226), ~ 1-month after the discontinuation of study medication, the subject had an accidental fall and muscle contusion.

On 13 Nov 2021 (Day 227) the subject was withdrawn from the study. The same day laboratory finding included clinically notable value for creatine phosphokinase (CPK) 4076 U/L (normal range 20-200 U/L) and increased lactate dehydrogenase (LDH), AST, ALT, GGT, and sodium and bicarbonate. Dyslipidemia was still ongoing with abnormal values for total cholesterol, triglycerides, VLDL, HDL, and LDL. Elevation of serum CPK, LDH, AST, and ALT were associated to muscle trauma (muscle contusion) injuries after the accidental fall. ECG, vital signs, physical and neurological examinations were normal. “No further information is available” because the subject refused to repeat the blood test.

Medical History and Concomitant Medication:

No relevant medical history was reported for this subject. The patient has a history of schizophrenia since 05 April 2011 (~ 10 years), and the current episode started on 22 Oct 2020 (~ 6 months).

Concomitant antipsychotic medication included olanzapine 20 mg daily ongoing since 17 Jun 2014. Other concomitant medication included atorvastatin for dyslipidemia 20mg od from 30 April 2021 to 25 June 2021 and 10 mg od from 26 June 2021.

Investigator Assessment:

The investigator initially rated the somnolence as mild, later as moderate in intensity, and possibly related to study medication (evenamide). Somnolence was cited as the reason for discontinuing the study medication.

The investigator considered hyperhidrosis and disturbance in attention as mild in intensity and possibly related to the study medication (evenamide).

Pertinent Positives and Negatives:

A 36-year-old Asian male subject with a diagnosis of schizophrenia (approx. 10 years), experienced somnolence of mild intensity after 114 days on evenamide, administered as add-on to olanzapine. The study medication was continued. On 11 Oct 2021 (Day 194) the somnolence worsened (moderate in intensity) and the study medication (evenamide 15 mg *bid*) was discontinued. The somnolence resolved without sequelae 21 days after the discontinuation of study medication. The subject also experienced hyperhidrosis and disturbance in attention (Day 192) that resolved without sequelae in 2 and 16 days, respectively. The subject was withdrawn from the study on 13 Nov 2021 (day 227). The history of schizophrenia, and the background treatment with olanzapine, are confounding factors to the onset of the adverse event, as it is known that antipsychotic can induce some degrees of sedation and somnolence. All adverse events resolved after the study medication was discontinued. The relationship to evenamide cannot be ruled out.

Study Number: NW-3509/015/II/2019-310003

Study Number:	**NW-3509/015/II/2019**
Country of Origin:	**India**
Type of Narrative:	**Adverse Event**
Subject Number:	**310003**
MFR Case ID	**2022NEW000002**
Treatment Group:	**Evenamide 7.5 mg bid**
Reported Term [Preferred Term]:	**Pregnancy**

Brief overview:

This 32-year-old Asian female subject with chronic schizophrenia on 09 Feb 2021 (Day 1), received the first dose of evenamide 7.5 mg *bid* in Study 014. She continued evenamide 7.5 mg *bid* until 14-Feb-2022, when she completed uneventfully Study 015 (1-year on evenamide). Laboratory tests performed at the last visit showed increased beta human chorionic gonadotropin level, indicating the subject was pregnant. On 04 Mar 2022, the subject electively terminated the pregnancy.

Clinical Summary:

This 32-year-old Asian female subject with chronic schizophrenia on 09 Feb 2021 (Day 1), received the first dose of evenamide 7.5 mg *bid* in Study 014. She continued evenamide 7.5 mg *bid* until 14-Feb-2022, when she completed uneventfully Study 015 (1-year on evenamide).

The subject showed a significant improvement in symptoms based on PANSS total score of 55 (--34% compared to a baseline of 83), a CGI-S of 3 (mildly ill) with 2-point improvement from baseline, and a CGI-C of 2 (Much improved).

A Serum Pregnancy Test performed at the End of study visit on 14 Feb 2022 (Day 371), showed increased beta human chorionic gonadotropin level (60778, units unknown). On 25 Feb 2022, 11 days after receiving the last dose of the study medication, a positive urine pregnancy test, performed when the subject visited the study site, confirmed the pregnancy.

She had her last menstrual period on 25 Jan 2022 and was using a condom as a barrier method of contraception.

The subject was followed up telephonically to visit the site for further investigations and treatment. However, she informed that she had decided to terminate her pregnancy, which was not recommended by the physician. She also informed that she was not willing to get any treatment for the same from the site hospital. On 04 Mar 2022, the subject electively terminated the pregnancy from an external hospital.

Medical History and Concomitant Medication:

The subject was diagnosed with schizophrenia in 2015, and the current episode was reported to start in Sep 2020. Medical history included rigidity and insomnia. The subject had no history of smoking, alcohol use, or drug use/abuse. Parity of two (girl and boy of age 10 years and 9 years now, respectively).

Past antipsychotic medication included risperidone, paliperidone, trifluoperazine. Since 11 Dec 2020, she was on oral trifluoperazine at a dose of 5 mg tid. No other any relevant subject's medical history was reported.

Investigator Assessment:

The investigator considered the pregnancy as a non-serious adverse event and not related to evenamide.

Sponsor Assessment:

The Sponsor agrees with the investigator's causality assessment that this event is not related to the study medication.

Pertinent Positives and Negatives:

This 32-year-old Asian female subject with 6-year history of chronic schizophrenia, after completing uneventfully Study 015 (1-year on evenamide), had the Serum Pregnancy Test performed at the EOS visit on 14 Feb 2022, which was positive for pregnancy. A urine pregnancy test performed ten days later was also positive for pregnancy. On 04 Mar 2022, the subject electively terminated the pregnancy. Despite the study protocol inclusion criteria strongly recommending the use of "highly effective contraception", women with schizophrenia, who are sexually active, could have limited knowledge about contraception, resulting in low contraceptive compliance, and pregnancy. This could be considered a contributory factor.

Pregnancy in this subject is not related to evenamide administered for 1-year, but most probably due to the subject's inadequate or low contraceptive compliance.

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16 Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

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16.1.3 List of Institutional Review Boards and Independent Ethics Committees and Representative Written Information for Subject and Sample Consent Forms

16.1.4 List and Description of Investigators and Other Important Participants in the Study, Including Brief Curricula Vitae

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16.1.9 Documentation of Statistical Methods

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16.1.11 Publications Based on the Study

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16.2.10 Physical Examinations

16.2.11 Electrocardiogram

16.2.12 Neurological Examination

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16.2.14 Extrapyramidal Symptom Rating Scale

Listing 16.2.14 Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) - Safety Population

16.2.15 Calgary Depression scale of Schizophrenia

Listing 16.2.15 Calgary Depression Scale for Schizophrenia (CDSS) - Safety Population

16.3 Electronic Case Report Forms

Electronic Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

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