Clinical Study Report

1 TITLE PAGE

A PILOT, OPEN-LABEL, RATER-BLINDED, RANDOMIZED, PARALLEL-GROUP, MULTI-CENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF THREE ADD-ON FIXED DOSES OF EVENAMIDE IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA (TRS) NOT RESPONDING ADEQUATELY TO THEIR STABLE, THERAPEUTICALLY ACTIVE DOSE OF A SINGLE ANTIPSYCHOTIC MEDICATION

Investigational Medicinal Product	Evenamide (NW-3509)
Indication studied	Treatment Resistant Schizophrenia
Protocol number	NW-3509/014/II/2019
EudraCT number	2020-000437-41
Development Phase	Phase II
First subject enrolled	16-Dec-2020
Last subject completed	22-Dec-2022
Company/Sponsor signatory	Ravi Anand MD, Chief Medical Officer Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano), Italy
Study Duration	16-Dec-2020 to 22-Dec-2022
Date of Report	17-Jun-2023

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 Finished Product: Evenamide		
Name of Active Ingredient: Evenamide		

Title of Study:

A pilot, open-label, rater-blinded, randomized, parallel-group, multi-center study to evaluate the safety, tolerability, and preliminary efficacy of three add-on fixed doses of evenamide in patients with treatment- resistant schizophrenia (TRS) not responding adequately to their stable, therapeutically active dose of a single antipsychotic medication.

Investigators:

A total of 22 Investigators (9 in India, 5 in Sri Lanka, 3 in Malaysia and 5 in Italy) took part in the study.

Study Centers:

The study was conducted at 22 centers (9 in India, 5 in Sri Lanka, 3 in Malaysia and 5 in Italy).

Publication (Reference):

None

Phase of Development:

II

Study Period:

16-Dec-2020 to 22-Dec-2022

Study Objectives:

Primary*:*

- To evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5, 15 and 30 mg *bid*)in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic doses of their current antipsychotic medication.

Secondary:

- To evaluate preliminary efficacy of the three fixed doses 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 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 6-week, open-label, randomized, rater-blinded, multi-center study designed to evaluate the safety, tolerability, and preliminary efficacy of fixed doses of evenamide 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* as add-on treatment in patients with treatment-resistant schizophrenia on a stable therapeutic dose of an antipsychotic. Approximately 180 patients meeting the selection criteria at baseline were to be enrolled to ensure that minimally

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50 patients were randomized to each of the three treatment groups. Doses were initiated in a stepwise fashion. Initially, only the 7.5 mg *bid* and 15 mg *bid* doses were evaluated with a 1:1 randomization scheme. After 50 patients (25 patients in each treatment group) were treated at these doses, key safety data from these patients was reviewed by an Independent Safety Monitoring Board (ISMB). Since the review of the data indicated that there were no safety issues, the 30 mg *bid* dose group was initiated, and additional patients randomly assigned (1:1:2) to the 7.5, 15 and 30 mg *bid* treatment groups. Subsequently, with implementation of an amendment (*Amendment 6, dated 17th June 2021*) to the study protocol, the 7.5 mg *bid* dose group was discontinued, and patients were randomized 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. No further patients were enrolled in the 7.5 mg *bid* group. The rationale for 1:3 randomization scheme was based on results of Study 008, which 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. Therefore, the decision to discontinue the 7.5 mg *bid* dose group in the current study was made based on the results of this efficacy analysis in Study 008. Since more than 25 patients had already been enrolled in the study in the 15 mg *bid* group, the randomization ratio was 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.

All patients received their initial starting dose (7.5 or 15 mg evenamide *bid*) on Day 1. Patients in the lowest dose group were initiated at a dose of 7.5 mg *bid*, while patients in the 15 and 30 mg *bid* dose groups were initiated at a dose of 15 mg *bid*. After one week, patients in the 7.5 mg *bid* and 15 mg *bid* groups continued treatment at those doses, whereas patients in the highest dose (30 mg) group had their dose increased to 30 mg *bid*, provided the starting dose (15 mg *bid*) was well tolerated (Synopsis Table 1). If intolerance developed, the patient could drop back 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 could be reduced to once daily (*od)* dosing and the patient could continue for the remainder of the study at this reduced dose.

Synopsis Table 1: Dosing type in Randomized Treatment Groups

	Randomized Treatment Group		
Dose Type	**Evenamide 7.5 mg *bid*****	**Evenamide 15 mg *bid***	**Evenamide 30 mg *bid***
Starting Dose	7.5 mg *bid*	15 mg *bid*	15 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 unable to tolerate the starting/target bid dose, could drop-back to once daily (od) dosing. Patients in the 30 mg bid group who began to experience tolerability issues at the 15 mg bid starting dose could remain at this dose.A drop-back from the 15 mg bid starting dose to 15 mg od in the high dose group was permitted, if necessary, due to intolerance.*

*** The 7.5 mg bid dose group was discontinued after the Amendment 6, dated 17th June 2021, to the protocol was approved, and all patients receiving a dose of 7.5 mg bid had completed the study.*

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Screening

All patients provided written informed consent prior to their participation in the trial. For each patient, the screening evaluations were performed at least 3 days and up to 21 days prior to baseline and consisted of a review of the patient's medical and psychiatric history and current use of medications, vital signs (including height, weight and waist circumference), 12-lead electrocardiogram (ECG), laboratory tests (hematology, blood chemistry, urinalysis, virology, thyroid function tests, and urine drug screen), serum pregnancy test (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 have had a tubal ligation), physical and neurological examination, standard eye examination, completion of a Seizure Checklist (SCL) evaluating symptoms and signs suggestive of seizures, PANSS, CGI-S, GAF and Calgary Depression Scale for Schizophrenia (CDSS). Resistance of the patient's schizophrenia symptoms to treatment was documented. The most recent episode of non-response to their antipsychotic was documented in the patient's clinical records.

Baseline (Day 0/ Day 1 pre-dose)

Baseline vital signs and ECG assessments were performed in triplicate, with an interval of at least 10 minutes between readings. Baseline assessments were performed for the PANSS, CGI-S, CDSS, LOF, GAF and MSQ. Evaluations of adverse events, including symptoms and signs suggestive of seizures and the Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A), and updating of any change in current medications, were completed at the baseline visit (Day 0).

Urine (immediate result) and serum (for confirmation) pregnancy tests were performed for all women of childbearing potential, as well as those who were post-menopausal or those who have had a tubal ligation. A blood sample was collected for measuring serum prolactin levels. Furthermore, a urine drug screen and alcohol breath test were performed at baseline. Laboratory tests, physical and neurological examinations, and standard eye examination were not repeated at baseline if performed at screening within 21 days before baseline.

6-Week Treatment Period

On Day 1, patients meeting all entry criteria at screening and baseline received an initial oral dose of study medication (evenamide 7.5 or 15 mg) in the clinic. During the initial 4-hour period after the first dose, safety evaluations (vital signs, 12-lead ECG, laboratory tests, and assessment of adverse events, including CNS symptoms and signs) were performed. Vital signs and 12-lead ECG were performed both at 1 and 4-hr post-dose. If no moderate/severe side effects were noted within the 4-hr period following the first dose, the patient was discharged from the in-patient facility and given a supply of study medication at their assigned dose for the remainder of the first week of dosing. The patients were directed to take the second dose at their residence not earlier than 6 hours after the first dose.

If the starting dose was not tolerated, a reduction to once daily (*od*) dosing could be performed, and the patient was to be instructed to take only the morning dose for the first week of dosing if symptoms persisted. If the reduced (*od)* dose was well tolerated, an increase to the starting/target *bid* dose could be performed at the next scheduled visit. If the reduced dose could not be tolerated, the patient was to be discontinued from the study. The dose of study medication was to be taken with food or after a meal, if possible. Any other medications were to be taken according to their usual schedule.

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The Investigator/site staff telephonically contacted the patient on Day 4 to inquire about the tolerability of the study medication and whether they experienced any adverse events. If the Investigator/site staff felt it was necessary, the patient's dose was reduced (*od* dosing) or, if significant tolerability issues were noted, the patient was asked to return for an unscheduled visit. The Investigator decided, based on the symptoms/signs that had been identified, whether the patient should come in for an evaluation, whether their dosing regimen should be modified, and/or whether a concomitant medication should be added. If 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 completed. These included hospitalization, performance of a full neurological examination, EEG, ECG, etc.

The patients returned for a scheduled visit on Day 8. During this visit selected safety and efficacy evaluations were performed. On the day of each scheduled clinic visit, patients/caregivers were instructed to withhold the morning dose of study medication, as it was to be administered in the clinic, and key efficacy assessments (PANSS, CGI-S/C) were conducted approximately 1-2-hr post dose. The dose administered in the clinic was the first dose of the study medication allocated for the next period of dosing, except for the last dose on Day 43. Patients were reminded to take their concomitant antipsychotic and other medications at their residence according to their usual schedule. Patients were instructed to bring their study medication bottle (s) with them to the clinic.

On Day 8, if no safety or tolerability issues were detected during the pre-dose assessment (including vital signs and ECG), the patient received their target dose. Patients in the evenamide 7.5 and 15 mg *bid* groups continued their assigned dose, while patients in the high dose group (30 mg *bid* group, initiated only after 50 patients at the lower doses had been evaluated by ISMB) had their dose increased from 15 mg *bid* to 30 mg *bid*, in the morning on Day 8 in the clinic. Subsequently, post-dose safety assessments were performed. If no moderate/severe side effects were noted within the 4-hr period after dosing, the patient was discharged from the clinic and given a supply of study medication for the next week of dosing. The patients were instructed to take the evening dose of the study medication at least 6 hours after the morning dose.

The patient received a telephone call from the Investigator/site staff on Day 11 to inquire if they had experienced any safety or tolerability issues. If significant tolerability issues were noted, the patient's dose was reduced to once daily dosing, or, the patient was asked to return for an unscheduled visit.

The patients returned for a scheduled visit on Day 15. At this visit selected safety and efficacy (PANSS, CGI-S/C, and MSQ) evaluations were performed by a blinded rater. If no safety or tolerability issues were detected during the pre-dose assessment that required reducing the dose, the patient continued receiving their assigned dose level on the morning of Day 15 in the clinic. A dose increase was permitted at this visit if the patient was receiving a drop-back dose and the tolerability issues had resolved. If there were no tolerability issues noted within the 4-hr period following this dose, the patient was discharged from the clinic and given a supply of study medication at the assigned dose level for the next 2-week dosing period. The patients were instructed to take the evening dose of the study medication at least 6 hours after the morning dose.

The patients returned on Day 29 for a scheduled visit for selected safety and efficacy (PANSS, CGI-S/C) assessments. A dose increase was permitted at this visit if the patient had been receiving a drop-back dose and the tolerability issues had resolved. The morning dose was administered in the clinic, and if there were no tolerability issues, the patient

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was dispensed a supply of their assigned dose level of study medication for the final 2-weeks of dosing in the 6-week treatment period and discharged from the clinic.

The patients were reminded not to take their morning dose of study medication on Day 43, as it was to be administered in the clinic, and all final safety [vital signs, 12-lead ECG, laboratory tests hematology, blood chemistry, urinalysis, serum prolactin, urine drug screen, and serum pregnancy test (for all women of child-bearing potential, as well as those who were post-menopausal or who have had a tubal ligation), ESRS-A, CDSS, physical/neurological examinations, and standard eye examination] were performed, and all efficacy (PANSS, CGI- S/C, LOF and MSQ) evaluations were done 1-2 hours post dose. An assessment of substance use, and a urine drug screen were also performed.

Extension Study

All patients, who completed 6 weeks of treatment, did not experience any moderate/severe side effects, and had not shown significant worsening of their symptoms of schizophrenia during the 6-week treatment period, were eligible to continue treatment in a separate 46-week open-label extension study (Study 015). Patients receiving 15 mg *bid* or 30 mg *bid* would continue the same dose of evenamide, while patients completing 'Study 014' on the 7.5 mg *bid* dose would have their dose increased to 15 mg *bid* upon entry into 'Study 015'. The duration of this extension study was increased by a 24-week additional period for a total of 70 weeks.

Safety Follow-up Evaluation

For patients who discontinued prematurely, as well as those who completed 6 weeks of treatment, but did not enter the open-label extension study, 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 for their in-clinic 7-day safety follow-up visit were contacted by telephone by the study site to follow up on the occurrence of any adverse events. In addition, the patients were contacted by telephone at least 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 were to come to the clinic for scheduled visits and return 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:

Approximately 180 patients (minimally 50 patients/group) were to be randomized to one of the three treatment groups (evenamide 7.5 mg, 15 mg, or 30 mg *bid*).

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

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

Demographics

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1. Age - 18 years, or older.
2. Sex – male, or female. *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 4, dated 18th September 2020).*

Psychiatric

3. Met current DSM-5 criteria for schizophrenia.

   Other psychiatric disorders may have been present only as lifetime diagnoses if they were not relevant to the current episode of schizophrenia. [see Exclusion criteria below]
4. Had been diagnosed with schizophrenia within the past 15 years. *(prior to Amendment 5, dated 4th February 2021, it was '10 years' in the original protocol Version 1.0, dated 7th November 2019).*
5. Had shown treatment-resistance according to psychiatric history, within the past 10 years *(added in Amendment 5, dated 04th February 2022)*, with the last failed treatment documented in the patient's clinical records. *"Treatment-resistant Schizophrenia" (TRS) is defined as a persistence of significant clinical symptoms despite adequate doses of two standard antipsychotic medications (other than clozapine) from two different chemical classes, including at least one atypical antipsychotic, for at least 6 weeks of treatment each. The last failed treatment trial must be documented.*
6. Had a Clinical Global Impression – Severity of disease (CGI-S) rating of moderately ill to severely ill (score of 4 to 6 [scale 1-7]).
7. Had a PANSS total score ≥ 70 at screening and baseline.
8. Had a score of **4 (**moderate) or more on at least 2 of the following 4 PANSS symptoms of psychosis: P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P6 (Suspiciousness/Persecution) and G9 (Unusual Thought Content); and a total score of at least **20** on the combined total of the PANSS symptomitems: P1 (Delusions), P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P4 (Excitement), P6 (Suspiciousness/Persecution), P7 (Hostility), and G9 (Unusual thought content).
9. Had a Global Assessment of Functioning (GAF) scale total score ≤ 50.
10. Needed anti-psychotic treatment and was receiving monotherapy at a stable dose (minimally for 4 weeks prior to screening) at a minimal recommended therapeutic or higher dose of one antipsychotic (atypical or typical, other than clozapine). Current use of quetiapine at a dose of 150 mg or less *(In the original protocol version 1.0, dated 7th November 2019, quetiapine dose was 50 mg and it was increased to 150 mg with Amendment 2, dated 7th February 2020) at night as a soporific was not considered polypharmacy.*
11. Current level of symptoms had been present for at least one month, but not exceeding one year.

Procedural

12. Patient was cooperative, able to take oral medication, able to understand the instructions and willing to complete all aspects of the study and was capable of doing so.
13. Patient was residing with a caregiver at his/her home or was either in a residential care facility or residing

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alone, with a caregiver available to help ensure compliance with dosing and scheduled office visits ineither situation.

14. Patient had provided written informed consent prior to participating in the study.
15. Patient agreed to be hospitalized overnight if required for trial purposes or if the Investigator deems it necessary to ensure the safety of the patient.

Exclusion Criteria:

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

Psychiatric

1. DSM-5 diagnosis of schizophreniform disorder (295.40), schizoaffective disorder (295.70), or other primary psychiatric diagnosis, such as bipolar disorder or major depressive disorder (depression was assessed at screening and baseline using the Calgary Depression Scale for Schizophrenia (CDSS); a score of 7 or higher was exclusionary).
2. History (within three months of study entry) or current diagnosis of Substance-Use-Disorder as defined by the DSM-5 criteria, with a severity of 'moderate' or 'severe', or patient was currently abusing drugs or alcohol or has done so in the past year. *A history of nicotine or caffeine dependence was acceptable; and patients testing positive for THC on the urine drug screen were not to be excluded from the study unless there was evidence of toxic psychosis.*
3. Severity of current episode of psychosis requires that the patient be hospitalized. *Patients who were chronically hospitalized or in psychiatric daycare, whose hospitalization was for logistic reasons and not due to the severity of their illness, were eligible for the study*.
4. Had a PANSS total score > 90 or a CGI-S rating of 7 (among the most extremely ill patients).
5. History or current diagnosis of other psychiatric or behavioral disorders that could interfere with the conduct or interpretation of the study.
6. Known suicidal risk, or a suicide attempt within the past 2 years, as assessed by the CDSS and/or by psychiatric history.
7. History of neuroleptic malignant syndrome, priapism or moderate or severe tardive dyskinesia.

Medical Status

8. An advanced, severe, or unstable disease of any type that could interfere with any of the study evaluations, including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical or mental status of the patient to a significant degree or put the patient at special risk (e.g., liver or kidney disease, severe uncontrolled asthma, malignancy).
9. Insulin-dependent diabetes mellitus. Patients with non-insulin-dependent diabetes were eligible if the following criteria were satisfied:
    a. Diabetes was considered well controlled, with no changes in treatment regimen for at least 4 weeks prior to screening,

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b. Diabetes was not newly diagnosed at screening.

10. History or current diagnosis of any neurodegenerative illness, dementia, significant concomitant neurological disease, organic cerebral disease, cerebrovascular disease, focal neurological lesions or history of any trauma resulting in loss of consciousness (during the past 2 years).
11. History or current diagnosis of epilepsy or seizure disorder, or occurrence of a seizure within the past year, or repeated drug-induced seizures (other than febrile seizures in childhood).
12. Prior surgery or current medical condition which could interfere with the absorption, distribution, metabolism or excretion of the study drug, e.g., peptic ulceration, gastric or intestinal surgery, impaired renal or hepatic function, inflammatory bowel disease.

Cardiovascular

13. Any clinically significant ECG abnormality, including a disorder of rate, rhythm, or conduction, or other morphological changes, or a QTcF interval prolongation (Fridericia's correction formula) on the ECG (> 450 msec for males; > 470 msec for females).

    The 12-lead ECG was used for determining the suitability of the patient for inclusion in the study (determination made by the Investigator). Values averaged from the 3 ECG measurements at baseline were used in determining eligibility.

14. Vital signs (supine) outside the following ranges (measured after 5 minutes supine):
    a. Systolic blood pressure below 90 or above 150 mm Hg
    b. Diastolic blood pressure below 50 or above 95 mm Hg
    c. Radial pulse (from vital signs) below 50 or above 100 bpm
    d. Orthostatic hypotension (decrease in SBP/DBP from supine to standing position exceeding 30 mm Hg).

Laboratory abnormalities

15. History of hepatitis B and/or C, and/or positive serology results, which indicate the presence of hepatitis B and/or C (Hepatitis B surface antigen and/or antibody to Hepatitis C).
16. Positive results from the HIV serology.
17. Positive results of the drug and alcohol tests at screening and/or baseline. Patients who test positive for drugs of abuse at screening, but had negative test results at baseline, were eligible, dependent on the type of drug and the likelihood of continued abuse during the study. *Possible inclusion of these patients in the study was to be discussed with the Medical Monitor.*

Concomitant therapy

18. History of or current treatment with clozapine for psychosis.
19. Required treatment with an anticholinergic drug, and the dose was not stable.
20. Was receiving benzodiazepine therapy, unless the dose had been stabilized for at least 2 months, excluding occasional *prn* dosing. Doses of benzodiazepines were not reduced or stopped during the study, unless

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clinically necessary. PRN dosing employed the lowest safe and effective dose possible. Any changes in the dose of a benzodiazepine were performed under close medical supervision.

21. Treatment with agents influencing dopamine, norepinephrine, or serotonin neurotransmission (e.g., tri- and tetracyclic antidepressants, MAO inhibitors, metoclopramide). *Treatment with SSRIs and SNRIs that were moderate/potent inhibitors of CYP2D6 (e.g., fluoxetine) was not permitted; however, patients on a stable dose of an SSRI or SNRI that is a weak inhibitor of CYP2D6 (e.g., escitalopram), for at least 4 weeks before screening, were eligible.*
22. Treatment with drugs capable of inducing/inhibiting hepatic enzyme metabolism (e.g., barbiturates, carbamazepine, phenylbutazone, phenytoin, primidone, rifampicin) four weeks prior to baseline or during the study.
23. Current treatment with sodium channel blockers (e.g., Class I antiarrhythmic agents, anticonvulsants, local anesthetics) or mood stabilizers (e.g., lithium, carbamazepine, oxcarbazepine, lamotrigine). *Valproic acid was permitted, if used as maintenance treatment*.
24. Exposure to any investigational drug within 5 weeks or 5 half-lives (whichever was longer) prior to screening.
25. A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to evenamide (e.g., lamotrigine, carbamazepine, oxcarbazepine, topiramate, etc.), or any components of the evenamide capsules.
26. Electroconvulsive therapy (ECT) or treatment with a transcranial magnetic stimulation (TMS) device within 6 months prior to screening.

General

27. Patient was female and of childbearing potential, pregnant or breastfeeding. For inclusion, female patients must have been post-menopausal (age 50 or older and 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 4, dated 18th September 2020*).
28. Patients with a reasonable likelihood of non-compliance with the protocol, or any other reason that, in the Investigator's opinion, would prohibit the inclusion of the patient in the study.

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.

Investigational Product Name	Formulation	Strength	Route	Manufacturing Authorization Holder	Batch Numbers
Evenamide (NW-3509)	Hard gelatin capsules	7.5 mg	Oral	Newron Pharmaceuticals S.p.A.	17245.4 17245.10 17245.16
		15 mg			17245.5 17245.11 17245.17

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					17245.24
		30 mg			17245.6 17245.12 17245.18 17245.25

Study medication with each different dosage (7.5, 15 and 30 mg evenamide) was provided in 30 ml HDPE bottles. The blinded rater was not aware of the dosage that each patient was taking. A 1–2-week supply of study medication was dispensed at the appropriate dose level for the patient at each visit.

Duration of Treatment:

The study was planned for up to 72 days, including a 3 to 21-day screening period, a one-day baseline evaluation, a 6-week (43-day) randomized open-label treatment period, and a 7-day safety follow-up period.

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 examination
- 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)
- Seizure Checklist
- Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)
- Calgary Depression Scale for Schizophrenia (CDSS).

Preliminary Efficacy Evaluations

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

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- 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
- MSQ – mean change from baseline to endpoint.

Safety Monitoring Board

Safety data from all patients was examined periodically by an Independent Safety Monitoring Board (ISMB). The ISMB was responsible for reviewing key safety data from the first 50 patients randomly assigned (1:1) to evenamide 7.5 or 15 mg *bid* and completing their participation in the study and determining whether it was safe to proceed with dosing of patients at 30 mg *bid.*

Statistical Methods:

Sample Size:

Approximately 180 patients (increased from 150 by *Amendment 8, dated 03rd May 2022*) with treatment-resistant schizophrenia were to be included in this study, with a minimum of 50 patients randomly assigned to each treatment group (evenamide 7.5 mg, 15 mg, and 30 mg, *bid*). The sample size determination was not based on statistical power considerations. The primary objective of this study was the assessment of safety and tolerability. The sample size was considered adequate for a preliminary evaluation of tolerability of the doses administered and for determining a potential signal of dose-dependent effect on efficacy.

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.) of enrolled patients was summarized by treatment group. Continuous variables were summarized by minimum, maximum, mean, median, and standard deviation, and discrete variables were summarized using frequencies and percentages.

Safety Analysis:

The Safety Population consisted of all patients who took at least one dose of study medication. 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 (treatment-emergent AEs [TEAEs]), and AEs leading to discontinuation (adverse dropouts [ADOs]) were also summarized; severity of each AE and relatedness to study medication were assessed and presented. Changes frombaseline in vital signs, ECG, and laboratory values (changes from baseline for Hematology and Biochemistry only; Urinalysis data were listed), and physical/neurological examinations and standard eye examination findings were summarized, with abnormal and clinically notable

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values/findings being identified. Mean changes from baseline in the total score on the CDSS and the total and sub-scale scores on the ESRS-A were presented.

Preliminary Efficacy Analysis:

The efficacy population comprised of all patients who had a baseline efficacy assessment, received at least one dose of the study medication, and had at least one post-baseline efficacy assessment. Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) was provided for all continuous efficacy measures for actual values and changes from baseline at each time-point. For categorical variables, the number and percentage of patients in each category was presented at each time-point. Mean changes from baseline to endpoint on the PANSS, CGI-S, MSQ and LOF, and the mean score at endpoint on the CGI-C, were summarized by dose group and overall combined dose group.

Summary – Conclusions:

Safety Results:

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

- A total of 41 subjects (25.6%) reported at least one TEAE which included 13 (26.0%), 10 (16.7%) and 18 (36.0%) 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 'General disorders and administration site conditions' and 'Nervous system disorders' by 10 subjects (6.3%) each. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were dizziness by 3 (1.9%) subjects; and asthenia, fatigue, postural dizziness, and hypersomnia by 2 (1.3%) subjects each.
- Of the 41 overall TEAEs reported, 32 (20.0%) were of mild severity and 9 (5.6%) were of moderate severity. None of the reported TEAEs were of severe intensity.
- Medication errors, asymptomatic and not associated with adverse events, were reported in 7 (4.38%) subjects in the evenamide 30 mg *bid* treated group. None of the subjects in any of the 3 treatment groups reported a treatment-related SAE.
- A total of 15 subjects (9.4%) reported at least one treatment-related TEAE which included 5 (10.0%), 4 (6.7%) and 6 (12.0%) 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' by 6 subjects (3.8%), and 'General disorders and administration site conditions' by 3 subjects (1.9%). Out of the 15 overall treatment-related TEAEs reported, 11 (6.9%) were of mild severity and 4 (2.5%) were of moderate severity. None of the reported treatment-related TEAEs were of severe intensity.
- Overall, 2 (1.3%) subjects reported a TEAE leading to study drug discontinuation, which included 1 (2.0%) subject each from the evenamide 7.5 mg and 30 mg *bid* treated groups.
- No TEAE resulting in death was reported during the study.

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- Very few clinical laboratory parameters (hematology and clinical chemistry) results 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 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. Low hemoglobin level (≤ 0.85 x lower limit of normal (LLN) g/L), was seen in 7 (14.0%), 10 (16.7%) and 6 (12.0%) subjects and low high density lipoprotein level (≤ 0.8 mmol/L) was seen in 19 (38.0%), 19 (31.7%) and 21 (42.0%) 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 significant 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 significant effects or trends were observed at the end of treatment compared to baseline for any of the three doses of evenamide on physical examination, neurological examination, extrapyramidal symptoms (assessed by Extrapyramidal Symptom Rating Scale - Abbreviated Version), changes in depressive symptoms (assessed by Calgary Depression Scale for Schizophrenia), eye examination, and seizure-like symptoms reported on the Seizure Checklist.

Overall, the results for the safety parameters assessed in the study indicated that evenamide given orally at three fixed doses (7.5, 15 and 30 mg *bid*) in patients with treatment-resistant schizophrenia was well tolerated and without any major safety concern.

Efficacy Results:

The secondary objectives of the study were to evaluate preliminary efficacy of the three fixed doses of evenamide, based on symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression - Change from baseline (CGI-C) and CGI - Severity of illness (CGI-S), and to determine the effects of evenamide on daily functioning, based on changes on the Strauss-Carpenter Level of Functioning (LOF) scale and patient's satisfaction with the current antipsychotic treatment compared to their previous treatment, based on ratings of the Medication Satisfaction Questionnaire (MSQ).

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 being randomized to an evenamide dose, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline in PANSS total score at Day 43*) using a paired *t-test* for the mITT Population.

The baseline mean value of the PANSS total score did not differ between treatment groups. A steady improvement in the PANSS total score (lowering of score) was observed at all study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups (evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group), reflecting a continuation of improvement in symptoms of schizophrenia. A significant ($p<0.001$) mean change from baseline of

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-9.0, -10.6 and -8.6 was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups respectively. The results were supported by trends for the decreasing PANSS total score (improvement) observed in different models (*Primary estimand, LOCF and Multiple imputations*) of the Sensitivity Analysis on change from baseline at Day 43.

Mean change from baseline to Day 43 or early discontinuation on the PANSS total score was compared between the evenamide dose groups using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. A statistically non-significant LS mean difference of -0.7 (p=0.569) in PANSS total score between the combined evenamide (15 + 30 mg *bid*) versus evenamide low dose (7.5 mg *bid*) groups was observed.

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 change from baseline at Day 43 was observed in all three treatment groups for each of the three subscales.

'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 (at least 20%) based on previous studies in TRS patients and the PANSS Positive Symptoms sub-scale (at least 4 points). By Day 43, the proportion of responders based on the PANSS total score increased to 18.8%, 18.6% and 8.2% subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively compared to no responders at Day 8. A similar trend was seen in the responder analysis of PANSS Positive Symptoms sub-scale score, with approximately 50% of patients in each group meeting the responder criterion at Day 43.

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

The results of the paired *t-test* performed at post-dose visits to analyze CGI-S change from baseline within each dose group showed a significant (*p<0.001*) reduction in the mean change from baseline of -0.6, -0.8 and -0.7 at Day 43 in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group. The results were confirmed by the trends for decreasing CGI-S score (improvement) and significant (*p<0.001*) reductions observed in different models (*Primary estimand, LOCF and Multiple imputations*) of the Sensitivity Analysis on change from baseline at Day 43.

A reduction in the mean CGI-C score was observed between Day 8 and Day 43, from 3.8 to 3.0 in evenamide 7.5 mg, from 3.7 to 2.9 in evenamide 15 mg, and from 3.8 to 3.1 evenamide 30 mg *bid* treated group, indicating continuing improvement in overall severity of illness. A responder analysis was done considering change in subject's condition from baseline, as indicated by the CGI-C score (CGI-C score change ≤ 3 [indicating improvement]) and (CGI-C score change >3 [indicating no change or worsening]). An increase in the proportion of responders (CGI-C score change ≤ 3 [indicating improvement]) was observed at all the timepoints from Day 8 to Day 43 (from 22.44% to 75.00% in overall subjects) in all three treatment groups, indicating that more subjects were experiencing meaningful benefit. The highest proportion of responders was seen in evenamide 15 mg *bid* treated group.

Strauss-Carpenter Level of Functioning (LOF) scale

A significant (*p<0.001*) increase in the mean change from baseline in the Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score at Day 43 of 0.9, 1.3 and 1.8 was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively. Similar trends were seen in the LOF subscales (Social Contacts, Work, Symptomatology,

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and Function) analysis indicating improvement in functionality of subjects after treatment with the three doses of evenamide.

Patient's Medication Satisfaction Questionnaire (MSQ)

An improvement in the MSQ score was observed at Day 15 and Day 43 compared to baseline in all the three treatment groups, indicating patient's greater satisfaction with the current antipsychotic treatment compared to their previous treatment. A significant ($p<0.001$) mean change from baseline in the MSQ scores at Day 43 of 0.9 was observed in each of the evenamide 7.5 mg, 15 mg and 30 mg *bid* treatment groups.

Conclusions:

In this prospective, randomized, blinded-rater, open-label, parallel-group, multi-center, 6-week study the safety and tolerability of fixed doses of evenamide of 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* as an add-on treatment in treatment-resistant schizophrenia patients on a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine) was demonstrated by the various safety parameters (low incidence of treatment related TEAEs; no trend of clinically significant effects on laboratory tests, vital signs, physical and neurological examinations, eye examinations, and ECG evaluations; and no increase in extrapyramidal symptoms, depressive symptoms, and seizure-like symptoms on the Seizure Checklist).

The preliminary efficacy of fixed doses of evenamide of 7.5, 15 and 30 mg *bid* as an add-on treatment was demonstrated by improvement in symptoms of schizophrenia assessed by the PANSS, total score and subscales, decrease in overall disease severity as assessed by the CGI-S score, overall improvement in the severity of illness from baseline as assessed by the CGI-C, enhancement in functionality of patients as assessed by the LOF, and patient's having greater satisfaction with the current antipsychotic treatment compared to their previous treatment as assessed by the MSQ Scores, in patients with treatment-resistant schizophrenia not responding adequately to their stable, therapeutically active dose of a single antipsychotic medication. These benefits were observed across all the timepoints and showed trends for greater improvement over time.

3 TABLE OF CONTENTS

3.1 LIST OF IN-TEXT TABLES

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)
ADR	=	Adverse Drug Reaction
AE	=	Adverse Event
AED(s)	=	Antiepileptic Drug (s)
ALT	=	Alanine-Aminotransferase
AP	=	Action Potential
AST	=	Aspartate-Aminotransferase
ATC	=	Anatomical Therapeutic Chemical
AUC	=	Area Under the 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
CRA	=	Clinical Research Associate
CRF	=	Case Report Form
CSR	=	Clinical Study Report
CYP2D6	=	Cytochrome P450 2D6
DBP	=	Diastolic Blood Pressure
DSM-5	=	Diagnostic And Statistical Manual of Mental Disorders – 5th Edition
DSM-IV-TR	=	Diagnostic And Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	=	Electrocardiogram
ECT	=	Electroconvulsive Therapy
EEG	=	Electroencephalogram
EM	=	Extensive Metabolizers
EPS	=	Extrapyramidal Symptoms
ESR	=	Erythrocyte Sedimentation Rate
ESRS-A	=	Extrapyramidal Symptom Rating Scale – Abbreviated Version
FGA	=	First Generation Antipsychotic Drugs
GAF	=	Global Assessment of Functioning
GCP	=	Good Clinical Practice
GGT	=	Gamma-Glutamyl Transpeptidase
HDL	=	High Density Lipoprotein
HED	=	Human Equivalent Dose

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
IEAC	=	Independent Eligibility Assessment Committee
IEC	=	Independent Ethics Committee
IRB	=	Institutional Review Board
ISMB	=	Independent Safety Monitoring Board
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
LS	=	Least Square
MBq	=	Megabecquerel (1 Mbq = 27 Microcuries)
MedDRA	=	Medical Dictionary for Regulatory Activities
MI	=	Multiple Imputation Method
Min	=	Minute(s)
mITT	=	Modified Intent To Treat
MMRM	=	Mixed Model Repeated Measures Analysis
MNAR	=	Missing Not at Random
MRSD	=	Maximum Recommended Starting Dose
MSQ	=	Medication Satisfaction Questionnaire
MTD	=	Maximum Tolerated Dose
N.S.	=	Not Statistically Significant
NMDA	=	N-Methyl-D-Aspartate
NOAEL	=	No Observed Adverse Effect Level
OC	=	Observed Cases
OTC	=	Over The Counter
PANSS	=	Positive And Negative Syndrome Scale
PAM		Prior Antipsychotic Medications
PET	=	Positron Emission Tomography
PK	=	Pharmacokinetics
PN	=	Preferred Name
PNS	=	Peripheral Nervous System
PPI	=	Pre-Pulse Inhibition
Prn	=	As Needed
PT	=	Preferred Term
q.s.	=	*Quantum Satis* (Amount That Is Sufficient)
RBC	=	Red Blood Cells
ROW	=	Rest Of World
SAE	=	Serious Adverse Event
SBP	=	Systolic Blood Pressure

SD	=	Standard Deviation
SE	=	Standard Error
SGA	=	Second Generation Antipsychotic Drugs
Sig-1R	=	Human Sigma-1 Receptor
SOC	=	System Organ Class
SOP	=	Standard Operating Procedure
$t_{1/2}$	=	Half-Life
T_3	=	Triiodothyronine
T_4	=	Thyroxine
TEAE	=	Treatment-Emergent Adverse Event
THC	=	Tetrahydrocannabinol
t_{max}	=	Time Of Maximum Plasma Concentration Post-Dose
TMS	=	Transcranial Magnetic Stimulation
TRS	=	Treatment-Resistant Schizophrenia
TSH	=	Thyroid Stimulating Hormone
US	=	United States
VGSC	=	Voltage-Gated Sodium Channels
VLDL	=	Very Low-Density Lipoprotein
WBC	=	White Blood Cells
WHO	=	World Health Organization

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). Written IRB/IEC approval was obtained by the Sponsor prior to shipment of study agent 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 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 audit/inspection by competent authorities and properly authorized persons. However, personal information was treated as strictly confidential and was not publicly available.

The sample ICF along with translations is provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted by 22 Investigators at 9 sites in India, 5 in Sri Lanka, 3 in Malaysia, and 5 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

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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 (AP) 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 side effects [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 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 (NW-3509) is an orally available new chemical entity that specifically targets 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 (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 antagonist activity 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 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 will be 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. For additional details, see the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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 telemetryin 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 pre-pulse inhibition [PPI] model), and the most conservative 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 has 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 increased 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 are 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). IC50 values could be 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 to be 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. Detailed results of Study 007 are provided in the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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. For additional details, see the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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 a 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 (Cmax) 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.

Detailed results of Study 001 are provided in the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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

Study Design. 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.

Conclusions. Evenamide was generally safe and well tolerated in 'Study 002' 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 – Severity of Illness [CGI-S] and Clinical Global Impression – Change from Baseline [CGI-C]), and an assessment of daily function (Strauss-Carpenter Level

of Functioning scale [LOF]).

Detailed results of Study 002 are provided in the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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 the study results, the Sponsor and the Independent Safety Monitoring Board (ISMB) concluded that evenamide, at doses of 7.5 and 15 mg *bid* given for 28 days, is well-tolerated and not associated with any evidence of symptoms/signs suggestive ofseizures, EEG changes or dose-limiting AEs. These results support evaluation of higher doses of 30 mg *bid* in the current study.

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 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 QTcF 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.

Detailed results of 'Study 010' are provided in the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

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 pharmacokinetics (PK) of a single oral dose of 60 mg of evenamide in 9 healthy adult male subjects (evenamide n=6 and placebo n=3). 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 Independent Safety Monitoring Board (ISMB) indicated that other evenamide studies could proceed as designed, with a maximum dose of 30 mg *bid*.

Detailed results of 'Study 011' are provided in the current edition of the 'Evenamide (NW-3509)' Investigator's Brochure.

8 STUDY OBJECTIVES

8.1 Primary Objective:

- To evaluate the safety and tolerability of evenamide given orally at three fixed doses (7.5, 15 and 30 mg *bid*) in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic dose of their current antipsychotic medication.

8.2 Secondary Objectives:

- To evaluate preliminary efficacy of the three fixed doses 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 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

This was a prospective, randomized, blinded-rater, open-label, parallel-group, multi-center, 6-week study to determine the safety, tolerability, and preliminary efficacy of fixed doses of evenamide of 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* as add-on treatment in TRS patients on a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine). Approximately 180 patients meeting the selection criteria at baseline were to be enrolled to ensure that minimally 50 patients were randomized to each of the three treatment groups. The 30 mg *bid* dose was introduced in a stepwise design. The two lower dose groups were initiated first, with 50 patients being randomized (1:1) to 7.5 and 15 mg *bid* (25 patients at each dose). After these patients completed their participation in this study, an ISMB reviewed the safety data that had emerged from the study.

Since the ISMB determined that these lower doses were safe, the 30 mg *bid* dose was introduced, and additional patients were enrolled according to a 1:1:2 randomization scheme to doses of 7.5, 15 and 30 mg *bid*, respectively.

Subsequently, with implementation of an amendment (*Amendment 6, 17th June 2021*) to the study protocol, the 7.5 mg *bid* dose group was discontinued, and patients were randomized 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. No further patients were enrolled in the 7.5 mg *bid* group. The rationale for 1:3 randomization scheme was based on results of Study 008, which 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. Therefore, the decision to discontinue the 7.5 mg *bid* dose group in the current study was made based on the results of this efficacy analysis in Study 008. Since more than 25 patients had already been enrolled in the study in the 15 mg *bid* group, the randomization ratio was 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 would be approximately equal at the end of the study.

Patients underwent screening assessments during a 3 to 21-day screening period. Patients meeting the inclusion criteria and none of the exclusion criteria at baseline (Day 0/1 pre-dose) were randomized to treatment and received their initial starting dose (7.5 or 15 mg evenamide *bid*) on Day 1. Patients in the 7.5 mg *bid* dose group started at a dose of 7.5 mg *bid*, whereas patients in the 15 mg *bid* and 30 mg *bid* (once it was initiated) treatment groups started at a dose of 15 mg *bid*. After one week, patients in the 7.5 mg *bid* and 15 mg *bid* dose groups continued to receive their target doses, whereas patients in the 30 mg *bid* group had their dose increased from 15 mg *bid* to the 30 mg *bid* target, provided the starting dose (15 mg *bid*) was well tolerated.

If intolerance developed, the patient could drop back 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, the patient had a reduction to *od* dosing, and continued for the remainder of the study at this reduced dose.

Patients returned for scheduled visits at Days 8, 15 and 29 for safety and efficacy assessments (Table 9-1) and received their study medication for the next dosing period. Patients had a final evaluation, including all safety and efficacy assessments, after the final dose on Day 43 (or at early discontinuation). All patients who completed 6 weeks of open-label treatment were eligible for continuing treatment with evenamide in a separate 46-week open-label extension study (Study NW-3509/015/II/2019), for 52 weeks of total treatment. The duration of this extension study may be increased, contingent on availability of data from chronic toxicology studies to support the additional treatment. To minimize bias in the assessment of changes from baseline in the safety and efficacy parameters, and comparison of data across treatment groups, all safety and efficacy assessments were performed by a clinician who was blind to the treatment assignment for each

patient.

For patients who discontinued prematurely, as well as those who completed 6 weeks of open-label treatment but did not enter the separate open-label extension study, 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. In addition, the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose was reported (this information was collected through a telephone contact). An overview of the study design is provided in Table 9-1.

The ISMB met at regular intervals to review the safety data emerging from the study. The ISMB was charged with safeguarding the interests of the study subjects, with assessing the safety of the intervention during the study, and with monitoring the overall conduct of the study. The ISMB provided recommendations to continue the trial as designed, or with modification through amendments to protocol, i.e., 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 6, dated 17th June 2021*).

Table 9-1: Summary of Study Design

Period	Pre-Treatment		6-Week, Open-Label, Treatment Period					Post-Treatment	
Visit	**Screening**	**Baseline[#]**	**Day 1[#]**	**Day 8**	**Day 15**	**Day 29**	**Final [$] (Day 43 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	-21 to -1	0/1 (pre-dose)	1 (in clinic)	1 to 7	8 to 14	15 to 28	29 to 43	7 days after last dose	30 days after last dose
Treatment/ Procedures	Informed consent, Screening evaluations performed; I/E criteria assessed; urine drug screen; serum pregnancy tests in women of child-bearing potential	Patient checks into clinic; baseline safety and efficacy evaluations; repeat urine drug screen; alcohol breath test; urine/ serum pregnancy tests in women of child-bearing potential; confirm I/E criteria met	Randomization to evenamide (7.5, 15 or 30 mg *bid*); administer first dose in clinic on Day 1; safety assessments up to 4 hr after first dose; discharge from clinic and continue dosing at their residence	Selected safety and efficacy assessments; increase dose in high dose group/ reduce dose if necessary; safety assessments, post dose; discharge after 4-hr	Selected safety and efficacy assessments; adverse event assessment; reduce dose if necessary	Selected safety and efficacy assessments; adverse event assessment	All safety and efficacy assessments; last dose of study medication on Day 43 (AM) in clinic for patients not continuing in extension study	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				Day 4 (AEs and Conc. Medication)	Day 11 (AEs and Conc. Medication)			If patient does not return for scheduled visit, contact to assess AEs	Information can be collected via telephone contact

[#] Day 0 and 1 would overlap, and all pre-dose (baseline) and post-dose (Day 1) assessments should be completed on the same day.

[$] Final evaluation for patients who discontinue prematurely and those not continuing in the separate open-label extension study (Study 015).

**To be performed for patients who discontinue prematurely, and those who complete 6 weeks of treatment, but do not continue in the separate open-label extension study.*

9.2 Discussion of Study Design, Including Choice of Control Groups

The primary objective of this study was to determine the safety and tolerability of three fixed doses of evenamide (7.5, 15 and 30 mg, *bid*) as add-on treatment in patients with treatment-resistant schizophrenia (TRS) not responding adequately to a stable, therapeutic dose of their current antipsychotic medication. Administration of evenamide had shown efficacy in animal models predictive of antipsychotic activity. In addition, preliminary evidence of efficacy in treating the symptoms of schizophrenia was obtained in Study 002, a 4-week, randomized, double-blind, placebo-controlled, multiple ascending dose study evaluating the safety, tolerability, and preliminary efficacy of evenamide in patients with chronic schizophrenia not responding adequately to their current antipsychotic (risperidone or aripiprazole). The study results showed that doses of evenamide in the range of 15-25 mg *bid* (30-50 mg/day) were well tolerated. (Details in Section 7.5.2).

An open-label study design was used for this pilot study; however, a clinician who was blinded to the treatment assignment (i.e., dose of evenamide) performed the assessment of safety and the ratings of the efficacy measures. The open-label study design was chosen to make it easier to optimize each patient's dose of evenamide and concomitant medications, as the treating physician would be aware of the dose that the patient was receiving. This flexibility in dosing options would have been difficult to achieve using blinded medication. The use of the blinded rater and the three parallel dose groups allowed determination of dose dependency for the incidence of adverse events, as well as changes from baseline in other safety parameters and efficacy measures, without introducing a bias from knowledge of the treatment by the investigators. The treatment period of the study was 6 weeks (43 days), followed by an additional 46 weeks of treatment in an optional open-label extension study (Study 015). The primary endpoint for assessment of efficacy was at the 6-week (Day 43) time-point, as this is a standard period for assessing efficacy of antipsychotic drugs. The study incorporated a fixed dose design in which patients would receive target doses of 7.5, 15 or 30 mg of evenamide, twice daily. Approximately 180 TRS patients were to be randomly assigned to treatment, with a minimum of 50 randomized to each evenamide dose, which was expected to allow an adequate assessment of safety and tolerability of each dose.

9.3 Selection of Study Population

Treatment-resistant schizophrenia" (TRS) is defined as a persistence of significant clinical symptoms despite adequate doses of two standard antipsychotic medications (other than clozapine) from two different chemical classes, including at least one atypical antipsychotic, for at least 6 weeks of treatment each. Patients with TRS show significantly lower dopamine capacity in the whole striatum than treatment-responsive patients based on 18F-DOPA PET (Kim et al, 2017). Dysfunction of glutamatergic transmission has been suggested to be a neurobiological basis for treatment resistance in some patients with schizophrenia (Mouchlianitis et al, 2016). The rationale for using evenamide in this TRS population is based on its pharmacology (see Section 7.2). The

addition of evenamide, with its known neurochemical effect of reducing stimulated release of glutamate, has been shown to potentiate otherwise ineffective doses of clozapine in the ketamine-induced PPI deficit model in rats. These animal findings suggest that evenamide may be a valuable add-on treatment in patients with TRS who are not responding adequately to a stable dose of their current antipsychotic monotherapy.

The study population was selected based on the patient's level of severity of psychosis. The acceptable level of psychosis was defined as one that would not preclude their ability to provide detailed and accurate feedback on their tolerance of the study medication, while allowing room for improvement and demonstration of potential beneficial effects of evenamide. The severity of the symptoms of these patients permitted them to be treated as outpatients for the greater part of the study. Furthermore, the absence of significant or severe concomitant medical illnesses and limiting the use of concomitant medications were expected to prevent bias in determining the tolerability and safety of evenamide. The selection criteria were also designed to maximize the safety of subjects and minimize current medical conditions or concomitant treatments that could confound the assessment of safety parameters or alter the PK of evenamide.

9.3.1 Inclusion Criteria

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

Demographics

1. Age - 18 years, or older.
2. Sex – male, or female. *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 4, dated 18th September 2020).*

Psychiatric

3. Met current DSM-5 criteria for schizophrenia.
   Other psychiatric disorders may be present only as lifetime diagnoses if they were not relevant to the current episode of schizophrenia. [see Exclusion criteria below]
4. Had been diagnosed with schizophrenia within the past 15 years (*prior to Amendment 5, dated 4th February 2021, it was '10 years' in the original protocol Version 1.0, dated 7th November 2019).*
5. Had shown treatment-resistance according to psychiatric history, within the past 10 years *(added in Amendment 5, dated 04th February 2021),* with the last failed treatment documented in the patient's clinical records. *"Treatment-resistant Schizophrenia" (TRS) is defined as a persistence of significant clinical symptoms despite adequate doses of two*

standard antipsychotic medications (other than clozapine) from two different chemical classes, including at least one atypical antipsychotic, for at least 6 weeks of treatment each. The last failed treatment trial must be documented.

6. Had a Clinical Global Impression – Severity of disease (CGI-S) rating of moderately ill to severely ill (score of 4 to 6 [scale 1-7]).
7. Had a PANSS total score ≥ 70 at screening and baseline.
8. Had a score of **4 (**moderate) or more on at least 2 of the following 4 PANSS symptoms of psychosis: P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior, P6 (Suspiciousness/Persecution) and G9 (Unusual Thought Content); and a total score of at least **20** on the combined total of the PANSS symptom items: P1 (Delusions), P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P4 (Excitement), P6 (Suspiciousness/Persecution), P7 (Hostility), and G9 (Unusual thought content).
9. Had a Global Assessment of Functioning (GAF) scale total score ≤ 50.
10. Needed anti-psychotic treatment and was currently receiving monotherapy at a stable dose (minimally for 4 weeks prior to screening) at a minimal recommended therapeutic or higher doseof one antipsychotic (atypical or typical, other than clozapine). Current use of quetiapine at a dose of 150 mg or less *(In the original protocol version 1.0, dated 7th November 2019, quetiapine dose was 50 mg and it was increased to 150 mg with Amendment 2, dated 7th February 2020) at night as a soporific was not considered polypharmacy.*
11. Current level of symptoms had been present for at least one month, but not exceeding one year.

Procedural

12. Patient cooperative, able to take oral medication, able to understand the instructions and willing to complete all aspects of the study and was capable of doing so.
13. Patient was residing with a caregiver at his/her home or was either in a residential care facility or residing alone, with a caregiver available to help ensure compliance with dosing and scheduled office visits in either situation.
14. Patient had provided written informed consent prior to participating in the study.
15. Patient agreed to be hospitalized overnight if required for trial purposes or if the Investigatordeems it necessary to ensure the safety of the patient.

9.3.2 Exclusion Criteria

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

Psychiatric

1. DSM-5 diagnosis of schizophreniform disorder (295.40), schizoaffective disorder (295.70), or other primary psychiatric diagnosis, such as bipolar disorder or major depressive disorder (depression was assessed at screening and baseline using the Calgary Depression Scale for Schizophrenia (CDSS); a score of 7 or higher was exclusionary).
2. History (within three months of study entry) or current diagnosis of 'substance use disorder' as defined by the DSM-5 criteria, with a severity of 'moderate' or 'severe', or patient was currently abusing drugs or alcohol or has done so in the past year. *A history of nicotine or caffeine dependence was acceptable; and patients testing positive for THC on the urine drug screen were not to be excluded from the study unless there was evidence of toxic psychosis.*
3. Severity of current episode of psychosis requires that the patient be hospitalized. *Patients who were chronically hospitalized or in psychiatric daycare, whose hospitalization was for logistic reasons and not due to the severity of their illness, were eligible for the study.*
4. Had a PANSS total score > 90 or a CGI-S rating of 7 (among the most extremely ill patients).
5. History or current diagnosis of other psychiatric or behavioral disorders that could interfere with the conduct or interpretation of the study.
6. Known suicidal risk, or a suicide attempt within the past 2 years, as assessed by the CDSS and/or by psychiatric history.
7. History of neuroleptic malignant syndrome, priapism or moderate or severe tardive dyskinesia.

Medical Status

8. An advanced, severe, or unstable disease of any type that could interfere with any of the study evaluations, including any medical condition that could be expected to progress, recur, or changeto such an extent that it may bias the assessment of the clinical or mental status of the patient to a significant degree or put the patient at special risk (e.g., liver or kidney disease, severe uncontrolled asthma, malignancy).
9. Insulin-dependent diabetes mellitus. Patients with non-insulin-dependent diabetes were eligible if the following criteria were satisfied:
    a. Diabetes was considered well controlled, with no changes in treatment regimen for at least 4 weeks prior to screening,
    b. Diabetes was not newly diagnosed at screening.
10. History or current diagnosis of any neurodegenerative illness, dementia, significant

concomitant neurological disease, organic cerebral disease, cerebrovascular disease, focal neurological lesions or history of any trauma resulting in loss of consciousness (during the past 2 years).

11. History or current diagnosis of epilepsy or seizure disorder, or occurrence of a seizure within the past year, or repeated drug-induced seizures (other than febrile seizures in childhood).

12. Prior surgery or current medical condition which could interfere with the absorption, distribution,metabolism or excretion of the study drug, e.g., peptic ulceration, gastric or intestinal surgery, impaired renal or hepatic function, inflammatory bowel disease.

Cardiovascular

13. Any clinically significant ECG abnormality, including a disorder of rate, rhythm, or conduction, or other morphological changes, or a QTcF interval prolongation (Fridericia's correction formula)on the ECG (>450 msec for males; >470 msec for females).

The 12-lead ECG was used for determining the suitability of the patient for inclusion in the study (determination made by the Investigator). Values averaged from the 3 ECG measurementsat baseline used in determining eligibility.

14. Vital signs (supine) outside the following ranges (measured after 5 minutes supine):
    a. Systolic blood pressure below 90 or above 150 mmHg
    b. Diastolic blood pressure below 50 or above 95 mmHg
    c. Radial pulse (from vital signs) below 50 or above 100 bpm
    d. Orthostatic hypotension (decrease in SBP/DBP from supine to standing position exceeding 30 mmHg).

Laboratory abnormalities

15. History of hepatitis B and/or C, and/or positive serology results, which indicate the presence of hepatitis B and/or C (Hepatitis B surface antigen and/or antibody to Hepatitis C).

16. Positive results from the HIV serology.

17. Positive results of the drug and alcohol tests at screening and/or baseline. Patients who test positive for drugs of abuse at screening, but had negative test results at baseline, was eligible,dependent on the type of drug and the likelihood of continued abuse during the study. *Possible inclusion of these patients in the study was to be discussed with the Medical Monitor.*

Concomitant therapy

18. History of or current treatment with clozapine for psychosis.
19. Requires treatment with an anticholinergic drug, and the dose was not stable.
20. Was receiving benzodiazepine therapy, unless the dose has been stabilized for at least 2 months, excluding occasional *prn* dosing. Doses of benzodiazepines was not reduced or stopped during the study, unless clinically necessary. PRN dosing should employ the lowest safe and effective dose possible. Any changes in the dose of a benzodiazepine were performed under close medical supervision.
21. Treatment with agents influencing dopamine, norepinephrine or serotonin neurotransmission (e.g., tri- and tetra-cyclic antidepressants, MAO inhibitors, metoclopramide). *Treatment with SSRIs and SNRIs that were moderate/potent inhibitors of CYP2D6 (e.g., fluoxetine) was not permitted; however, patients on a stable dose of an SSRI or SNRI that is a weak inhibitor of CYP2D6 (e.g., escitalopram), for at least 4 weeks before screening, were eligible.*
22. Treatment with drugs capable of inducing/inhibiting hepatic enzyme metabolism (e.g., barbiturates, carbamazepine, phenylbutazone, phenytoin, primidone, rifampicin) four weeks prior to baseline or during the study.
23. Current treatment with sodium channel blockers (e.g., Class I antiarrhythmic agents, anticonvulsants, local anesthetics) or mood stabilizers (e.g., lithium, carbamazepine, oxcarbazepine, lamotrigine). *Valproic acid was permitted, if used as maintenance treatment.*
24. Exposure to any investigational drug within 5 weeks or 5 half-lives (whichever was longer) prior to screening.
25. A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to evenamide (e.g., lamotrigine, carbamazepine, oxcarbazepine, topiramate, etc.), or any componentsof the evenamide capsules.
26. Electroconvulsive therapy (ECT) or treatment with a transcranial magnetic stimulation (TMS) device within 6 months prior to screening.

General

27. Patient was female and of childbearing potential, pregnant or breastfeeding. For inclusion, female patients must have been post-menopausal (age 50 or older and 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 4, dated 18th September 2020*).

28. Patients with a reasonable likelihood of non-compliance with the protocol, or any other reason that, in the Investigator's opinion, could prohibit the inclusion of the patient in the study.

9.3.3 Removal of Subjects from Therapy or Assessment

A subject was considered to have completed the study when he/she returned for the final evaluation on Day 43, regardless of whether the subject returned for the safety follow-up assessment approximately 7 days after the last dose of study medication, if the patient completed 43 days of treatment, but did not continue in the separate extension treatment study. Discontinuation referred to any subject who did not complete the full 43-day randomized treatment period of the study, exclusive of missed doses during the period.

In the absence of a medical contraindication or significant protocol violation that could put the subject at risk, every effort was to be made by the Investigator to keep the subject in the study; however, should the subject be withdrawn, 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 to be replaced.

Interrupting or permanently discontinuing a subject's treatment with the study medication was to be 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 be discontinued from the study prior to Day 43 were listed below. A subject was to be 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 requires 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 (e.g., subject was unwilling to attend the scheduled clinic visits);
- 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 to be 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 to be entered on the Study Completion/Termination CRF, and one of the following reasons for discontinuation 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.

Patients who discontinued from the study prematurely (i.e., before completing the 43-day randomized treatment period) were to have their reason for discontinuation entered in the CRF. Patients who were discontinued from the study after having received at least one dose of study medication were not replaced. All patients who discontinued prematurely were to be asked to return for a final assessment, at which time all Day 43 visit assessments were to be performed. Patients were also to be requested to return for the safety follow-up assessment 7 days after their

last dose of study medication. Additionally, patients were to be contacted by telephone for the safety follow-up assessment 30 days after their last dose of study medication.

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 for oral administration in 30 ml HDPE bottles with a child-proof screw cap. 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 according to a computer-generated randomization scheme provided to the site pharmacist by the Sponsor. The Principal Investigator, study coordinator, nurses, and other site staff, as well as the patients, were aware of what was being administered to the patient; however, the blinded safety and efficacy rater was not aware of the treatment assignment. Special care was taken so that the blinded rater was not accidentally unblinded, 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 reveal the treatment assignment.

The first dose of study medication (starting dose) was administered to the patient in the clinic in the presence of a licensed physician. Following administration of the study drug, appropriate hand and/or mouth checks were performed to ensure that the dose was swallowed. The date, time, and number of capsules taken during the in-patient period were recorded on the CRFs. The oral doses of evenamide taken by the patient for each randomized dose group were 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 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		
Dose Type	**Evenamide 7.5 mg *bid*****	**Evenamide 15 mg *bid***	**Evenamide 30 mg *bid******
Starting Dose	7.5 mg *bid*	15 mg *bid*	**15** 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*

** If the Starting/Target Dose (bid) was not tolerated, a dose reduction to **once daily (**od) dosing (Drop-back Dose) was performed. Patients in the 30 mg bid group who began to experience tolerability issues at the 15 mg bid*

starting dose remained at this dose. A drop-back from the 15 mg bid starting dose to 15 mg od in the high dose group was permitted, if necessary, due to intolerance.

***The 7.5 mg bid dose was no longer administered, once the amended protocol (Amendment 6, 17th June 2021) was implemented and any ongoing patients receiving a dose of 7.5 mg bid had completed the study.*

**** 30 mg bid group was initiated after review of data from the first 50 patients who completed treatment at the two lower doses.*

Overdose

To date, the maximum single dose of evenamide given to a subject in 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 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.

Procedure to be 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 reported immediately to the Investigator. Any instance of overdose, whether symptomatic or not, was to be communicated to the CRO within 24 hours and 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.

Procedure to be followed in Italy, Malaysia, and Sri Lanka for reporting overdose

If the investigational site staff administering the study medication, the caregiver, or the subject reports that a subject inadvertently took more than the requisite number of capsules or a higher dose than was assigned, this was to be considered an overdose and 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 to be considered an overdose.

Any instance of a suspected overdose (based on pill counting), that was asymptomatic and for which there was no explanation, was to be considered a 'medication error', and did not need to be 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.

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. 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-3509-014-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 (7.5, 15 or 30 mg) were dispensed for the planned doses of 7.5, 15 and 30 mg, which were administered orally twice daily. 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., one bottle on Days 1 and 8, and two bottles on Days 15 and 29. 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. Patients who have had their dose reduced to once daily dosing still received the same number of bottles of study medication for twice daily dosing at the target dose but 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	No. of Bottles*	Total number of evenamide capsules dispensed		
		7.5 mg *bid***	**15 mg *bid***	**30 mg *bid***
1-7	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x **15 mg**
8-14	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x 30 mg
15-28	2	32 caps x 7.5 mg	32 caps x 15 mg	32 caps x 30 mg
29-43	2	32 caps x 7.5 mg	32 caps x 15 mg	32 caps x 30 mg

**16 capsules/bottle*

*** Once the amended protocol (Amendment 6, dated 17th June 2021) had been implemented, the 7.5 mg dosage strength was no longer dispensed. Details of IP Batch Numbers are presented in Appendix 16.1.6.*

The patients were instructed to keep the study medication at room temperature (15 to 25ºC), as it was stored at the investigational site. All unused study medication and medication bottles were to be returned to the Sponsor or their designee at the end of the trial or destroyed by the study site upon authorization by the Sponsor. The destruction of unused medication was to be documented in accordance with ICH GCP.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subject Number

Each screened patient received a unique six-digit **subject number**, with the first three digits specifying the center number and the last three digits the subject at the center. The subject number was entered in the CRF and appeared in the header of each CRF page. The subject numbers were assigned sequentially, beginning with ###-001, in the order of the patient's signing of the informed consent form at the center.

Should a patient have been discontinued from the study for any reason after having been assigned a subject number, the number was not to be reassigned to another patient. Information regarding the demographics of the patient and reason for discontinuation was to be recorded in an End of Screening Log.

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.

Patient Randomization

Approximately180 patients were to be randomized in this study. The two lower dose groups (7.5 mg *bid* and15 mg *bid*) were initiated first, and 50 patients were randomly assigned (1:1) to one of

the two doses (approximately 25 patients per group). After these 50 patients completed their participation in the study, an ISMB reviewed the safety data that emerged from the study. Since the ISMB determined that the lower doses were safe, the 30 mg *bid* dose was introduced according to a 1:1:2 randomization scheme, with patients being randomized to doses of 7.5, 15 and 30 mg *bid*, respectively. Subsequently, with implementation of an amendment (*Amendment 6, 17th June 2021*) to the study protocol, the 7.5 mg *bid* dose group was discontinued, and patients were randomized 1:3 to doses of 15 mg *bid* and 30 mg *bid*, respectively. No further patients were enrolled in the 7.5 mg *bid* group.

Randomization was performed according to a computer-generated randomization scheme presented in Appendix 16.1.7 of the CSR. This scheme was generated in three parts, dependent on the decision of the ISMB regarding addition of the 30 mg *bid* dose group. A **randomization number** corresponding to the treatment was assigned to each randomized subject and registered in the subject's files for identification. Randomization was done on a per site basis, and each patient randomized at the site received the next sequential randomization number and treatment assignment according to the randomization scheme for that site.

In summary, randomization was performed in 3 parts, as follows.

For the Part 1 randomization, in which only the 7.5 and 15 mg *bid* dose groups were included, the format of the randomization number were seven characters as follows:

P101001 (P1 + 01 + 001)

- P1 – represents Part 1 of the randomization.
- 01 – two-digit number that was unique to each site, which did not match the 3-digit site number that was part of the 6-digit subject numbers assigned at screening.
- 001 – three-digit number that represented the patient, assigned in order of randomization at the site; may not be the same as the last 3 digits of the patient's 6-digit subject number assigned at screening.

Once the 30 mg *bid* dose group was added, as approved by the ISMB, the Part 2 randomization list was generated and used until protocol *Amendment 6, dated 17th June 2021*, was implemented. Patients were randomized **1:1:2** to doses of 7.5, 15 and 30 *mg bid*, respectively, under the Part 2 scheme.

Part 2 randomization numbers was formatted as follows:

P201001 (P2 + 01 + 001)

- P2 – represented Part 2 of the randomization (used only if the 30 mg *bid* dose group was added).
- 01 – two-digit number that was unique to each site, which did not match the 3-digit site number that was part of the 6-digit subject numbers assigned at screening.

- 001 – three-digit number that represents the patient, assigned in order of randomization at the site, once Part 2 of the randomization was implemented; may not be the same as the last 3 digits of the patient's 6-digit subject number assigned at screening.

Once the 30 mg *bid* dose group was added and protocol *Amendment 6, dated 17th June 2021*, was implemented, the 7.5 mg *bid* dose group was discontinued, and patients were randomized 1:3 to the 15 mg *bid* and 30 mg *bid* dose groups, respectively, under the Part 3 scheme.

The Part 3 randomization list, in which only the 15 mg *bid* and 30 mg *bid* dose groups were included, was generated and used for the remainder of the study. The format of the Part 3 randomization numbers were seven characters as follows:

P301001 (P3 + 01 + 001)

- P3 – represented Part 3 of the randomization.
- 01 – two-digit number that was unique to each site, which did not match the 3-digit site number that was part of the 6-digit subject numbers assigned at screening.
- 001 – three-digit number that represented the patient, assigned in order of randomization at the site; may not be the same as the last 3 digits of the patient's 6-digit subject number assigned at screening.

9.4.4 Selection of doses in the Study

The doses of evenamide selected (7.5 mg *bid*, 15 mg *bid*, and 30 mg *bid*) 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. 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. The patients randomized to treatment at 30 mg *bid* were titrated to this dose starting from a lower dose (15 mg *bid*).

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, presented in Appendix 16.1.1.

9.4.5 Timing of Dosing for Each Patient

Evenamide (NW-3509) 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 well tolerated, 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.

All randomized patients received their initial starting dose (7.5 or 15 mg evenamide, *bid*) on Day 1 in the clinic. At all subsequent visits (Days 8, 15, 29 and 43), the morning dose was administered in the clinic from a medication bottle dispensed for the next dosing period. After one week, patients in the 7.5 mg *bid* and 15 mg *bid* dose groups continued to receive their target doses of 7.5 or 15 mg *bid*, respectively, while patients in the 30 mg *bid* dose group had their dose increased to 30 mg *bid*, provided the starting dose (15 mg *bid*) was well tolerated. Patients in the 30 mg *bid* group who experienced tolerability issues at the 15 mg *bid* starting dose, remained at this dose. The planned dose levels used in the study are shown in Table 9-2 above.

If intolerance developed, the patient could drop back 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 an increase of dose, the patients were to revert to once daily (*od*) dosing and could continue for the remainder of the study at this reduced dose. Dose reductions due to intolerance were to be performed at any time, whereas dose increases were to be done only at scheduled visits.

Patients were instructed to take their morning dose of study medication at least 10 minutes after the time of dosing for their concomitant antipsychotic. The patients were instructed to take study medication with food or after a meal. Any other medications were required to be taken according to their usual schedule. However, on the day of a scheduled office visit, the patients were reminded to withhold their morning dose of study medication, as it was required to be administered in the clinic. On these days, the doses of their antipsychotic and any other medications were to be taken

at their residence according to their usual schedule.

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. To ensure that the chance for bias in assessing safety and efficacy in this open-label study was minimized, an appropriately trained psychiatrist or clinician, who was blinded to the treatment (i.e., dose of evenamide) patients received, performed all baseline and post-baseline assessments for each of the safety and efficacy rating scales. This psychiatrist/clinician was not involved in the routine care of the patient. Measures were taken at the site to ensure that this rater was not accidentally unblinded, for example by restricting access to the patient's medical records, minimizing interaction with unblinded personnel, etc. Blinded psychiatrist or clinician raters were trained to assess the study outcome measures.

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.

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 Day 43 was recorded in the CRF (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 Day 43.

Restrictions specified in the exclusion criteria were to be 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 sedative in patients who had been taking it for at least 4 weeks prior to Screening. In addition, patients were allowed to start quetiapine (up to 150 mg *hs*) for sedation post-randomization. Also, valproic acid was

permitted, if used as a prophylaxis of clozapine-induced seizures, and/or maintenance treatment. Drugs that could increase the risk of seizures, e.g., bupropion, were not allowed to be administered.

9.4.7.2 Rescue Medication

If a patient had an exacerbation of his/her schizophrenia while in 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. The need for administering 'rescue medication' to an individual patient was left to the clinical judgment of the Investigator; however, any of the following changes from baseline in the patient's status was considered as adequate justification for considering a rescue by making a change in the patient's treatment regimen:

- > 20% worsening on the PANSS total score (e.g., increase from 70 to 85);
- Rating on the CGI-C of 'very much worse' (score of 7);
- Patient was demonstrating worsening of violent, threatening, homicidal or suicidal behavior;
- Patient has worsened to the extent that he/she requires hospitalization.

Benzodiazepines

Patients receiving chronic dosing with lorazepam or other benzodiazepine, were to have been on a stable dose for at least 2 months prior to screening, excluding occasional *prn* dosing. The lowest possible dose was suggested to be used, and no dose was to be given within 8 hours of a scheduled efficacy assessment. The dose of benzodiazepine was not to be reduced or stopped during the study, unless clinically necessary.

For patients not receiving chronic dosing with lorazepam or another benzodiazepine, lorazepam 0.5 mg or an equivalent short half-life benzodiazepine was suggested to be used on a *prn* basis to treat episodes of agitation or severe restlessness during the study. The dose of lorazepam was limited to 2 mg/day, unless clinically necessary. For other short-acting benzodiazepines, the dose was limited to 2 mg/day of lorazepam, unless clinically necessary. The use of intramuscular lorazepam for emergent agitation was permitted, but only if deemed absolutely necessary by the Investigator, and in consultation with the Medical Monitor, if possible.

9.4.8 Treatment Compliance

The first dose of the study medication was to be administered to the patient in the clinic in the presence of a licensed physician. Following administration of the study drug, appropriate hand and/or mouth checks were to be performed to ensure that the dose was swallowed. The date, time and number of capsules taken during the in-patient period were to be recorded on the CRFs.

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.

9.5 Safety and Efficacy Variables

9.5.1 Safety and Efficacy Measurements Assessed and Flow Chart

Screening

The screening evaluations were performed at least 3 days and up to 21 days prior to baseline and included a review of the patient's medical and psychiatric history and current use of medications, vital signs (including height, weight and waist circumference), 12-lead electrocardiogram (ECG), laboratory tests (hematology, blood chemistry, urinalysis, virology, thyroid function tests, and urine drug screen), serum pregnancy test (for all women of child-bearing potential, as well as those who were post-menopausal or who have had a tubal ligation), physical and neurological examination, standard eye examination, completion of a Seizure Checklist evaluating symptoms and signs suggestive of seizures (e.g., seizures or fits, convulsions, absence seizures, unconsciousness, biting of tongue), PANSS, CGI-S, GAF and Calgary Depression Scale for Schizophrenia (CDSS). Resistance of the patient's schizophrenia symptoms to treatment was documented. The most recent episode of non-response to their antipsychotic was documented in the patient's clinical records. Adverse events were assessed from the time of signing the consent form.

Baseline (Day 0 and Day 1 pre-dose)

Baseline vital signs and ECG assessments were performed in triplicate, with an interval of at least 10 minutes between readings. Baseline assessments were performed for the PANSS, CGI-S, CDSS, LOF, GAF and MSQ. Evaluations of adverse events, including symptoms and signs suggestive of seizures (and the Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A), and updating of any change in current medications, were completed at the baseline visit (Day 0). Urine (immediate result) and serum (for confirmation) pregnancy tests were performed for all women of childbearing potential, as well as those who were post-menopausal or those who have had a tubal ligation. A blood sample was collected for measuring serum prolactin levels. Furthermore, a urine drug screen and alcohol breath test were performed at baseline. Laboratory tests (hematology, blood chemistry and urinalysis) and physical, neurological and standard eye examinations were to be repeated at baseline if performed more than 21 days prior.

6-Week Treatment Period

On Day 1, patients meeting all entry criteria at screening and baseline received an initial oral dose of study medication (evenamide 7.5 or 15 mg) in the clinic. During the initial 4-hour period after the first dose, safety evaluations (vital signs, 12-lead ECG, laboratory tests, and assessment of adverse events, including CNS symptoms and signs) were performed. Vital signs assessment and

12-lead ECG were performed both at 1 and 4-hr post-dose. If no moderate/severe side effects were noted within the 4-hr period following the first dose, the patient was discharged from the in-patient facility and given a supply of study medication at their assigned dose for the remainder of the first week of dosing. The patients were asked to take the second dose at their residence not earlier than 6 hours after the first dose. If the starting dose was not tolerated, patients were instructed to implement a reduction to once daily (*od*) dosing. Further, the patients were instructed to take only the morning dose for the first week of dosing if symptoms persisted. If the reduced (*od*) dose was well tolerated, an increase to the starting/ target *bid* dose was done at the next scheduled visit. If the reduced dose could not be tolerated, the patient was discontinued from the study. Patients were instructed to take study medication with food or after a meal. Any other medications were to be taken according to their usual schedule.

Patients were contacted via a telephone call from the Investigator/site staff on Day 4 to inquire about the tolerability of the study medication and whether any adverse events had been experienced. If necessary, the patient's dose was reduced (*od* dosing) or, if significant tolerability issues were noted, they were asked to return for an unscheduled visit.

The patients were required to return for a scheduled visit on Day 8. During this visit selected safety and efficacy evaluations were performed. On the day of each scheduled clinic visit, patients/caregivers were instructed to withhold the morning dose of study medication, as it was administered in the clinic, and key efficacy assessments (PANSS, CGI-S/C) were conducted approximately 1-2-hr post dose. The dose administered was the first dose of the study medication allocated for the next period of dosing, except for the last dose on Day 43. Patients assigned to the 30 mg *bid* dose group had their dose increased from 15 to 30 mg *bid* on Day 8, provided the 15 mg *bid* dose was well tolerated. Patients were reminded to take their concomitant antipsychotic and other medications at their residence according to their usual schedule. Patients were asked to bring their study medication bottle(s) with them to the visit.

The patient received a telephone contact from the Investigator/site staff on Day 11 to inquire regarding any safety or tolerability issues that he/she may have experienced. Based on this report, the patient's dose was reduced to once daily dosing, if needed, or, if significant tolerability issues were noted at the current dose level, the patient was asked to return for an unscheduled visit.

The patients were required to return for a scheduled visit on Day 15. At this visit, selected safety and efficacy (PANSS, CGI-S/C, MSQ) evaluations were performed by a blinded rater. If no safety or tolerability issues were detected during the pre-dose assessment that would require reducing the dose, the patient continued receiving their current dose level on the morning of Day 15 in the clinic. A dose increase was permitted at this visit if the patient had been receiving a drop-back dose and the tolerability issues had resolved. If there were no tolerability issues noted within the 4-hr period following this dose, the patient was discharged from the clinic and given a supply of study medication at the current dose level for the next 2-week dosing period. The patient was asked to take the evening dose of the study medication atleast 6 hours after the morning dose.

The patients were required to return on Day 29 for a scheduled visit for selected safety and efficacy (PANSS, CGI-S/C) assessments. A dose increase was permitted at this visit if the patient was receiving a drop-back dose and the tolerability issues had resolved. The morning dose was administered in the clinic, and if there were no tolerability issues, the patient was dispensed a supply of their current dose level of study medication for the final 2 weeks of dosing in the 6-week treatment period and was discharged from the clinic.

The patients were reminded not to take their morning dose of study medication on Day 43, as it was to be administered in the clinic, and all final safety [vital signs, 12-lead ECG, laboratory tests (hematology, blood chemistry, urinalysis, serum prolactin), and serum pregnancy test (for all women of child-bearing potential, as well as those who were post-menopausal or who have had a tubal ligation), ESRS-A, CDSS, physical/neurological examinations, and standard eye examination] and efficacy (PANSS, CGI-S/C, LOF and MSQ) evaluations were done 1-2 hours post dose. An assessment of substance use and a urine drug screen were also performed.

Extension Study

All patients who completed 6 weeks of treatment and were not experiencing any moderate/severe side effects and had not shown significant worsening of their symptoms of schizophrenia during the 6-week treatment period, were eligible to continue treatment in a separate 46-week open-label extension study (Study 015). Patients receiving 15 mg *bid* or 30 mg *bid* would continue the same dose of evenamide, while patients completing 'Study 014' on the 7.5 mg *bid* dose would have their dose increased to 15 mg *bid* upon entry into 'Study 015'. The duration of this extension study was increased by a 24-week additional period.

Safety Follow-up Evaluation

For patients who discontinued prematurely, as well as those who completed 6 weeks of treatment, but did not enter the separate open-label extension study, 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 for their 7-day safety follow-up visit were contacted by telephone by the study site to follow up on the occurrence of any adverse events. In addition, the patient was contacted by telephone 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 for Screening, Days 0/1, Day 8, Day 15, Day 22, Day 29 and Day 43, 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

Period	Pre-Treatment		Treatment Phase							Post-Treatment	
Visit / Assessment	Screening Days -21 to -3	Baseline[A] Day 0	Day 1	Day 4	Day 8	Day 11	Day 15	Day 29	Day 43 (Final) [E,J]	7-day Safety follow-up[I]	30-day Safety follow-up[K]
Informed consent (before any study procedure was completed)	X										
Inclusion/Exclusion Criteria	X	X									
Demography/Background Information	X										
Psychiatric History	X										
Medical History and Current Medical Conditions	X										
Physical Examination	X	X[B]							X		
Neurological Examination	X	X[B]							X		
ESRS-A		X							X		
Standard Eye Examination	X	X[B]							X		
Vital Signs	X[M]	X[C]	X[C]		X[C]		X[C]	X[C]	X[C, M]	X[C]	
Electrocardiogram (12-lead ECG)	X[D]	X[D]	X[D]		X[D]		X[D]	X[D]	X[D]		
Laboratory (Hematology, Biochemistry, Urinalysis)	X	X[B]	X		X[S]		X[S]	X[S]	X		
Virology (Hepatitis B/C, HIV)	X										
Thyroid Function Tests (TSH, free T4 and free T3)	X										
Serum prolactin		X							X		
Alcohol Breath Test		X									
Urine Drug Screen	X	X							X		
Urine/Serum Pregnancy Test L	X	X							X		
Dosage administration and drug label record			X[A]		X[F]		X[F]	X[F]	X[G]		
Prior and Concomitant Medications and Significant Non-Drug Therapies	X	X	X	X	X	X	X	X	X		
Adverse Events	X[Q]	X[O]	X[P]	X[O]	X[O,P]	X[O]	X[O,P]	X[O]	X[O]	X[O]	X[K]
Seizure Checklist	X	X[N,O]	X[N,P]	X	X[N,O,P]	X	X[N,O,P]	X[N,O,P]	X[O]	X	
PANSS	X	X			X[R]		X[R]	X[R]	X[R]		
CGI-S	X	X			X[R]		X[R]	X[R]	X[R]		
CGI-C					X[R]		X[R]	X[R]	X[R]		

Period	Pre-Treatment		Treatment Phase							Post-Treatment	
Assessment / Visit	Screening Days -21 to -3	Baseline[A] Day 0	Day 1	Day 4	Day 8	Day 11	Day 15	Day 29	Day 43 (Final) [E,J]	7-day Safety follow-up[I]	30-day Safety follow-up[K]
CDSS	X	X							X		
LOF		X							X		
MSQ		X					X		X		
GAF	X	X									
Telephone contact				X[H]		X[H]				(X) [I]	(X)[K]

[A] *Following completion of baseline evaluations on Day 0, subjects meeting all eligibility criteria can be randomized and dosed on Day 1. Thus, the baseline (Day 0) evaluations and Day 1 post-dose evaluations should be performed on the same day, if possible.*

[B] *This evaluation needs to be performed at baseline only if the screening assessment was done more than 21 days beforehand, or there was a finding at screening that requires follow-up.*

[C] *Vital signs were to be performed at baseline in triplicate, with measurements at least 10 min apart, and then on Day 1 at approximately 1 hr and 4 hr post-dose. On Day 8, vital signs were performed prior to dosing, and then at approximately 1 hr and 4 hr post-dose. On Day 15 vital signs were performed prior to the morning dose of study medication and at approximately 1 hr post-dose. On Days 29 and 43, vital signs can be performed at any time after dosing. At each assessment, blood pressure and pulse were repeated in 3 positions (supine for 5 minutes, within 1 minute of standing and after 3 minutes of standing). Baseline (Day 0) vital signs do not need to be repeated if dosing was postponed until the following day (Day 1).*

[D] *On Day 1 a single 12-lead ECG was obtained approximately 1 hr and 4 hr post-dose. On Day 8 ECGs were obtained prior to the morning dose of study medication and again approximately 1 hr post-dose. On Days 15, 29 and 43, the ECG may be performed at any time during the visit. A single reading was acceptable for all planned ECG evaluations, except for Baseline, where triplicate ECGs were collected with an interval of at least 10 min between readings.*

[E] *All Day 43 evaluations should be performed when a subject discontinues from the study prematurely before completing the 6-week treatment period. This was the final evaluation for patients not continuing in the separate open-label extension study.*

[F] *At the Day 8, Day 15 and Day 29 visits, the morning dose of study medication were administered in the clinic. Prior to the visit, patients should be reminded not to take their morning dose of study medication at home.*

[G] *The last dose of study medication was taken in the morning on Day 43 in the clinic.*

[H] *Patients being treated as outpatients were contacted by telephone on Days 4 and 11; medication satisfaction, adverse events and concomitant medication use were assessed. If the patient reports significant intolerance, a dose reduction can be performed, and he/she may be asked to return to the hospital for an unscheduled visit.*

[I] *To be performed 7 days after the last dose of study medication for patients who discontinue prematurely, and those not continuing in the separate open-label extension study. If the patient does not attend the in-clinic visit, a phone call was made to the patient (or caregiver) to encourage attendance; or if unavailable, to collect adverse event information via the telephone.*

[J] *Subjects completing the 6-week treatment period were eligible for continuing treatment with evenamide in a separate open-label extension study.*

[K] *The patient was contacted 30 days after the last dose of study medication to assess the occurrence of any SAEs. This information can be collected through a telephone contact.*

[L] *Urine/serum pregnancy tests were performed for all women of childbearing potential using contraception, as well as those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or have had a tubal ligation. A serum pregnancy test was performed at Screening, Baseline and Day 43. In addition, at Baseline, a urine pregnancy test was performed for an immediate result, with the serum test providing confirmation.*

[M] *Weight and height were measured at screening and used for calculating BMI, and waist circumference were measured at screening and Day 43, in addition to routine vital signs.*

[N] *The Seizure Checklist was completed before administration of study drug and again 4 hours after dosing, assessing the entire 4-hour post-dose period.*

Period	Pre-Treatment		Treatment Phase							Post-Treatment	
Visit Assessment	Screening Days -21 to -3	Baseline[A] Day 0	Day 1	Day 4	Day 8	Day 11	Day 15	Day 29	Day 43 (Final) [E,J]	7-day Safety follow-up[I]	30-day Safety follow-up[K]

[O] *Assess since prior visit.*

[P] *Assess since prior observed dosing.*

[Q] *Adverse events were assessed from the time the patient signs the informed consent form at screening. Adverse events occurring prior to the first dose of study medication were tabulated separately from post-dose events.*

[R] *Assessments of the PANSS, CGI-S and CGI-C were to be performed approximately 1-2 hours after the dose of study medication on Days 8, 15, 29 and 43.*

[S] *Sample collection for laboratory tests on Days 8, 15 and 29 was to be performed before the dose of study medication.*

9.5.1.1 Safety Assessments

The assessment of safety was based on 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 examination
- 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)
- Seizure Checklist
- Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)
- Calgary Depression Scale for Schizophrenia (CDSS).

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 during the Screening period (from the time of signing the consent form), at Baseline, and at each visit of the study. Every untoward medical event was to be 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 to be recorded in the CRF. In addition, the patients were to be followed up for 30 days after their last dose of study medication for the occurrence of any Serious AE.

In the CRF, AEs were to be 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 to be 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 014 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 considered as "overdose" and reported immediately to the Investigator.

The details regarding reporting of overdose in India, Italy, Malaysia 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 to be 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 had a tubal ligation, at Screening and Baseline, and on Day 43 (or at early discontinuation). In addition, a urine pregnancy test was performed at Baseline for an immediate result to determine eligibility for the study; the results of the serum test were used for confirmation. Additional serum or urine pregnancy tests were to be 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) were 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.

9.5.1.1.4 Vital Signs

Vital signs assessment was performed at all scheduled evaluations. Vital signs included height (screening only; used to calculate BMI), body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. For all vital signs assessments, pulse and blood pressure were measured after the subject had been in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing. At the **baseline** visit, prior to the first dose of study medication, measurements of temperature, respiratory rate, and blood pressure and pulse (supine, standing 1 minute, standing 3 minutes), were repeated 3 times, at least 10 minutes apart, and the values were averaged to obtain the baseline values (body weight measured only once). The mean values were used in determining eligibility for the study. On Day 1, vital signs were repeated at approximately 1 and 4-hr after the first dose of study medication.

If a change *of clinical relevance* from pre-dose to post-dose was observed, the vital signs

assessment was required to be repeated as often as needed, at the discretion of the Investigator. Findings were documented on theVital 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 at all visits. In addition, virology tests (hepatitis B core and surface antibodies and surface antigen, hepatitis C antibodies, and a HIV test) and tests of thyroid function (TSH, free thyroxine [T4] and free triiodothyronine [T3]) were performed at screening.

A serum pregnancy test was performed at screening, baseline, and the final visit (Day 43 or early discontinuation) for all women of childbearing potential using contraception, and those who were post-menopausal or have had a tubal ligation. In addition, a urine pregnancy test was performed at baseline to provide an immediate result for determining eligibility of the patient for randomization, and the serum test was used for confirmation. Serum prolactin was measured at baseline and at the last visit to assess the effect of the concomitant antipsychotic, as well as any potential effect of evenamide treatment, on prolactin levels.

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 (evaluated at Screening and/or Baseline)			
- Thyroid function: TSH, free triiodothyronine (T3), and free thyroxine (T4) (Screening) - Virology: Hepatitis B and C; HIV (Screening) - Urine drug screen (Screening, Baseline and final visit) - Alcohol breath test (Baseline) - Serum prolactin (Baseline and final visit) - Serum/urine pregnancy test (Screening, Baseline and final visit) - for women of childbearingpotential using contraception, and those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or have had a tubal ligation.			

Subjects also underwent a urine drug screen at screening, and both a urine drug screen and an alcohol breath test were performed upon admittance to the hospital at baseline. A urine drug screen, along with an assessment of substance use, were 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). Subjects who were found to have positive urine results for any substances of abuse (except THC) or a positive breath alcohol, measured using a breathalyzer or similar device, were excluded from the study. In cases where the drug screen was positive at screening but was repeated at baseline and the results were negative, the patient was eligible for enrollment, dependent on the type of drug and the likelihood of abuse during the study. Patients who tested positive for THC were not to be excluded from the study; however, the diagnosis of schizophrenia was to be confirmed to ensure that they were not experiencing toxic psychosis. These cases were to be discussed with the Medical Monitor if the patient was considered for enrollment. In the current study, none of the patients tested positive for THC.

The Investigator reviewed screening laboratory values prior to the first administration of the study agent, to ensure that the subject met the protocol's inclusion/exclusion criteria. Abnormal tests at screening were repeated, and results were made available before baseline to determine if the patient was eligible for the study. 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 to be recorded on the Adverse Events CRF.

9.5.1.1.6 Electrocardiogram (ECG)

All subjects were required to have a standard 12-lead ECG performed as specified in the schedule of evaluations (Table 9-4). If the ECG was abnormal at screening, the evaluation could be

repeated, and if no clinically significant abnormalities were noted, the patient could be eligible for the study. At the baseline visit, at least 1 hour prior to the first dose, the 12-lead ECG was repeated 3 times, at least10 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. On Day 1, the ECG was repeated at approximately 1 and 4-hr after the first dose of study medication. Each ECG was to be performed before collecting the scheduled blood samples for laboratory assessments.

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 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 page of CRF.

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

9.5.1.1.7 Physical Examinations

A physical examination was performed at screening, baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline) and at the final visit (Day 43 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.

9.5.1.1.8 Neurological Examinations

A neurological examination was performed at screening, baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline), and at the final visit (Day 43 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.

9.5.1.1.9 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) were performed at screening, baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline) and Day 43 (or at early discontinuation). The examination was performed by a physician at the site who has 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.

9.5.1.1.10 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 et al, 1980; Chouinard and Margolese 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 at baseline (Day 0), and on Day 43 (or at early discontinuation).

9.5.1.1.11 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 screening and baseline to assess depressive symptoms. A score of **7 or more** at baseline excluded the patient from participating in the study. In addition to its use as a screening tool, the CDSS assessment was performed at the final visit (Day 43 or at early discontinuation) to assess changes from baseline in depressive symptoms.

9.5.1.1.12 Seizure Checklist

The Seizure Checklist was completed before administration of the study drug and again 4 hours after dosing, assessing the entire 4-hour post-dose period. 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*

9.5.1.1.13 Metabolic Syndrome

Most antipsychotics cause significant cardio-metabolic and endocrine side effects, including weight gain, insulin resistance, dyslipidemia, and hypertension (Henderson et al, 2015; Riordan et al, 2011). Up to 50% of patients treated with antipsychotics developed these complications comprising a metabolic 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.

9.5.1.1.14 Independent Safety Monitoring Board

An independent board of experts in Psychiatry and Medicine appointed by the Sponsor /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 014’. 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 014', the ISMB, based on their review of the safety data, made recommendations to the Sponsor /Newron regarding study modification/or amendment. In the current study, 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 6, dated 17th June 2021*)

The current study protocol could be 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 to be notified of 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.

9.5.1.2 Efficacy Assessments

All efficacy assessments were to be performed by the same blinded rater(s) at the site. To ensure consistency of ratings for key efficacy measures, these assessments were to be performed at the approximately the same time relative to the morning dose of study medication during the scheduled clinic visits on Days 8, 15, 29 and 43. 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 to be conducted approximately 1-2 hours post-dose. Patients were to take their concomitant antipsychotic and other medications at their residence according to their usual schedule.

9.4.3.1.1 Efficacy-related Endpoints

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
- MSQ – 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 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 evaluation was conducted at screening, baseline (Day 0), and at Days 8, 15, 29 and 43 (or at early discontinuation), and has been 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 1976) 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. 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 secondary/tertiary efficacy measures.

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 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 assessment was conducted at Screening, Baseline (Day 0), and Days 8, 15, 29 and 43 (or at early discontinuation), while the CGI-C was assessed on Days 8, 15, 29 and 43 (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. The baseline interview covered all aspects of the patient's schizophrenia symptomatology, including positive symptoms, negative symptoms, suicidality, cognition, etc., and their impact on functioning. Further details are provided in Section 12.4.2 of Study 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 Baseline (Day 0) and on Day 43 (or at early discontinuation).

9.5.1.2.4 Patient's Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, 7-point Likert-type scale for patients with schizophrenia to rate their satisfaction with their antipsychotic medication (Vernon et al, 2010). The patient's response to the question "Overall, how satisfied are you with your current antipsychotic medication(s)?" is rated by the clinician as follows: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = somewhat dissatisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat satisfied, 6 = very satisfied, and 7 = extremely satisfied. The scale has been shown to be a reliable and valid instrument for assessing antipsychotic treatment satisfaction. It has been used previously in a large placebo-

controlled study comparing antipsychotic treatments in patients with schizophrenia experiencing an acute exacerbation and was able to show a statistically significant difference between treatment groups in satisfaction with the medication (Potkin et al, 2006). The MSQ was assessed at Baseline (Day 0), Day 15 and Day 43 (or at early discontinuation).

9.5.1.2.5 Rater Training

All raters in this study 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 to be made to ensure uniform conditions across evaluations for all ratings.

If a rater was not going to be present to conduct a scheduled assessment, another qualified rater who was familiar with the patient and could be 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 12.4.5 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, LOF, and MSQ.

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. 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 16.1.10.

9.6.1 Data collection

9.6.1.1 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. If requested, copies of the eCRFs were to be made available to the appropriate regulatory agencies.

9.6.1.2 Study Monitoring

CROs [CliniRx Research Pvt Ltd., India (lead CRO); Jigsaw Clinical Research Solutions SDN Bhd, Malaysia; Remedium One Pvt Ltd, Sri Lanka; and Pharma D&S, Italy] were selected by the Sponsor to oversee the conduct of the trial. The Sponsor transferred all local responsibilities for the conduct of the trial to the respective CRO in each country. An appropriate representative of the CRO (Study Monitor) maintained contact with the Investigator and visited the site to discuss and/or retrieve data. 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 to be 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.

9.6.1.3 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 used during the analysis and reporting of data collected under Newron Pharmaceuticals S.p.A. clinical study protocol NW-3509/014/II/2019 (*Version 8, Amendment 7 dated 16th March 2022*). Complete details of the statistical methods were outlined separately in the Statistical Analysis Plan (SAP) presented in Appendix 16.1.9 of this clinical study report (CSR).

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

9.7.1.1 Analysis Populations

The following populations were defined for analysis purposes:

All Subjects Screened: This included all subjects screened for the study, including the screen failures.

Randomized population: The randomized population consisted of all subjects who were randomized to any treatment, regardless of whether any dose was taken.

Safety Population: The Safety Population consisted of all subjects who took at least one dose of study medication.

Modified Intent-to-Treat Population: A modified Intent-to-Treat (mITT) population comprised of all patients who received at least one dose of the study medication and had both a baseline and at least one post-baseline PANSS efficacy assessment.

9.7.1.2 General Considerations

All data collected in this study was documented using summary tables, patient data listings and figures. Results were displayed by each dose level of evenamide.

Continuous variables (e.g., Age) 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 count and percentages. The percentages were derived based on the total number of subjects in each dose group within the specified population.

9.7.1.2.1 Data Processing

Data was 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 014 or had discontinued from the study prior to this visit (Day 43/Early Termination visit), and the database was clean and locked. This extraction was performed even if the patients from Study 014 were continuing in Study 015.

Baseline (Day 0 and Day 1 pre-dose) was defined as the last non-missing (including unscheduled visits) measurement prior to the administration of the first dose of study drug.

For the PANSS endpoints, the baseline value was defined as follows:

If the Baseline (Day 0) value was a greater than 10% improvement from the Screening value, the baseline was to be set to missing. These values were excluded as this change in the PANSS, and variability, did not provide an unbiased assessment of the subject's baseline measure for the study.

If the Baseline (Day 0) value was missing, then baseline was to be the last non-missing value prior to administration of the first dose of study drug unless the screening assessment was performed more than 21 days before baseline.

The Baseline (Day 0) value if the assessment was done prior to one hour* after first dose of study drug.

> *The median T_{max} for evenamide is approximately 1.5 hours (generally between 1.5 and 2 hours), and thus it was unlikely that the PANSS scores would have been affected by the ingestion of evenamide.

In the case of multiple observations taken at pre-dose (e.g., vital signs and ECG), the average value of observed data was considered as baseline, as specified in the study protocol.

Day 43/ Early Termination visit: All Day 43 evaluations were to be performed when a subject discontinued from the study prematurely before completing the 6-week treatment period. Data was shown closest to the scheduled visit, in other words data were grouped with the next scheduled visit if the prior visit was completed as planned.

Study Completion and Discontinuation: The study completion date of any patient (either rolled over into Study 015 or not) from Study 014 was the Day 43 date, irrespective of whether the subject attended the Safety Follow-up (SFUP) visits or not.

Date of discontinuation was the date captured in the Day 43 form, documented by the PI, and documented in source documents, regardless of the date on which the last dose of study medication was administered.

Unscheduled Visits: All unscheduled visit data were listed regardless of whether it was collected pre-dose or post-dose. However, for the statistical analysis, unscheduled assessment data was utilized in case scheduled visit data were not available. In case of duplicates (both sets of data were available), unscheduled visit data were ignored from the analysis. All unscheduled visit data (commonly noted in ECGs, drug accountability, vital signs, etc.) were displayed as 'Unsch' and sorted by date.

9.7.1.2.2 Missing Safety Data Dates

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

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

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

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

9.7.1.3.1 Subject Disposition

Screen failures were summarized with primary reason for screening failure. A subject enrollment listing with enrollment details and screen failure reasons was provided.

The number and percentage of subjects in each analysis population (Randomized Population, Safety Population, mITT Population), disposition category (completed study, discontinued or early withdrawal, with a breakdown of the reasons for early discontinuation, and rolled over into extension or reason for not rolling over) of randomized subjects were summarized by each evenamide dose group and total. Rollover subjects were also displayed, with the percentage based on the total number of patients that completed Study 014 and were thereby eligible for continuing long-term treatment with evenamide in Study 015.

Subject listings were presented for disposition, including details of randomization (Randomization number and date) and reason for discontinuation for all randomized subjects.

9.7.1.3.2 Protocol Deviations

Protocol deviations were collected by the clinical team and provided to 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 Demographics and Baseline Characteristics

The demographic and baseline characteristics (age, sex, childbearing potential, ethnicity, race, weight, height, BMI, education, marital status, employment, housing status) were summarized by each evenamide dose group and total for the Safety, mITT, and Randomized populations.

BMI was calculated using the following formula: BMI (kg/m^2) = Weight (kg)/ (Height (m))^2

Demographics and baseline characteristics were presented in individual subject data listings for the Safety Population and screen failure subjects, separately.

9.7.1.3.4 Disease Characteristics

The disease characteristics, including duration of illness, duration of current episode, number of hospitalizations, family history of schizophrenia, and CDSS total score only at baseline, were summarized for the Safety Population. Family history of schizophrenia was also summarized as first-degree and second-degree relatives, by considering the subject's parent, sibling, or child 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 Medical History

Medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA v23.0) version. Summaries were presented for the Safety Population by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages for each evenamide dose group, and total. Each subject was counted only once in each SOC or SOC/PT summary.

9.7.1.3.7 Psychiatric History

The count and percentage of subjects in each of the reported psychiatric history categories were provided by each evenamide dose group, and total for the Safety Population.

Subject level data listings were provided for psychiatric history of schizophrenia and other psychiatric disorders.

9.7.1.3.8 Prior and Concomitant Medication

Prior medication was considered as those medications that had started and concluded before ICF signature (screening start date).

Concomitant medication was considered as those medications taken at any time during the study irrespective of the start date.

The prior antipsychotic medications (PAM) were those prior medications that were reported by sites in the PAM form within the eCRF.

Prior and concomitant medications were coded using the WHO Drug Dictionary B3 Mar2019.

Medications were presented for the Safety Population by Anatomical Therapeutic Chemical (ATC) level 4 and Preferred Name (PN) with counts and percentages for each dose group, and total. A subject who took more than one medication was counted only once if these medications belonged to the same extended ATC4 classification. In case the ATC level 4 classification was not available, the next available classification in the coding dictionary was provided.

Prior and concomitant medications were provided separately on the subject listings and summary tables. Concomitant procedures were presented in a separate subject listing, if applicable.

9.7.1.3.9 Prior and Current Antipsychotic Medication

The prior and current antipsychotic medication was summarized by each evenamide dose group, and total for the Safety Population.

Listings and summary tables of prior and current antipsychotic medication were provided separately.

9.7.1.3.10 Study Drug Accountability

Study drug accountability data were presented as an individual data listing.

9.7.1.4 Safety and Tolerability Analyses

9.7.1.4.1 Exposure and Treatment Compliance

A drug exposure table summarizes the duration of exposure and treatment compliance, by evenamide dose group for the Safety Population.

Duration of exposure was the days from Treatment start date to Treatment end date. Dosing compliance (% compliance) was assessed by calculating the number of capsules consumed and comparing that to the number of capsules expected to be consumed as follows:

> % Compliance = [Number of capsules consumed / Number of capsules expected to be consumed] * 100.

The number of capsules consumed per kit was calculated as number of dispensed capsules in the kit – number of returned/lost capsules in the kits.

The Investigator's judgement was considered in cases where the kit had been not returned/not dispensed. If the Investigator's judgement said "Complied? YES", despite the kit not being returned, then all capsules were counted in the calculation.

The number of capsules expected to be consumed per kit was estimated as (number of days from dispensation of the kit to last intake from the kit) * 2. In case there was a gap due to IP non-availability, that was adjusted in the denominator.

Compliance was summarized overall. There were some exceptional cases where manual coding was performed for compliance calculation, as per eCRF text data.

Study exposure data was presented 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, were provided. Note that more than one reason per subject may be provided for dose adjustment 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.

9.7.1.4.2 Adverse Events

Adverse events (AEs) were coded according to MedDRA v23.0.

Treatment-emergent AEs (TEAEs) are adverse events that were newly occurring or worsened in severity, compared to the pre-existing condition, after the first administration of the study medication. 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 AE were missing, then that event was considered treatment-emergent.
- If the start date for a particular event was missing and the stop date fell after the first dose date, then that event was considered treatment-emergent.
- If the start date was the same as the first dose date, then that event was considered treatment-emergent.

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

The frequency and percentage of subjects experiencing a TEAE for the Safety Population were summarized using the MedDRA SOC and PT, by evenamide dose group, and the total of all dose groups.

AE summary tables included the following, as applicable:

- Overall incidence of SAEs, AEs leading to withdrawal and AEs leading to study drug discontinuation (ADOs), and AEs leading to death for all TEAEs.
- Summary of TEAEs by SOC and by PT

- Summary of TESAEs (Treatment-emergent serious AEs) by SOC and by PT
- Summary of Treatment-related TEAEs by SOC and by PT
- Summary of AEs leading to study drug discontinuation (ADOs) by SOC and by PT
- Summary of TEAEs by maximum Severity.

Treatment-related TEAEs are the TEAEs which were considered possibly or probably related to study drug, or the relationship was unknown (not reported).

A subject with multiple occurrences of the same AE or an ongoing AE that changes in severity were counted only once under the highest reported severity or relationship. All AEs, TEAEs, and SAEs were presented in individual subject data listings.

Any information collected during the 30-day safety telephone follow-up was merged in the pharmacovigilance database for those subjects who were not rolled over into Study 015.

9.7.1.4.3 Seizure Checklist

The counts and percentages of occurrence of subjects for each seizure-like symptom reported on the Seizure Checklist was tabulated by visit, time point (pre-dose and 4 hours post dose), and dose group for the Safety Population. A subject level data listing of findings reported on the Seizure Checklist was provided.

9.7.1.4.4 Vital Signs

Vital signs assessments were performed at all scheduled evaluations. Vital signs included height (screening only and used for calculating BMI), body weight, temperature, waist circumference (collected at screening and endpoint), respiratory rate, pulse, and systolic and diastolic blood pressure. Note that at Day 29/43 there were no timepoints for tabulation as some subjects' data were collected at Day 29 or anytime and Day 43 or Post-dose. Both data were considered for summarization.

Tables presenting descriptive statistics for all the observed vital signs were provided. Changes from baseline at each visit and at endpoint (Day 43 or early discontinuation) were presented by evenamide dose group for temperature, respiratory rate, pulse, weight, waist circumference, BMI, systolic blood pressure and diastolic blood pressure at each time point.

The counts and percentages of subjects in each visit meeting the clinically notable abnormalities criteria 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.

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

9.7.1.4.5 Laboratory Evaluations

The number and percentage of subjects meeting the newly emergent clinically notable abnormalities criteria for hematology and biochemistry parameters were presented for each evenamide dose group in the Safety Population.

Urinalysis data was listed only, along with clinical significance as evaluated by the Investigator. Clinical notable value determinations for urine parameters were selected for Specific Gravity, RBC and WBC casts only.

The summary of changes from baseline to each visit were also provided for hematology and biochemistry parameters mentioned in Table 9-5 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 in Section 7.4.5 of the SAP, presented in Appendix 16.1.9.

Metropolis Healthcare Ltd, the central laboratory for all sites in India, were considered as the standard laboratory for normalization for Lanka central laboratory and Italy local laboratories, as most subjects were evaluated using the Metropolis central laboratory. Standard laboratory reference ranges for each laboratory are summarized in Appendix 4 of the SAP (Appendix 16.1.9).

The following Special Diagnostic Tests (Screening and Baseline) were listed only, without any SI unit conversion and transformation, due to the qualitative nature of these variables, except for Serum prolactin and Thyroid function tests [TSH, triiodothyronine (T3), and free thyroxine (T4)]:

- Virology: Hepatitis B and C; HIV
- Urine drug screen
- Alcohol breath test
- Serum/urine pregnancy tests

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

Cancelled laboratory tests were excluded from the SAS listings. Some of the laboratory tests were performed twice, and the latest value closest to the time of dosing was retained in the SAS listing. One subject's prolactin was taken at Day 1 instead of baseline; for statistical purposes it was considered as the baseline value. All the details are available in the vendor external data file in the study folder.

Note that some Biochemistry laboratory test results (AST/ALT) had been reported with <X (below X) and >X (higher X) values. These values were treated as X+0.1 for statistical analysis purposes.

9.7.1.4.6 Electrocardiogram (ECG)

The summary was provided for the following by each dose group at each scheduled time point for the Safety Population:

1) Change from baseline at each visit and at endpoint (Day 43 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 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.

ECG listings consisted 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.

9.7.1.4.7 Physical Examinations

Treatment-emergent post-baseline abnormal findings by 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) were summarized and listed by evenamide dose group for the Safety Population.

9.7.1.4.8 Neurological Examinations

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

9.7.1.4.9 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) were summarized and listed by evenamide dose group for the Safety Population.

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

Ratings of the ESRS-A were 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 were presented by evenamide dose group.

9.7.1.4.11 Calgary Depression Scale for Schizophrenia (CDSS)

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

CDSS scores at screening, baseline and final assessment in the Safety Population were listed.

9.7.1.4.12 Global Assessment of Functioning (GAF)

The GAF assigns a clinical judgment in numerical fashion to the individual's overall level of functioning. Impairments in psychological, social and occupational functioning are considered, but those related to physical or environmental limitations are not. The GAF should be used to rate functioning for the current period (i.e., the level of functioning at the time of the evaluation).

The scale ranges from 0 (inadequate information) to 100 (superior functioning) and is divided into 10-point ranges of functioning. The description of each 10-point range has two components: the first part covers severity, and the second part covers functioning. The rater is instructed to start at either the top or the bottom of the scale and go up/down the list until the most accurate description of functioning for the individual is reached. Either the symptom severity or the level of functioning, whichever is the worse of the two, should be assessed. The categories above and below should be checked to ensure that the most accurate one has been chosen. Within the 10-point category in the chosen range the number that is most descriptive of the overall functioning of the individual should be selected.

In this study, the GAF was used as a screening tool. A score of 50 or less at the screening and baseline visits was required for inclusion of the patient in the study. Data were listed and summarized for the Safety Population.

9.7.1.5 Analysis of Efficacy Parameters

9.7.1.5.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS evaluation was conducted at Screening, Baseline (Day 0), and at Days 8, 15, 29 and 43 (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 were 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 presented for mean, median, and range (min, max), and analyzed by using a paired t-test.

A non-parametric signed Rank test was required, as data size in each dose group was more than 30 subjects with multiple visits (in fact, the number of subjects in each dose group was minimally 50, and there were data from 4 post-dose interval assessments); therefore, testing of normality was not done.

Demonstration of a clinically relevant improvement from baseline to endpoint (Day 43 or early discontinuation) on the PANSS total score for any dose of evenamide was to be considered as evidence of benefit as adjunctive therapy in patients with TRS showing inadequate response to their current antipsychotic.

'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 Symptoms sub-scale.

For improvement categorization - 4 points change (improvement) was used instead of 20% improvement point.

To date, no prospective trial has been published that evaluated the benefit of a new chemical entity as an add-on to an antipsychotic in patients with TRS. Currently, available data suggest that the benefits of an intervention as an add-on in TRS patients is of low magnitude, i.e., 10% to 20%. An exploratory analysis was performed to describe the magnitude of reduction in PANSS total score over the 6-week treatment period.

A graph, including mean change from baseline of PANSS Total Score, Total Positive Score, Total Negative Score, and Total General Psychopathology Score for each of the dose groups was presented by visit.

All the above analyses were performed on the modified Intent-to-Treat (mITT) population.

9.7.1.5.2 Clinical Global Impression (CGI)

The CGI 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-S assessment was conducted at Screening, Baseline (Day 0), and Days 8, 15, 29 and 43 (or at early discontinuation), while the CGI-C was assessed on Days 8, 15, 29 and 43 (or at early discontinuation).

Change from baseline to endpoint on the CGI-S was summarized, and a graph, including mean change from baseline of CGI-S of the treatment groups, 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.

The proportion of patients rated improved (score of 1, 2 or 3, corresponding to 'very much', 'much'

or 'minimally' improved, respectively) on the CGI-C at Days 8, 15, 29 and 43 (or at early discontinuation) were summarized with n (%). In addition, the mean ratings at each post-dose visit of CGI-C were summarized.

All the above analyses were performed on the modified Intent-to-Treat (mITT) population.

9.7.1.5.3 Strauss-Carpenter Level of Functioning (LOF) scale

The LOF was conducted at Baseline (Day 0) and on Day 43 (or at early discontinuation). Change from baseline to endpoint on the Total score and Sub-scale scores on the LOF were summarized and analyzed within each dose group by using a paired t-test. A graph depicting mean change from baseline was presented.

Analyses were performed on the modified Intent-to-Treat (mITT) population.

9.7.1.5.4 Patient's Medication Satisfaction Questionnaire (MSQ)

The MSQ was assessed at Baseline (Day 0), Day 15 and Day 43 (or at early discontinuation). Changes from baseline to endpoint on the MSQ were summarized and analyzed by using a paired t-test within each dose group. A graph depicting mean change from baseline was presented by visit.

Analyses were performed on the modified Intent-to-Treat (mITT) population.

9.7.1.5.5 Efficacy Estimands

In view of the recent guideline ICH E9 R1, efficacy estimands have been explained below for the evaluation of the efficacy endpoint (PANSS Total score).

The Section 9.3.3 in the CSR describes details of Intercurrent Events (ICEs), e.g., adverse events, lack of efficacy, loss to follow-up and major protocol deviations, that could lead to treatment disruption and discontinuation, or discontinuation from the study.

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 Day 43.

The 'Hypothetical estimand' was considered as the primary efficacy estimand where base analysis was based on data observed (OC) prior to the study treatment withdrawal. Those discontinued subjects who had provided post withdrawal data due to rescue medication were removed from the analysis, as applicable.

'Treatment policy' strategy was considered as a Supportive efficacy estimand where actual values of the variable were used, regardless of whether the intercurrent event had occurred. In other words, all observations, including those made by patients withdrawn from treatment and returning

at Day 43, regardless of other medication taken, were utilized.

In cases where a subject had not taken any rescue medication and had not added any further efficacy data, LOCF was considered as a supportive efficacy estimand.

Table 9-6: The Estimand Panel

Endpoint	Estimand Attributes				Analysis
	Population	Variable	Intercurrent events	Summary	
Primary efficacy endpoint	mITT	Change from baseline to Day 43 in PANSS total score	Hypothetical: What was the effect if patients continue treatment until completion (OC).	Mean change at Day 43	Paired t- test
Supportive Efficacy estimand@	mITT	Change from baseline to Day 43 in PANSS total score	Treatment policy: What was the effect if withdrawn patients start on rescue medication.	Mean change at Day 43	Paired t- test
Sensitivity: LOCF@	mITT	Change from baseline to Day 43 in PANSS total score	Robustness analysis (Treatment Policy): Use of LOCF for imputation of post dose withdrawal data.	Mean change at Day 43	Paired t- test
Sensitivity: Multiple Imputation	mITT	Change from baseline to Day 43 in PANSS total score	Robustness analysis (Treatment Policy): Use of Multiple Imputation for imputation of post dose withdrawal data.	Mean change at Day 43	Paired t- test

@ In cases where a subject had not taken any rescue medication and not had added any further efficacy data, LOCF was considered as supportive.

9.7.1.5.6 Additional Exploratory Efficacy Analysis – Between Group Comparisons

Additional analyses were planned to explore the dose-response relationship, based on the design (i.e., patients were randomized to doses of 7.5, 15 and 30 mg *bid*, and raters were blinded to the dose being administered) the comparisons between dose groups were performed for the primary efficacy parameter - change from baseline to endpoint, and the responder (≥20% reduction) analysis for the PANSS total score.

Mean changes from baseline to endpoint (Day 43 or early discontinuation) on the PANSS total score were compared between the evenamide dose groups using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline in the PANSS total score obtained at the scheduled visits at Days 8, 15, 29 and 43, respectively. An unstructured covariance (UN) matrix was used to model the within-subject errors. The Kenward-Roger (KR) approximation was used to estimate denominator degrees of freedom. If the model for unstructured covariance matrix failed to converge, the heterogeneous Toeplitz covariance structure, followed by heterogeneous auto regressive covariance structure, was to be used. The assumptions of the model, including normality, were evaluated using residual and other diagnostic plots of model fit.

The null hypothesis is that the mean difference between the dose groups is zero, versus the alternative hypothesis that this difference is not zero. The order of testing was as described in Section 9.7.1.5.7 below. Inferential statistics to be presented based on this model are least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals as estimated at endpoint Day 43.

9.7.1.5.7 Multiplicity Adjustment – Gate-Keeping Strategy

If the overall treatment p-value was significant at a 5% two-sided alpha level, the following gate-keeping strategy was performed to adjust for false positives arising due to multiple comparisons between dose groups.

First, a combined dose group (15 + 30 mg *bid*) was tested versus the low dose (7.5 mg *bid*). If it was significant, the high dose (30 mg *bid*) was to be tested against the low dose (7.5 mg *bid*), followed 15 mg *bid* vs low dose (7.5 mg *bid*) at the same 5% alpha level.

9.7.1.6 Interim analysis

An interim safety analysis was performed at the request of the ISMB after 50 patients were randomized to the 7.5 mg (n=26) and 15 mg (n=24) *bid* doses and completed their participation in this study, to determine the safety of the doses administered. The results of this analysis were reviewed by the ISMB, which determined that it was safe to proceed with the introduction of the 30 mg *bid* dose group. The ISMB also requested a review of the safety data from the first 100 patients who completed their participation in the study. After their review, the ISMB recommended that the study could continue as designed.

Later, as requested by the ISMB and implemented in protocol *Amendment 7 dated 16th March 2022*, an interim efficacy analysis was performed for this study after the first 100 patients completed their participation in the trial. This analysis was performed to assess the risk/benefit ratio of evenamide in patients with TRS and determine whether continuing these patients on long-term treatment with evenamide in Study 015 was justified. To maintain the blind on the treatment assignments, the data from all patients were combined in a single evenamide group for the analysis, and treatment assignments for individual patients were not revealed. Descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum, and 95% confidence intervals) were provided for actual values and changes from baseline at each time-point for the following continuous efficacy measures: PANSS - Total score, Positive Symptoms sub-scale, General Psychopathology sub-scale, Negative Symptoms sub-scale, and Marder Factors; CGI-S; MSQ; and LOF. For the CGI-C, the number and percentage of patients in each category was presented at each time-point, and the proportion of patients showing improvement (score of 1, 2 or 3), as well as the mean score at endpoint, were calculated. For each of these variables, additional analyses were performed to assess the effects of demographic factors and patient characteristics (e.g., age, gender, and duration of illness) on the outcome.

9.7.2 Determination of Sample Size

Approximately 180 patients with treatment-resistant schizophrenia were to be included in this study, with a minimum of 50 patients randomly assigned to each treatment group (evenamide 7.5 mg, 15 mg and 30 mg, *bid*). The sample size determination was not based on statistical power considerations. The primary objective of this study was the assessment of safety and tolerability. The sample size was considered adequate for a preliminary evaluation of tolerability of the doses administered and for determining a potential signal of a dose-dependent effect on efficacy.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The original protocol dated 7th November 2019 was amended [total 8 amendments overall and one country level for India (8.1) * and Sri Lanka (8.2)] during conduct of the study. Copies of the protocol and protocol amendments are provided in Appendix 16.1.1. Information related to each of these amendments is outlined below.

**Both the protocol amendments 8.0, dated 03rd May 2022 and 8.1, dated 29th Jun 2022 could not be implemented in India due to Sponsor's decision (on 4th Nov 2022) to stop enrolment after experiencing long delays in getting approval and execution of Amendment 8.0.*

9.8.1.1 Amendment 1, dated 10th December 2019 implemented the following changes:

This amendment to the original protocol for Study NW-3509/014/II/2019 (Study 014) was made based on the recommendation of the Subject Experts Committee (SEC - Neurology and Psychiatry) of the Drugs Controller General of India (DCGI) in their review of the original protocol (version 1.0, dated 07 November 2019):

- Section 13.1.6 of the protocol, Reporting of Overdose, was modified to include the procedures to be followed based on Newron's safety reporting standards. The new language conforms to the reporting requirements specified in previous clinical study protocols for evenamide.

The changes made in this amendment were specific to India.

9.8.1.2 Amendment 2, dated 7th February 2020 implemented the following changes:

This amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) was made to increase the number of centers and countries participating in the study to facilitate enrolment and expedite completion of the trial.

- The study centers were extended to up to 25 centers, with sites in Sri Lanka and Italy added.
- 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 Van de Griend, 2014) and feedback from treating physicians, the maximum dose of quetiapine that can be used as a soporific was increased from 50 mg to 150 mg hs. Patients could be enrolled into the study on this dose of quetiapine, if stable for at least 4 weeks, or could receive this dose as rescue medication to treat insomnia during the treatment period of the study.

- There were no restrictions on the maximum dose of lorazepam, or equivalent short half-life benzodiazepine, being given at screening; however, as required in the current protocol, the dose must have been stable for at least 2 months. A stipulation that this stable dose should not be reduced, or the drug discontinued during the 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.
- Section 13.1.6, Reporting of overdose was updated. Procedures to be followed in Italy, Malaysia and Sri Lanka were included.

Other minor changes to the protocol made in this amendment included 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 would be 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 for 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.

9.8.1.3 Amendment 3, dated 5th July 2020 implemented the following changes:

This amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) updated information related to the study and corrected some errors and inconsistencies in the protocol. The changes implemented in this amendment included the following:

- Change in the local CRO managing the study in Malaysia. The contact information for the new CRO, Jigsaw Clinical Research Solutions SDN Bhd, was updated.
- Addition of the local CRO for Italy.

- Modification in the estimated Planned Trial Period in the Synopsis, to better reflect the status of the study at that time, and the expectations for enrolment in light of the global COVID-19 pandemic.
- Modification of the number of sites expected to participate in the study.
- 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 incorporation of the information into the sections on rationale for dose and overdosage was added.
- Replaced "Triiodothyronine (T3) uptake" with "free T3" in the thyroid panel, as measurement of T3 uptake was not performed as a standard at most sites.
- Requirements for pregnancy testing were revised. Pregnancy testing was to be performed for all post- menopausal women, and not just those who had been post-menopausal for less than 2 years.
- The language regarding the use of a central laboratory was modified to indicate that laboratories within in each country were to be used.
- Corrected clinically notable values for several laboratory hematology parameters.
- Other minor errors or omissions noted in the protocol were also corrected.

9.8.1.4 Amendment 4, dated 18th September 2020, implemented the following changes.

This amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) was done in response to the requests made by the Agenzia Italiana del Farmaco (AIFA) to allow opening of investigational centers in Italy.

- 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 discontinue treatment but remain in the study and return for scheduled visits.
- The inclusion and exclusion 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 summary of Clinical Pharmacology Study NW3509-007 was updated.
- 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.

- Additional details of the procedures to be followed in the telephone contacts with the patients on Days 4 and 11 were provided.
- An appendix was added to the protocol summarizing the guidelines for prior and concomitant medications that were permitted or prohibited in the study. The summary was presented by drug class.
- Additional modifications were made to the Study 014 protocol in this amendment to correct minor errors and omissions.

9.8.1.5 Amendment 5, dated 4th February 2021, implemented the following changes:

This amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) modified the inclusion criteria related to the duration of the diagnosis of schizophrenia and the classification of the patient as "treatment-resistant." Investigators participating in the study had indicated that the requirement that the diagnosis of schizophrenia has been made within the past 10 years was too restrictive and excludes many patients who would otherwise be eligible for the trial. Their inclusion would increase the generalizability of data from this trial. Based on these observations and findings in published literature, amendment 5 made the following changes to the protocol:

- Patients were eligible for the study if the diagnosis of schizophrenia was made within the past **15 years**.
- Additionally, patients must be identified as being treatment-resistant within the past **10 years**.

Additional modifications were made to the Study 014 protocol in this amendment to correct minor errors and omissions, including the following:

- Corrections were made to Section 10.4 of the protocol describing the procedure for randomization of subjects to treatment, including the format of the randomization numbers.
- Clarification of the timing of the following assessments was added in the Schedule of Evaluations; Section 11.4 Visit Schedule and Assessments, and in Section 12.3 Safety Assessments: vital signs; ECGs; ratings of PANSS, CGI-S and CGI-C; sample collection for laboratory tests.

9.8.1.6 Amendment 6, dated 17th June 2021, implemented the following changes:

This amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) modified the dosing and the randomization to the three treatment groups, based on the interim safety assessment by the ISMB of the data from the first 50 patients randomized in Study 014, as well as the available results from Study 008 (NW-3509/008/II/2019). Based on their review of the data, the ISMB determined that it was safe to proceed with initiation of the 30 mg *bid* dose and the originally planned randomization ratio of 1:1:2 to the 7.5, 15 and 30 mg *bid* dose groups, respectively. Subsequently, data from Study 008 showed no evidence of efficacy for doses of

7.5 and 15 mg *bid* 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. Therefore, this amendment led to the discontinuation of the evenamide 7.5 mg *bid* dose group from the study, and the modification of the randomization to a 1:3 ratio for the 15 mg *bid* and 30 mg *bid* dose groups, respectively, so that the number of patients randomized to each of the three treatment groups would be approximately equal at the end of the study.

As a result of the 7.5 mg *bid* dose group being discontinued from the study, newly enrolled patients would no longer be continuing on this dose in the optional open-label extension study (NW-3509/015/II/2019 [Study 015]). In addition, those patients currently enrolled in Study 014 at 7.5 mg *bid* under the previous version of the protocol had their dose increased to 15 mg *bid* upon entry into Study 015. The sections of the protocol describing patient randomization were updated to reflect the discontinuation of the 7.5 mg *bid* dose group and the revised randomization ratio of 1:3 for the 15 mg *bid* and 30 mg *bid* dose groups, respectively. Related to this, a new Part 3 randomization paradigm was added in the protocol.

Additional modifications were made to the Study 014 protocol in this amendment related to the discontinuation of the 7.5 mg *bid* dose group and to correct minor errors and omissions, including the following:

- The planned trial period dates were modified to reflect the status of the study more accurately.
- The number of patients expected to be enrolled in each of the three treatment groups was modified.
- The Background Information (Section 7.1) was updated to include summaries of the completed Study 008 and Study 010.
- The information on Overdosage (Section 10.6) was updated to include data on the 60-mg single dose from the Study 010.
- The section on informed consent (Section 11.1) was revised to indicate that the Informed Consent Form would be updated to include information on the discontinuation of the 7.5 mg *bid* dose, and to specify that patients would need to be reconsented.
- Corrections were made to the definition of women requiring pregnancy tests 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 description of the interim safety assessment by the ISMB, based on data from the first 50 patients completing their participation in the study, was revised in Section 15.8 to indicate that it had been completed.
- The requirements for financial disclosure were clarified in Section 17.12.
- The Benefit/Risk Assessment for evenamide (Appendix 7) was updated to incorporate results from completed studies and make it more specific to Studies 014 and 015.

9.8.1.7 Amendment 7, dated 16th March 2022, implemented the following changes:

- The primary purpose of this amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) was to add an interim analysis of the data for all efficacy measures from the first 100 patients who completed their participation in the study. This analysis was performed as the ISMB had requested evidence of benefit following their review of the safety data from these 100 patients, to determine whether a benefit-risk assessment justified the long-term treatment of patients with evenamide. To avoid bias, this analysis was performed in a group-blinded manner (all evenamide dose groups combined), and results were not made available to any personnel directly involved in the conduct of the study.
- Section 15, Statistical methods was updated to include details of interim efficacy analysis and its reference was included in Section 17, References.

9.8.1.8 Amendment 8*, dated 03 May 2022, implemented the following changes:

- The primary purpose of this amendment to the protocol for Study NW-3509/014/II/2019 (Study 014) was to increase the sample size from 150 to 180 patients. This increase in sample size was performed to ensure that minimally 50 patients were randomized to each of the three treatment groups. The following sections of the protocol were updated: Synopsis, Section 7.3 Study rationale, Section 9.1 Study design and methods, Section 10.4 Blinding and Randomization, and Section 15.1 Sample size and power considerations.
- Additionally, this amendment removed Malaysia as a participating country in the study, due to extensive delays in obtaining regulatory approval and the fact that no patient had been randomized to treatment.

**Both the protocol amendments 8.0, dated 03rd May 2022 and 8.1, dated 29th Jun 2022 could not be implemented in India due to the Sponsor's decision (on 4th Nov 2022) to stop enrolment after experiencing long delays in getting approval and execution of amendment 8.0.*

9.8.1.9 Amendment 8.1*, dated 29 June 2022, implemented the following changes:

The purpose of this amendment, which was specific to India, was to modify recent changes to the contraception requirements for Study NW-3509/014/II/2019 (Study 014) that had been previously approved in India and led to the enrollment of 103 patients in the study. The changes introduced new language that had made the protocol virtually impossible to recruit patients and would have

been difficult for patients to comply with. The changes were also objected to by Investigators. Changes made to the contraception requirements in Amendment 4 to the protocol (dated 18 September 2020), based on a request from the Italian regulatory authority (AIFA), were no longer considered necessary in light of the fact that all reproductive and developmental toxicity studies had been completed without any evidence of maternal or fetal toxicities. Based on this, the following changes were made to the protocol:

- The language in Inclusion Criterion #2 and Exclusion Criterion #27 was modified to revert to the original language for Study 014 that was approved by the DCGI on 18 February 2020. The language once again stated that women of child-bearing potential who were using "adequate contraception, as determined by their Health Care Provider", would be eligible for the study.
- The new language in the selection criteria 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.*
- Similar changes were made in Section 13.1.8, Pregnancy, and in Appendix 5, Contraception Requirements for Women.

**Both the protocol amendments 8.0, dated 03rd May 2022 and 8.1, dated 29th Jun 2022 could not be implemented in India due to the Sponsor's decision (on 4th Nov 2022) to stop enrolment after experiencing long delays in getting approval and execution of amendment 8.0.*

9.8.1.10 Amendment 8.2, dated 15 July 2022, implemented the following changes:

The purpose of this amendment, which was specific to Sri Lanka, was to modify recent changes to the contraception requirements for Study NW-3509/014/II/2019 (Study 014) that had been previously approved in Sri Lanka and led to the enrollment of 103 patients in the study. The changes introduced new language that had made the protocol virtually impossible to recruit patients and would have been difficult for patients to comply with. The changes were also objected to by Investigators. Changes made to the contraception requirements in Amendment 4 to the protocol (dated 18 September 2020), based on a request from the Italian regulatory authority (AIFA), were no longer considered necessary in light of the fact that all reproductive and developmental toxicity studies had been completed without any evidence of maternal or fetal toxicities. Based on this, the following changes were made to the protocol:

- The language in Inclusion Criterion #2 and Exclusion Criterion #27 was modified to revert to the original language for Study 014 that was approved by the NMRA on 21 December 2020. The language would now once again state that women of child-bearing potential who

were using “adequate contraception, as determined by their Health Care Provider”, would be eligible for the study.

- Similar to Amendment 8.1, changes were made in Section 13.1.8, Pregnancy, and in Appendix 5, Contraception Requirements for Women.

9.8.2 Changes in the Planned Analyses

Additional exploratory efficacy analysis – between group comparisons for efficacy measures described in Section 9.7.1.5.6, had been added, which were not mentioned in the protocol.

Also, post hoc analyses were performed for all efficacy measures to analyze changes from baseline for all evenamide doses combined in a single group.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 186 subjects were screened, and 25 (13.44%) of these subjects were screen failures (Table 14.1.1.1). The reasons for screen failure were as follows: withdrawal of consent by 9 subjects (4.84%), not meeting entry criteria for 7 subjects (3.76%), other reasons for 5 subjects (2.69%), and lost to follow-up for 4 subjects (2.50%). Eligibility criteria for all subjects are presented in Listing 16.2.1.1.

The subject disposition, including details of the number of subjects randomized, completed, and discontinued, along with the reason for discontinuation, is provided in Table 10-1 and summarized in Listing 16.2.1.2.

A total of 161 subjects were randomized into the study, 153 subjects (95.03%) completed the study, and 8 subjects (4.97%) prematurely discontinued from the study. The most common reason for premature discontinuation was withdrawal of consent (7 subjects, 4.35%). Overall, 144 subjects (94.12%) rolled over into the Extension study (Study 015); of the 9 subjects who were not rolled over, 7 subjects (4.58%) did not give consent and 2 subjects (1.31%) were due to non-compliance.

Table 10-1: Subject Disposition – Randomized Population

Disposition	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=51) n (%)	Total (N=161) n (%)
Randomized Population [a]	50 (100.0)	60 (100.0)	51 (100.0)	161 (100.0)
Safety Population [b]	50 (100.0)	60 (100.0)	50 (98.0)	160 (99.4)
Modified Intent-to-Treat Population [c]	48 (96.0)	59 (98.3)	49 (96.1)	156 (96.9)
Completed Study	49 (98.0)	56 (93.3)	48 (94.1)	153 (95.0)
Discontinuation or Early Withdrawal	1 (2.0)	4 (6.7)	3 (5.9)	8 (5.0)
Primary Reason for Discontinuation or Early Withdrawal				
Withdrawal of consent	0 (0.0)	4 (6.7)	3 (5.9)	7 (4.4)
Adverse Event	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.62)
Major protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	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)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rolled over into Extension (Study 015)	45 (66.2)	53 (93.0)	46 (164.3)	144 (94.1)
Did not roll over into Extension	4 (5.9)	3 (5.3)	2 (7.1)	9 (5.9)
Reason for Non-Roll over				
Did Not Consent	4 (5.9)	1 (1.7)	2 (7.1)	7 (4.6)
Non-Compliance	0 (0.0)	2 (3.5)	0 (0.0)	2 (1.3)

Abbreviations: N - Total number of subjects in the Randomized Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Randomized Population.
Percentage for Rolled over/ non-Rolled over subject was based on total number of subjects in each group (N) under number of subjects completed study.

[a] Randomized Population consists of all subjects who were randomized to any treatment, regardless of whether any dose was taken.
[b] Safety Population: The safety Population consists of all subjects who took at least one dose of study medication.
[c] Modified Intent-to-Treat Population (mITT): A mITT population comprises all patients who received at least one dose of the study medication and had both a baseline and at least one post-baseline PANSS efficacy assessment.
Source: Table 14.1.1.2; Listing 16.2.1.2

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 23 subjects (14.4%) had a major protocol deviation, of which 14 (28%) were from evenamide 30 mg *bid*, 6 (12%) from evenamide 7.5 mg *bid*, and 3 (5%) from evenamide 15 mg *bid* groups.

Table 10-2: Summary of Major and Critical Protocol Deviations - Safety Population

Category	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Subjects with Major Protocol Deviation	6 (12.0)	3 (5.0)	14 (28.0)	23 (14.4)
Subjects with Critical Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: 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.
Source: Table: 14.1.2; Listing 16.2.2

11 SAFETY EVALUATION

11.1 Data Sets Analyzed

Overall, 161 subjects (100.0%) were allocated to treatment and included in the Randomized Population, including 50 subjects in evenamide 7.5 mg *bid*, 60 in evenamide 15 mg *bid* group and 51 in evenamide 30 mg *bid* group (Table 10-1). Of these, 160 subjects (99.38%) received at least 1 dose of study drug and qualified for inclusion in the Safety Population. A total of 156 subjects (96.89%) had received at least one dose of the study medication and had both a baseline and at least one post-baseline PANSS efficacy assessment and thereby qualified for the mITT Population. The allocation of each subject to treatment is detailed in 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 (69.38%), Asian (98.13%), single (50.00%), not employed (78.13%), living with family (100%) and had education of 9-16 years (69.38%).

The mean (SD) age of the subjects was 37.7 (9.71) years, ranging from 20 to 68 years. The mean (SD) weight, height and body mass index were 67.5 (15.14) kg, 163.8 (8.37) cm. and 25.1 (5.16) kg/m^2, respectively. No demographic or baseline characteristics differed notably between the treatment groups.

Demographic and baseline characteristics data for the Safety, mITT and Randomized Populations are presented in Table 14.1.3.1.1, Table 14.1.3.1.2 and Table 14.1.3.1.3, respectively and by subject details for 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=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
Age (years)	n	50	60	50	160
	Mean (SD)	37.7 (10.38)	37.2 (9.74)	38.3 (9.13)	37.7 (9.71)
	Median	37.0	35.0	38.0	37.0
	Min, Max	23,68	21,62	20,64	20,68
Weight (kg)	n	50	60	50	160
	Mean (SD)	66.6 (15.56)	66.2 (12.63)	69.9 (17.33)	67.5 (15.14)
	Median	66.6	64.8	65.8	65.8
	Min, Max	34,120	45,91	42,143	34,143
Height (cm)	n	50	60	50	160
	Mean (SD)	163.8 (9.85)	163.8 (7.87)	163.9 (7.44)	163.8 (8.37)

Characteristics	Statistic	Evenamide 7.5 mg *bid* (N=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
	Median	164.5	164.1	164.0	164.0
	Min, Max	137,183	145,183	149,182	137,183
BMI (kg/m^2)	n	50	60	50	160
	Mean (SD)	24.8 (5.28)	24.7 (4.60)	26.0 (5.65)	25.1 (5.16)
	Median	24.3	24.5	24.7	24.5
	Min, Max	15,37	17,35	16,44	15,44
Sex					
Male	n (%)	32 (64.00)	42 (70.00)	37 (74.00)	111 (69.38)
Female	n (%)	18 (36.00)	18 (30.00)	13 (26.00)	49 (30.63)
Childbearing Potential [a]					
Yes	n (%)	14 (77.78)	11 (61.11)	9 (69.23)	34 (69.39)
No	n (%)	4 (22.22)	7 (38.89)	4 (30.77)	15 (30.61)
Race					
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	n (%)	49 (98.00)	60 (100.0)	48 (96.00)	157 (98.13)
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 or Caucasian	n (%)	1 (2.00)	0 (0.0)	2 (4.00)	3 (1.88)
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 / Not Latino	n (%)	50 (100.0)	60 (100.0)	50 (100.0)	160 (100.0)
Education					
1-8 years	n (%)	11 (22.00)	12 (20.00)	10 (20.00)	33 (20.63)
9-16 years	n (%)	35 (70.00)	42 (70.00)	34 (68.00)	111 (69.38)
>16 years	n (%)	4 (8.00)	6 (10.00)	6 (12.00)	16 (10.00)
Marital Status					
Married	n (%)	18 (36.00)	26 (43.33)	21 (42.00)	65 (40.63)
Single	n (%)	29 (58.00)	26 (43.33)	25 (50.00)	80 (50.00)
Stable union	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Widow / Widower	n (%)	0 (0.0)	2 (3.33)	0 (0.0)	2 (1.25)
Divorced	n (%)	3 (6.00)	6 (10.00)	4 (8.00)	13 (8.13)
Employment					

Characteristics	Statistic	Evenamide 7.5 mg *bid* (N=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
Full-Time Employment	n (%)	4 (8.00)	10 (16.67)	3 (6.00)	17 (10.63)
Part-Time Employment	n (%)	5 (10.00)	5 (8.33)	8 (16.00)	18 (11.25)
Not employed	n (%)	41 (82.00)	45 (75.00)	39 (78.00)	125 (78.13)
Housing Status					
Living alone	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living with family	n (%)	50 (100.0)	60 (100.0)	50 (100.0)	160 (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)

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

11.2.2 Disease Characteristics

The study subjects enrolled in the current study must have 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.

The mean (SD) duration of schizophrenia was shortest in evenamide 15 mg *bid* treated group [6.3 (3.12)] compared to evenamide 7.5 mg *bid* and 30 mg *bid* treated groups with 7.1 (2.54) years and 7.1 (3.50) years, respectively, with an overall mean (SD) of 6.8 (3.09) years. The mean (SD) duration of the current episode of schizophrenia was 7.9 (4.90) months. The mean (SD) duration of the current episode in evenamide 30 mg *bid* treated subjects was shorter [6.2 (3.23) months] compared to evenamide 7.5 mg *bid* treated subjects [8.6 (5.46) months] and evenamide 15 mg *bid* treated subjects [8.7 (5.27) months]. The mean (SD) number of psychiatric hospitalizations was 0.3 (0.71) with a range of 0-4. Most of the subjects [121 (75.6%)] did not have a family history of schizophrenia. Among those who had a family history of schizophrenia, it was usually the 1st degree relatives [22 (13.8%)]. 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 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=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
Duration of Illness - Schizophrenia (Years)[a]	n	50	60	50	160
	Mean (SD)	7.1 (2.54)	6.3 (3.12)	7.1 (3.50)	6.8 (3.09)
	Median	7.2	6.2	7.3	6.6
	Min, Max	1,15	1,15	1,15	1,15
Duration of Current Episode of Schizophrenia (Months)[b]	n	50	60	50	160
	Mean (SD)	8.6 (5.46)	8.7 (5.27)	6.2 (3.23)	7.9 (4.90)
	Median	6.4	8.3	5.6	6.4
	Min, Max	3,25	2,23	2,15	2,25
Number of Psychiatric Hospitalizations	n	50	60	50	160
	Mean (SD)	0.2 (0.48)	0.3 (0.72)	0.4 (0.88)	0.3 (0.71)
	Median	0	0	0	0
	Min, Max	0,2	0,4	0,3	0,4
Family History of Schizophrenia					
None	n (%)	36 (72.0)	46 (76.7)	39 (78.0)	121 (75.6)
1st Degree Relatives [c]	n (%)	7 (14.0)	8 (13.3)	7 (14.0)	22 (13.8)
Father	n (%)	1 (2.0)	3 (5.0)	2 (4.0)	6 (3.8)
Mother	n (%)	2 (4.0)	4 (6.7)	1 (2.0)	7 (4.4)
Brother	n (%)	2 (4.0)	1 (1.7)	3 (6.0)	6 (3.8)
Sister	n (%)	2 (4.0)	0 (0.0)	1 (2.0)	3 (1.9)

Abbreviations: 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.
Source: Listing 16.2.4.3.1, Listing 16.2.15; Table 14.1.3.2

11.2.3 Medical History and Psychiatric History

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

Overall, 33 subjects (20.6%), including 10 subjects (20.0%) in evenamide 7.5 mg *bid* treated

group, 14 subjects (23.3%) in evenamide 15 mg *bid* treated group and 9 subjects (18%) in evenamide 30 mg *bid* treated group reported having any medical history. Diabetes Mellitus was the most reported medical history by 10 subjects (6.3%) overall, including 5 subjects (10.0%) in evenamide 7.5 mg *bid* treated group, 3 subjects (5.0%) in evenamide 15 mg *bid* treated group and 2 subjects (4.0%) 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, 24 subjects (15%), including 3 subjects (6%) in evenamide 7.5 mg *bid* treated group, 8 subjects (13.3%) in evenamide 15 mg *bid* treated group and 13 subjects (26.0%) in evenamide 30 mg *bid* treated group reported at least one psychiatric history finding other than schizophrenia. The most common finding in the psychiatric records was, by preferred term (PT): mental disorder (verbatim term, psychiatric illness) in 11 subjects (6.9%) overall [1 subject (2%) in evenamide 7.5 mg *bid* treated group, 2 subjects (3.3%) in evenamide 15 mg *bid* treated group and 8 subjects (16.0%) in evenamide 30 mg *bid* treated group], followed by insomnia (PT) in 6 subjects (3.8%) overall [2 subjects (4.0%) in evenamide 7.5 mg *bid* treated group, 3 subjects (5.0%) in evenamide 15 mg *bid* treated group and a single subject (2.0%) in evenamide 30 mg *bid* treated group].

The proportion of subjects with each of the reported medical or psychiatric history terms did not differ notably between the treatment groups, except mental disorder which was reported more frequently in evenamide 30 mg *bid* treated group.

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. These were generally characteristic of subjects with schizophrenia.

Overall, 101 subjects (63.1%), including 32 subjects (64.0%) in evenamide 7.5 mg *bid* treated group, 37 subjects (61.7%) in evenamide 15 mg *bid* treated group and 32 subjects (64.0%) in evenamide 30 mg *bid* treated group had a record of prior medications other than antipsychotics. The most commonly used prior medications were Trihexyphenidyl (ATC class: Tertiary amines) [69 subjects (43.1%) overall] and Lorazepam (ATC class: Benzodiazepine derivatives) [28 subjects (17.5%) overall].

Overall, 138 subjects (86.3%), including 41 subjects (82.0%) in evenamide 7.5 mg *bid* treated group, 55 subjects (91.7%) in evenamide 15 mg *bid* treated group and 42 subjects (84.0%) 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) [106 subjects (66.3%) overall] and Lorazepam (ATC class: Benzodiazepine

derivatives) [33 subjects (20.6%) overall]. The number of subjects who had a record of concomitant medications did not differ notably 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 160 subjects in the Safety Population (100%), including 50 subjects (100%) in evenamide 7.5 mg *bid* treated group, 60 subjects (100%) in evenamide 15 mg *bid* treated group and 50 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 PAM were Risperidone [135 subjects (84.4%) overall] and Olanzapine [117 subjects (73.1%) overall].

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 160 subjects who were currently on antipsychotics during the study treatment, 88 subjects (55.0%) were taking Risperidone and 42 subjects (26.3%) were taking Olanzapine (Table 11-3). Most patients were taking atypical (second-generation) antipsychotics (e.g., Aripiprazole, Olanzapine, Paliperidone, Quetiapine, Risperidone), with only 18 (11.3%) 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. None of the subjects in the study population required administration of any rescue medication during the study (Table 14.1.4.3, Listing 16.2.4.4.3.3).

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

Drug Name	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Current Antipsychotic Medication				
Aripiprazole	3 (6.0)	4 (6.7)	1 (2.0)	8 (5.0)
Olanzapine	13 (26.0)	15 (25.0)	14 (28.0)	42 (26.3)
Paliperidone	1 (2.0)	0 (0.0)	1 (2.0)	2 (1.3)
Quetiapine	2 (4.0)	0 (0.0)	0 (0.0)	2 (1.3)
Risperidone	26 (52.0)	33 (55.0)	29 (58.0)	88 (55.0)
Other	5 (10.0)	8 (13.3)	5 (10.0)	18 (11.3)
Other Specify				
Amisulpride	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
Blonanserin	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Haloperidol	2 (4.0)	1 (1.7)	2 (4.0)	5 (3.1)
Trifluoperazine	3 (6.0)	6 (10.0)	0 (0.0)	9 (5.6)
Trifluoperazine Hydrochloride	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.3)

Abbreviations: 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.
Source: Listing 16.2.4.4.3.2; Table 14.1.4.2.2

11.2.5 Prior and Concomitant Procedures

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

11.2.6 Global Assessment of Functioning

Global Assessment of Functioning (GAF) scale scores for the Safety Population are summarized in Table 14.1.5 and by subject details in Listing 16.2.4.4.4. At Screening and Baseline visits, the mean (SD) GAF scale scores for subjects in the Safety Population were 42.2 (4.68), ranging from 29 to 50, and 42.4 (4.67), ranging from 30 to 50, respectively.

11.3 Measurements of Treatment Compliance

The treatment compliance was monitored throughout the study as described in Section 9.4.8 and analyzed as detailed in Section 9.7.1.4.1.

The mean (SD) overall treatment compliance was 95.9% (9.97), with a median of 98.8% (range: 25 to 105%). 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 97.0% (5.98), 95.9% (11.26) and 94.7% (11.47), respectively. The maximum treatment compliance was reported for a subject in the evenamide 30 mg *bid* group of 105% and minimum was reported for a subject in the evenamide 15 mg *bid* group of 25%. Overall, 9 subjects reported treatment compliance less than 80% (a single subject from 7.5 mg, 4 each from 15 mg and 30 mg treated groups) (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=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
Overall Treatment Compliance (%) [a]	n	50	60	50	160
	Mean (SD)	97.0 (5.98)	95.9 (11.26)	94.7 (11.47)	95.9 (9.97)
	Median	98.8	98.8	98.8	98.8
	Min, Max	62,100	25,100	47,105	25,105

Abbreviations: N - Total number of subjects in the Safety Population, n = number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum.
*[a] Treatment compliance was computed as [Number of capsules consumed / Number of capsules expected to be consumed] * 100*
Source: Listing 16.2.5.2; Table 14.3.0.1

11.4 Extent of Exposure

The mean (SD) overall study drug exposure was 42.5 (7.02) days, with a median of 43.0 (range: 1 to 61) days. The mean (SD) study drug exposure for subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups was 43.2 (6.73), 41.4 (7.40) and 43.0 (6.82) days, respectively. The maximum study drug exposure was reported for subjects in the evenamide 15 mg and 30 mg *bid* groups of 61 days and minimum was reported for a subject in the evenamide 30 mg *bid* group of 1 day. (Table 11-5)

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 single subject (Subject No: 310006) from evenamide 7.5 mg group had a dose adjustment (dose decreased) due to start of an adverse event (AE) during the study. Maximum kit replacement was seen in evenamide 30 mg *bid* group subjects (9 subjects (18.0%) due to other causes (non-AE reasons).

Table 11-5: Study Drug Exposure - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *bid* (N=50)	Evenamide 15 mg *bid* (N=60)	Evenamide 30 mg *bid* (N=50)	Total (N=160)
Duration of Exposure (days) [a]	n	50	60	50	160
	Mean (SD)	43.2 (6.73)	41.4 (7.40)	43.0 (6.82)	42.5 (7.02)
	Median	43.0	43.0	43.0	43.0
	Min, Max	4,61	8,56	1,61	1,61

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) = Treatment end date - Treatment start date + 1.
Source: Listing 16.2.5.2; Table 14.3.0.1

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, 15 and 30 mg *bid*) in patients with TRS not responding adequately to a stable, therapeutic dose of their current antipsychotic medication.

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, 41 (25.6%) subjects reported at least one TEAE, which included 13 (26.0%), 10 (16.7%) and 18 (36.0%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Medication errors, asymptomatic and not associated with adverse events, were reported in 7 (4.4%) subjects in the evenamide 30 mg *bid* treated group (reported as per protocol as SAE). None of the

subjects in any of the 3 treatment groups reported a treatment-related SAE.

A total of 15 (9.4%) subjects reported at least one treatment-related TEAE, which included 5 (10.0%), 4 (6.7%) and 6 (12.0%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Overall, 2 (1.3%) subjects reported a TEAE leading to study drug discontinuation, which included a single (2.0%) subject each from evenamide 7.5 mg and 30 mg *bid* treated groups.

No TEAE resulting in death was reported during the study.

Of the 41 overall TEAEs reported, 32 (20.0%) were of mild severity and 9 (5.6%) were of moderate severity. None of the reported TEAEs were of severe intensity.

Out of the 15 overall treatment-related TEAEs reported, 11 (6.9%) were of mild severity and 4 (2.5%) were of moderate severity. None of the reported treatment-related TEAEs were of severe intensity.

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

Category	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
No. of Subjects with at least one TEAE	13 (26.0)	10 (16.7)	18 (36.0)	41 (25.6)
No. of Subjects with at least one Serious TEAE	0 (0.0)	0 (0.0)	7 (14.0)	7 (4.4)
No. of Subjects with at least one Treatment-related TEAE [a]	5 (10.0)	4 (6.7)	6 (12.0)	15 (9.4)
No. of Subjects with Any Serious and Treatment-related TEAE	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)
No. of Subjects with Any TEAE Leading to Study Drug Discontinuation	1 (2.0)	0 (0.0)	1 (2.0)	2 (1.3)
No. of Subjects with Any TEAE Resulting in Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TEAE by Severity				
Mild	8 (16.0)	8 (13.3)	16 (32.0)	32 (20.0)
Moderate	5 (10.0)	2 (3.3)	2 (4.0)	9 (5.6)
Any Treatment-related TEAE by Severity				
Mild	4 (8.0)	3 (5.0)	4 (8.0)	11 (6.9)
Moderate	1 (2.0)	1 (1.7)	2 (4.0)	4 (2.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: 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 were 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 was possibly or probably related to study drug, or not reported.
Source: Listing 16.2.7.1 and Listing 16.2.7.2; Table 14.3.1.1

11.5.2 Display of Adverse Events

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, 41 (25.6%) subjects reported at least one TEAE, which included 13 (26.0%), 10 (16.7%) and 18 (36.0%) 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 'General disorders and administration site conditions' and 'Nervous system disorders' with 10 (6.3%) subjects each. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were dizziness with 3 (1.9%) subjects; and asthenia, fatigue, postural dizziness, and hypersomnia with 2 (1.3%) subjects each (Table 14.3.1.2).

Summary of Treatment-emergent Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.3 and by subject details in Listing 16.2.7.2.

Overall, 7 (4.4%) subjects reported at least one Serious TEAE, and all 7 subjects belonged to the evenamide 30 mg *bid* treated group. None of the subjects from evenamide 7.5 mg and 15 mg *bid* treated groups reported any Serious TEAE. All the 7 reported serious TEAEs were due to medication error (Preferred term).

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 15 (9.4%) subjects reported at least one treatment-related TEAE, which included 5 (10.0%), 4 (6.7%) and 6 (12.0%) 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 6 (3.8%) subjects, and 'General disorders and administration site conditions' with 3 (1.9%) subjects overall. The most frequently reported treatment-related TEAEs (those reported by more than one subject) by the PT were asthenia and dizziness with 2 (1.3%) subjects overall (Table 14.3.1.4).

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.

Overall, 2 (1.3%) subjects reported a TEAE leading to study drug discontinuation, which included a single (2.0%) subject each from evenamide 7.5 mg and 30 mg *bid* treated groups.

11.5.3 Analysis of Adverse Events

11.5.3.1 Overall Incidence of Treatment-Emergent Adverse Events

A summary of TEAEs that occurred with a ≥ 5% incidence of events (SOC) in overall subjects is presented by SOC and PT in Table 11-7, and by Subject listing is included in Listing 16.2.7.1.

The maximum number of TEAEs was reported by subjects in evenamide 30 mg *bid* treated group [18 (36%) subjects], followed by subjects in evenamide 7.5 mg *bid* treated group [13 (26%) subjects], and lowest in evenamide 15 mg *bid* treated group [10 (16.7%) subjects].

The most frequently reported TEAEs (those with a ≥5% incidence of events in overall subjects) by SOC were 'General disorders and administration site conditions' and 'Nervous system disorders' by 10 (6.3%) subjects each.

Overall, 10 (6.3%) subjects reported 'General disorders and administration site conditions', with 4 (8.0%) subjects each in evenamide 7.5 mg and 30 mg *bid* treated groups, and 2 (3.3%) subjects in evenamide 15 mg *bid* treated group. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were pyrexia by 4 (2.5%) subjects overall, including 2 (4.0%) subjects in evenamide 7.5 mg *bid* treated group and one each in evenamide 15 mg and 30 mg *bid* treated group; asthenia by 2 (1.3%) subjects overall, including one subject each in evenamide 7.5 mg (2.0%) and 15 mg (1.7%) *bid* treated group; and fatigue by 2 (4.0%) subjects in evenamide 30 mg *bid* treated group.

Overall, 10 (6.3%) subjects reported 'Nervous system disorders', with 5 (10.0%) subjects in evenamide 7.5 mg, 3 (5.0%) subjects in evenamide 15 mg *bid* treated group and 2 (4.0%) subjects in evenamide 30 mg *bid* treated group. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were dizziness by 3 (1.9%) subjects overall, including a single (2.0%) subject in evenamide 7.5 mg *bid* treated group and 2 (4.0%) subjects in evenamide 30 mg *bid* treated group; postural dizziness by 2 subjects (1.3%) overall, including one subject each in evenamide 7.5 mg (2.0%) and 15 mg (1.7%) *bid* treated group; and hypersomnia by 2 (1.3%) subjects overall, both (4.0%) from evenamide 7.5 mg *bid* treated group.

Table 11-7: TEAEs Occurring in ≥5% (in overall subjects) of Subjects by SOC and Preferred Term – Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Any TEAE	13 (26.0)	10 (16.7)	18 (36.0)	41 (25.6)
General disorders and administration site conditions	4 (8.0)	2 (3.3)	4 (8.0)	10 (6.3)
Pyrexia	2 (4.0)	1 (1.7)	1 (2.0)	4 (2.5)
Asthenia	1 (2.0)	1 (1.7)	0 (0.0)	2 (1.3)

System Organ Class Preferred Term	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Fatigue	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.3)
Feeling hot	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Peripheral swelling	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nervous system disorders	5 (10.0)	3 (5.0)	2 (4.0)	10 (6.3)
Dizziness	1 (2.0)	0 (0.0)	2 (4.0)	3 (1.9)
Dizziness postural	1 (2.0)	1 (1.7)	0 (0.0)	2 (1.3)
Headache	2 (4.0)	0 (0.0)	0 (0.0)	2 (1.3)
Extrapyramidal disorder	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Somnolence	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hypersomnia	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
Tremor	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)

Abbreviations: 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 were newly occurring or pre-existing conditions 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.
Source: Listing 16.2.7.1; Adapted from Table 14.3.1.2

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 15 subjects (9.4%) reported at least one treatment-related TEAE, which included 5 (10.0%), 4 (6.7%) and 6 (12.0%) 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 evenamide 15 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 6 (3.8%) subjects, and 'General disorders and administration site conditions' with 3 (1.9%) subjects overall.

Overall, 6 (3.8%) subjects reported 'Nervous system disorders', with 2 subjects each in evenamide 7.5 mg (4.0%), 15 mg (3.3%) and 30 mg (4.0%) *bid* treated group. The most frequently reported treatment-related TEAE (those reported by more than one subject) by the PT was dizziness by 2 (4.0%) subjects in evenamide 30 mg *bid* treated group.

Overall, 3 (1.9%) subjects reported 'General disorders and administration site conditions', with a single subject each in evenamide 7.5 mg (2.0%), 15 mg (1.7%) and 30 mg (2.0%) *bid* treated groups. The most frequently reported treatment-related TEAE (those reported by more than one subject) by the PT was asthenia by 2 (1.3%) subjects overall, including a single subject each in

evenamide 7.5 mg (2.0%) and 15 mg (1.7%) *bid* treated groups.

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=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Any Treatment-Related TEAE	5 (10.0)	4 (6.7)	6 (12.0)	15 (9.4)
Gastrointestinal disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Gastritis	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
General disorders and administration site conditions	1 (2.0)	1 (1.7)	1 (2.0)	3 (1.9)
Asthenia	1 (2.0)	1 (1.7)	0 (0.0)	2 (1.3)
Feeling hot	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Investigations	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Metabolism and nutrition disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Decreased appetite	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nervous system disorders	2 (4.0)	2 (3.3)	2 (4.0)	6 (3.8)
Dizziness	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.3)
Dizziness postural	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hypersomnia	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
Somnolence	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Tremor	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Aggression	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Frustration tolerance decreased	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Insomnia	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Personality change	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)

Abbreviations: 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 were newly occurring or pre-existing conditions worsened in severity after the first administration of the study medication Treatment related TEAE's are the TEAE's which was possibly or probably related to study drug, or not reported. Subjects are counted only once per system organ class and per preferred term.
Adverse events are coded with MedDRA Version 23.0.
Source: Listing 16.2.7.1; Table 14.3.1.4

11.5.3.3 Incidence of Treatment-Emergent Adverse Events by Severity

All TEAEs by maximum severity are presented by SOC and Preferred Term 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.

All the reported TEAEs were assessed as either mild or moderate in severity. Of the overall 41 TEAE, 32 (20.0%) were of mild severity [reported by 8 subjects each in evenamide 7.5 mg (16.0%) and 15 mg (13.3%) treated groups; 16 (32.0%) subjects in evenamide 30 mg *bid* treated group] and 9 (5.6%) were of moderate severity [reported by 5 (10.0%) subjects in evenamide 7.5 mg *bid*, and 2 subjects each from 15 mg (3.3%) and 30 mg (4.0%) *bid* treated groups]. None of the reported TEAE were of severe intensity.

One subject (2.0%) from evenamide 7.5 mg *bid* group reported the following TEAEs (PT) of moderate severity: gastritis, toothache, increased blood creatine phosphokinase levels, dyslipidemia, and headache.

One subject (1.7%) from evenamide 15 mg *bid* group reported the following TEAEs (PT) of moderate severity: Asthenia and dyslipidemia.

One subject (2.0%) from evenamide 30 mg *bid* group reported the following TEAEs (PT) of moderate severity: Feeling hot, increased blood creatine phosphokinase levels, increased blood lactate dehydrogenase levels, aggression, frustration tolerance decreased, insomnia, and personality change.

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

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Any TEAE	Mild	8 (16.0)	8 (13.3)	16 (32.0)
	Moderate	5 (10.0)	2 (3.3)	2 (4.0)
	Severe	0	0	0

Abbreviations: 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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE was counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.
Source: Listing 16.2.7.1; Adapted from Table 14.3.1.6

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.

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

Listing 16.2.7.2 includes all the cases of suspected overdose/medication errors that, as per protocol, have to be reported following the same procedure (and timeframe) of SAEs.

All the AEs leading to discontinuation by subject are presented in Listing 16.2.7.3, in Appendix 16.2 of the CSR.

No fatalities were reported during the study.

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

11.6.2.1 Narrative of Serious Adverse events

Based on the protocol guideline, the asymptomatic medication errors were reported by the investigator. No adverse events were noted in conjunction with these events. These medication errors were unintentional and not due to evenamide.

1. Narrative for Subject Number: 304018; Medication error [Medication error].

This 48-year-old Asian male subject with schizophrenia (diagnosed in 2013; current episode onset - Dec-2020) met all the eligibility criteria and signed the informed consent on 30-Jun-2021. The subject had a past medical history of insomnia. The subject had been taking olanzapine at a dose of 30 mg daily since 04-Apr-2021 for schizophrenia. The subject was taking vitamin supplements as concomitant medications. A physical examination and standard eye examination conducted at the time of screening were normal. Psychiatric examination revealed mental status abnormalities including auditory hallucination, the delusion of reference, irritable mood, poor insight, and lack of judgment. As per the randomization chart, the subject was assigned to evenamide at a dose of 30 mg twice daily treatment arm on 19-Jul-2021. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily and continue it for 1 week before switching over to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. However, no adverse event or any safety related concern was reported by the subject or observed by the investigator site team along with this medication error. The investigator considered the event as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error an important medical event, not related to evenamide. Based on the protocol guideline, this asymptomatic medication error was reported by the investigator. No adverse events were noted in

conjunction with this event. The Sponsor agreed with the investigator that this medication error was unintentional and not due to evenamide.

2. Narrative for Subject Number: 304019; Medication error [Medication error].

This 34-year-old Asian male subject with schizophrenia (diagnosed on 06-Sep-2013; current episode onset–Feb-2021) met all the eligibility criteria and signed the informed consent on 17-Jul-2021. The subject had been taking risperidone at a dose of 9 mg daily since 10-May-2021 for schizophrenia. A physical examination and standard eye examination conducted at the time of screening were normal. Psychiatric examination revealed mental status abnormalities including delusion of reference, delusion of persecution, poor judgement, poor insight, and speech rate decreased. As per the randomization chart, the subject was assigned to evenamide at a dose of 30 mg twice daily treatment arm. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily and continue it for 1 week before switching over to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. The site reported that this happened inadvertently and was identified by the clinical research associate (CRA) during the monitoring visit. However, no adverse event or any safety related concerns were reported by the subject or observed by the investigator site team along with this medication error. The investigator considered the event as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error an important medical event, not related to evenamide. Based on the protocol guideline, this asymptomatic suspected medication error was reported by the investigator. No adverse changes were noted in conjunction with this event. The Sponsor agreed with the investigator that this suspected medication error was unintentional, and it was not due to evenamide.

3. Narrative for Subject Number: 304020; Medication error [Medication error].

This 40-year-old Asian male subject with schizophrenia (diagnosed in 15-Apr-2018; current episode onset– Feb-2021) met all the eligibility criteria and signed the informed consent on 20-Jul-2021. The subject's medical history and relevant concurrent conditions were not reported. The subject had been taking risperidone at a dose of 12 mg daily since 22-Apr-2021 for schizophrenia. A physical examination and standard eye examination conducted at the time of screening were normal. No clinically significant abnormalities were observed in neurological examination. Psychiatric examination revealed delusion of infidelity, poor judgement, poor attention, and pressure of speech. As per the randomization chart, the subject was assigned to evenamide at a dose of 30 mg twice daily treatment arm. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily and continue it for 1 week before switching over to 30 mg twice daily for the rest of the trial period. The site reported that this happened inadvertently

and was identified by the CRA during the monitoring visit. However, no adverse event or any safety related concerns was reported by the subject or observed by the investigator site team along with this medication error. The medication error was not associated with any clinical symptoms or abnormal laboratory results, the investigator considered it as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error an important medical event, not related to evenamide. Based on the protocol guideline, this asymptomatic suspected medication error was reported by the investigator. No adverse changes were noted in conjunction with this event. The Sponsor agreed with the investigator that this suspected medication error was unintentional, and it was not due to evenamide.

4. Narrative for Subject Number: 401009; Medication error [Medication error].

This 43-year-old Asian male subject with schizophrenia (diagnosed on 13-Feb-2021; current episode onset: May-2021) met all the eligibility criteria and signed the informed consent on 19-Apr-2022. The subject had been taking risperidone at a dose of 8 mg orally once daily since 05-Mar-2022 for schizophrenia, clonazepam for poor sleep and trihexyphenidyl hydrochloride (Benzhexol) for extrapyramidal symptoms as concomitant medications. All the examinations and lab tests done at the time of screening were found to be normal except mental status. On 25-May-2022, the subject was randomized to arm C with evenamide at a dose of 30 mg twice daily treatment. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily for 1 week and after that up-titrated to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. The site reported that this happened inadvertently. However, no adverse event nor any safety related concern was reported by the sub-investigator for this subject along with this medication error. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error an important medical event, but not related to evenamide. Based on the protocol guideline, this asymptomatic medication error was reported by the investigator. No adverse events were noted in conjunction with this event. The Sponsor agrees with the investigator that this medication error was unintentional and not due to evenamide.

5. Narrative for Subject Number: 401010; Medication error [Medication error].

This 43-year-old Asian female subject with schizophrenia (diagnosed in 2008; current episode onset: 18-Sep-2021) met all the eligibility criteria and signed the informed consent on 17-May-2022. The subject had been taking risperidone at a dose of 8 mg orally once daily since 02-Apr-2022 for schizophrenia and trihexyphenidyl hydrochloride (Benzhexol) at a dose of 2 mg in morning for extrapyramidal symptoms as concomitant medications. All the examinations and lab

tests done at the time of screening were found to be normal except mental status. On 16-Jun-2022, the subject was randomized to arm C with evenamide at a dose of 30 mg twice daily treatment. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily for 1 week and after that up-titrated to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. The site reported that this happened inadvertently. However, no adverse event nor any safety related concern was reported by the sub-investigator for this subject along with this medication error. The investigator considered the event as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error an important medical event, but not related to evenamide. Based on the protocol guideline, this asymptomatic medication error was reported by the investigator. No adverse events were noted in conjunction with this event. The Sponsor agreed with the investigator that this medication error was unintentional and not due to evenamide.

6. Narrative for Subject Number: 407002; Medication error [Medication error].

This 30-year-old Asian female subject with schizophrenia (diagnosed in 2018; current episode onset: 04-Apr-2022) met all the eligibility criteria and signed the informed consent on 02-Jul-2022. The subject had been taking trifluoperazine (Stelazine) at a dose of 10 mg orally twice daily since 15-May-2022 for schizophrenia, clonazepam at a dose of 0.5 mg orally once daily since 15-May-2022 for anxiety relief, metformin at a dose of 500 mg twice daily since 15-May-2022 for weight reduction, and trihexyphenidyl hydrochloride (Benzhexol) at a dose of 2 mg orally twice daily since 01-Jun-2022 for relief of extrapyramidal side effects of antipsychotics as concomitant medications. All the examinations and lab tests done at the time of screening were found to be normal except mental status. On 23-Jul-2022, the subject was randomized to arm C with evenamide at a dose of 30 mg twice daily treatment. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily for 1 week and after that up-titrated to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. The site reported that this happened inadvertently. However, no adverse event nor any safety related concern was reported by the sub-investigator for this subject along with this medication error. The investigator considered the event as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error to be mild in intensity and an important medical event, not related to evenamide. Based on the protocol guideline, this asymptomatic medication error was reported by the investigator. No adverse events were noted in conjunction with this event. The Sponsor agreed

with the investigator that this medication error was unintentional and not due to evenamide.

7. Narrative for Subject Number: 407003; Medication error [Medication error].

This 37-year-old Asian female subject with schizophrenia (diagnosed on 10-Jun-2014; current episode onset: 25-Jun-2021) met all the eligibility criteria and signed the informed consent on 19-Jul-2022. The subject had been taking trifluoperazine (Stelazine) at a dose of 20 mg orally daily at night since Aug-2021 for schizophrenia, clonazepam at a dose of 1 mg orally daily at night since 24-Jan-2019 for sleep and anxiety relief and trihexyphenidyl hydrochloride (Artane) at a dose of 2 mg orally twice daily since Aug-2021 for relief of extrapyramidal side effects of antipsychotics as concomitant medications. All the examinations and lab tests done at the time of screening were found to be normal except mental status. On 09-Aug-2022, the subject was randomized to arm C with evenamide at a dose of 30 mg twice daily treatment. As per the protocol, the subject should have started with evenamide at a dose of 15 mg twice daily for 1 week and after that up-titrated to 30 mg twice daily for the rest of the trial period. On the day of randomization, the subject was however dispensed evenamide 30 mg twice daily instead of 15 mg twice daily for the first week. The site reported that this happened inadvertently. However, no adverse event nor any safety related concern was reported by the sub-investigator for this subject along with this medication error. The investigator considered the event as not related to evenamide. After taking evenamide 30 mg twice daily instead of evenamide 15 mg twice daily for the first week, the patient took evenamide 30 mg twice daily for the rest of the study period as per the protocol. The investigator considered the medication error to be mild in intensity and an important medical event, not related to evenamide. Based on the protocol guideline, this asymptomatic medication error was reported by the investigator. No adverse events were noted in conjunction with this event. The sponsor agreed with the investigator that this medication error was unintentional and not due to evenamide.

11.6.2.2 Narrative of TEAEs leading to Study Drug Discontinuation

1. Narrative for Subject Number: 401001; Vomiting [Vomiting], Headache [Headache], Fever [Pyrexia].

This 24-year-old Asian female with schizophrenia was screened in the study on 12-Feb-2021. She was then randomized and received the first dose of investigational drug (evenamide, 7.5 mg) on 04-Mar- 2021. The subject was diagnosed with schizophrenia in the year 2015. She was on Tab olanzapine 20 mg daily for the same since November 2020. She was hospitalized once for schizophrenia. There was no family history of schizophrenia. She was on trihexyphenidyl (Benzhexol) 2 mg twice a day for her extrapyramidal symptoms as concomitant medication since 2020. The patient developed adverse events of vomiting, headache, and fever on Day 5. This led to study medication discontinuation and withdrawal from the study by the subject. All adverse events resolved without any sequalae. At the baseline evaluation on 04-Mar-2021, vital sign measurements were blood pressure of 122/84 mmHg, Temperature 36.6°C, pulse 86 beats per

minute (bpm), and respiratory rate 19 resp/min; and a normal ECG. Vital signs 1-hour post-dose on Day 1 were blood pressure of 121/88 mmHg, pulse 90 beats per minute (bpm), and respiratory rate 18 resp/min; 4-hour post dose blood pressure of 120/90 mmHg, pulse 86 beats per minute (bpm), and respiratory rate 19 resp/min., and a normal ECG. On 8-Mar-2021, the subject experienced vomiting and fever which were mild in intensity and headache which was moderate in intensity. The relationship to the study medication was assessed as unlikely by the PI. The subject discarded the study medication once she developed the adverse events and refused to return to the site for early termination visit. The last dose of study medication was taken on 07-Mar-2021. The adverse events resolved without any sequalae. The subject did not have any significant medical conditions. The investigator assessed the vomiting and fever to be mild in intensity and headache to be moderate in intensity. The relationship to the study medication was assessed to be unlikely.

2. *Narrative for Subject Number: 605004; Insomnia [Insomnia], Bursts of Heat [Feeling hot], Aggression [Aggression], oppositional and polemical attitude [Personality change] and Poor tolerance to Frustration [Frustration tolerance decreased]*

This 30-year-old male subject received the first dose of investigational study drug (evenamide, 15 mg) for schizophrenia on 28-Sep-2021 (Day 1). The subject was diagnosed with schizophrenia 09-Aug-2018. He was prescribed 4 mg of Haloperidol once daily to be taken orally. There is no family history of schizophrenia. Concomitant medications included 100 mg of Quetiapine prescribed for treatment of insomnia associated with schizophrenia. At the baseline evaluation on 28-Sep-2021, vital sign measurements were blood pressure of 119/82 mmHg, temperature 36.4°C, pulse rate 89 beats per minute (bpm), and respiratory rate 14 resp/min and a normal ECG. The subject was then randomized to evenamide 30 mg *bid* arm. He received 15 mg *bid* for the first week. This was then increased to 30 mg *bid* from the day 8 visit. Vital signs 1-hour post-dose on Day 1 were blood pressure of 125/75 mmHg, pulse rate 80 beats per minute (bpm), and respiratory rate 14 resp/min, temperature 36.2°C and a normal ECG; 4-hour post dose blood pressure of 130/75 mmHg, pulse 85 beats per minute (bpm), and respiratory rate 15 resp/min., and a normal ECG. There were no abnormalities detected in the vital signs during the Day 29 visit (26-Oct-2021) of the subject. The temperature was 36.7°C, respiratory rate was 15 breaths/min, blood pressure was 130/75 mm Hg, and the pulse rate was 87 beats per minute (bpm). On 27-Oct-2021 (Day 30), the subject developed adverse events of insomnia, bursts of heat, aggression, oppositional and polemical attitude, and poor tolerance to frustration. The events were assessed to be possibly related to the study medication by the PI. The dose of Quetiapine (concomitant medication taken by the subject) was increased from 100 mg once daily to 150 mg once daily by the sub-investigator to treat the adverse events.

The subject reduced dose of the study medication once he developed the adverse events and finally discontinued the medication. The last dose of study medication was taken on 08-Nov-2021. The

adverse event insomnia resolved on the 26-Nov-2021 and the remaining adverse events resolved on 8-Dec-2021. All the adverse events resolved without any sequalae. The subject had one more adverse event of cold, which lasted from the 6-Oct-2021 to 10-Oct-2021 and was mild in intensity. It was treated with betamethasone 2 mg daily and cefixime 400 mg daily and resolved without any sequelae. The causality was assessed as unrelated to the study medication. The investigator assessed all the other adverse events (insomnia, bursts of heat, aggression, oppositional and polemical attitude, and poor tolerance to frustration) to be of moderate intensity and possibly related to the study medication.

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

11.6.3.1 Deaths

No deaths were reported during the study (Table 11-6).

11.6.3.2 Other Serious Adverse Events

Summary of Treatment-Emergent SAEs by SOC and PT in the Safety Population is presented in Table 14.3.1.3, and by subject details are presented in Listing 16.2.7.2.

The Listing 16.2.7.2 and Table 11-10 include all the cases of suspected overdose/medication errors that as per protocol had to be reported following the same procedure (and timeframe) of SAEs. The Medication errors, asymptomatic and not associated with adverse events, were reported in 7 (4.4%) subjects in the evenamide 30 mg bid treated group. None of the subjects in any of the 3 treatment groups reported a treatment-related SAE.

Table 11-10: Treatment-Emergent SAEs by SOC and Preferred Term – Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Any Serious TEAE	0 (0.0)	0 (0.0)	7 (14.0)	7 (4.4)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	7 (14.0)	7 (4.4)
Medication error	0 (0.0)	0 (0.0)	7 (14.0)	7 (4.4)

Abbreviations: 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 once per system organ class and per preferred term.
Adverse events are coded with MedDRA Version 23.0.
Source: Listing 16.2.7.2; Table 14.3.1.3

11.6.3.3 Other Significant Adverse Events

TEAEs leading to Study Drug Discontinuation

Summary of TEAEs leading to study drug discontinuation by SOC and PT for the Safety Population is presented in Table 14.3.1.5, and by subject details in Listing 16.2.7.3.

Overall, 2 (1.3%) subjects reported a TEAE leading to study drug discontinuation, which included 1 (2.0%) subject each from evenamide 7.5 mg and 30 mg *bid* treated groups. The TEAEs leading to study drug discontinuation reported by a single subject in evenamide 7.5 mg *bid* treated group by SOC were 'Gastrointestinal disorders' (PT: vomiting), 'General disorders and administration site conditions' (PT: pyrexia), and 'Nervous system disorders' (PT: headache). A single subject in evenamide 30 mg *bid* treated group reported 'Psychiatric disorders' (PT: insomnia), which led to study drug discontinuation (Table 11-11).

None of the subjects in evenamide 15 mg *bid* treated group reported a TEAE which led to study drug discontinuation.

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

System Organ Class Preferred Term	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)	Total (N=160) n (%)
Any TEAE Leading to Study Drug Discontinuation	1 (2.0)	0 (0.0)	1 (2.0)	2 (1.3)
Gastrointestinal disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Vomiting	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
General disorders and administration site conditions	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Pyrexia	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nervous system disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Headache	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)
Insomnia	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.6)

Abbreviations: 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 pre-existing conditions worsened in severity after the first administration of the study medication, Subjects are counted only once per SOC and per PT.
Adverse events are coded with MedDRA Version 23.0.
Source: Listing 16.2.7.3; Table 14.3.1.5

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 thyroid function test) 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.

11.7.2 Hematology

11.7.2.1 Laboratory Values over Time

Summary statistics of change from baseline by visit are presented for hematology parameters in Table 14.3.2.1 (Observed values and change from baseline). There were no clinically meaningful changes from baseline in mean values for hematology 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 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 parameter with the maximum number of newly emergent clinically notable abnormal findings was low hemoglobin level (≤ 0.85 x lower limit of normal (LLN) g/L), seen in 7 (14.0%), 10 (16.7%) and 6 (12.0%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 11-12).

Table 11-12: Laboratory Hematology; Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline - Safety Population

Test Unit	Notable Criteria	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Eosinophils (Absolute) (10^9/L)	>= 1.5	2 (4.0)	0 (0.0)	2 (4.0)

Test Unit	Notable Criteria	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Hemoglobin (g/L)	<= 0.85 x LLN	7 (14.0)	10 (16.7)	6 (12.0)
Hematocrit (Proportion of 1.0)	<= 0.85 x LLN	2 (4.0)	5 (8.3)	4 (8.0)
Platelets (10^9/L)	<= 100	0 (0.0)	0 (0.0)	1 (2.0)
	>=600	1 (2.0)	1 (1.7)	0 (0.0)
White Blood Count (10^9/L)	<= 3.0	1 (2.0)	3 (5.0)	0 (0.0)

Abbreviations: 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: 32/14, Evenamide 15 mg BID: 36/10 and Evenamide 30 mg BID: 37/9) whenever the criterion is specific for Male/ Female. Source: Listing 16.2.8.1, Clinical notable values source = Appendix 16.1.10 (Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023); Table 14.3.2.3

11.7.3 Blood Chemistry

11.7.3.1 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.

11.7.3.2 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 observed in any of the three treatment groups. The number of newly emergent clinically notable abnormalities were low across all the treatment groups, with no meaningful differences.

The blood chemistry parameter with the maximum number of newly emergent clinically notable abnormal findings was low high density lipoprotein level (≤ 0.8 mmol/L), seen in 19 (38.0%), 19 (31.7%) and 21 (42.0%) subjects in the evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 11-13).

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

Test (Unit)	Notable Criteria	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Bicarbonate (mmol/L)	<= 18	12 (24.0)	16 (26.7)	10 (20.0)
	>=33	0 (0.0)	1 (1.7)	0 (0.0)
Calcium (mmol/L)	<= 1.9	3 (6.0)	2 (3.3)	1 (2.0)
	>= 2.7	1 (2.0)	1 (1.7)	0 (0.0)
Creatine Kinase (U/L)	>= 400	2 (4.0)	9 (15.0)	7 (14.0)
Creatinine (µmol/L)	>= 177	2 (4.0)	3 (5.0)	0 (0.0)
Glucose (mmol/L)	>= 11.1	7 (14.0)	5 (8.3)	0 (0.0)
High-Density Lipoprotein (mmol/L)	<= 0.8	19 (38.0)	19 (31.7)	21 (42.0)
	>= 2.3	1 (2.0)	0 (0.0)	1 (2.0)
LDH (U/L)	>= 500	2 (4.0)	1 (1.7)	0 (0.0)
Low-Density lipoprotein (mmol/L)	>= 4.1	4 (8.0)	6 (10.0)	7 (14.0)
Potassium (mmol/L)	>= 6.0	1 (2.0)	1 (1.7)	0 (0.0)
Total Bilirubin (µmol/L)	>= 34	0 (0.0)	0 (0.0)	2 (4.0)
Total Cholesterol (mmol/L)	>= 7.25	1 (2.0)	3 (5.0)	1 (2.0)
Triglycerides (mmol/L)	>= 4.5	2 (4.0)	5 (8.3)	4 (8.0)

Abbreviations: Glucose = Fasting Glucose or Random Glucose.
N = Total number of subjects in the Safety Population, n = number of subjects with available data.
Source: Listing 16.2.8.2, Clinical notable values source = Appendix 16.1.10 (Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023); Table 14.3.2.4

11.7.4 Urinalysis

Urinalysis data was listed (Listing 16.2.8.3) only, along with clinical significance 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 number of clinically notable abnormalities was low across all the treatment groups, with no meaningful differences (Table 11-14).

Table 11-14: Incidence of Clinically Notable Abnormalities for Vital Signs - Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Diastolic Blood Pressure (mmHg)	Day 43/Early Withdrawal		Value <= 50 and >= 15 decrease from Baseline	0 (0.0)	1 (1.7)	0 (0.0)

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
Pulse Rate (bpm)	Day 1	Post-dose 4h	Value >= 120 and >= 15 increase from Baseline	0 (0.0)	0 (0.0)	1 (2.0)
Respiration Rate (Breaths/minute)	Day 1	Post-dose 4h	RR > 25 per minute	0 (0.0)	0 (0.0)	1 (2.0)
	Day 8	Post-dose 1h	RR < 12 per minute	0 (0.0)	1 (1.7)	0 (0.0)
		Post-dose 4h	RR < 12 per minute	0 (0.0)	1 (1.7)	0 (0.0)
	Day 15	Pre-dose	RR < 12 per minute	0 (0.0)	1 (1.7)	0 (0.0)
		Pre-dose	RR > 25 per minute	0 (0.0)	1 (1.7)	0 (0.0)
	Day 43/Early Withdrawal		RR > 25 per minute	0 (0.0)	0 (0.0)	1 (2.0)
Systolic Blood Pressure (mmHg)	Day 8	Pre-dose	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0 (0.0)	0 (0.0)
		Post-dose 1h	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0 (0.0)	0 (0.0)
		Post-dose 4h	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0 (0.0)	0 (0.0)
Weight (kg)	Day 8	Post-dose 1h	>= 7% decrease from Baseline	0 (0.0)	0 (0.0)	1 (2.0)
		Post-dose 4h	>= 7% decrease from Baseline	0 (0.0)	0 (0.0)	1 (2.0)
	Day 15	Pre-dose	>= 7% decrease from Baseline	0 (0.0)	0 (0.0)	1 (2.0)
		Post-dose 1h	>= 7% decrease from Baseline	0 (0.0)	0 (0.0)	1 (2.0)
	Day 29	Pre-dose	>= 7% decrease from Baseline	0 (0.0)	0 (0.0)	1 (2.0)

Abbreviations: 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.
Refer to Appendix 2 of the Statistical Analysis Plan.
Source: Listing 16.2.9; Table 14.3.3.2

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 was 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. 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 (Day 43 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 parameter 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 5 (10.0%) subjects each in the evenamide 7.5 mg and 30 mg *bid* treated groups and 6 (10.0%) subjects in the evenamide 15 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 Investigators assessed 12 (24.0%) subjects in the evenamide 7.5 mg *bid* treated group and 9 subjects each in the 15 mg (15.0%) and 30 mg (18.0%) *bid* treated groups had non-clinically significant treatment-emergent abnormalities in the ECG recordings.

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.

The data at 1- and 4-hours post-dose on Days 1 and 8, as well as at Day 43, did not indicate any pattern of notable values for any of these ECG parameters (Table 11-15).

The following findings were noted in ≥ 5% of the subjects in an individual treatment group:

At pre-dose on Day 8, a change from baseline in QTcB interval of > 30 msec and ≤ 60 msec was observed in 4 (8.0%) subjects in evenamide 7.5 mg *bid* treated group. At 1-hour post dose on

Day 8, a change from baseline in QTcB interval of > 30 msec and ≤ 60 msec was observed in 4 (8.0%), 5 (8.3%) and 3 (6.0%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. On Day 43, an absolute QTcB interval >450 msec and ≤480 msec was observed in 3 (6.0%) subjects in evenamide 30 mg *bid* treated group, and a change from baseline of > 30 msec and ≤ 60 msec was observed in 3 (5.0%) subjects in evenamide 15 mg *bid* treated group. At Day 43, a change from baseline in QTcF interval of > 30 msec and ≤ 60 msec was observed in 3 (6.0%) subjects in evenamide 7.5 mg *bid* treated group. None of the treatment groups had ≥5% subjects with categorical values or changes that met criteria for QRS duration or PR interval.

Table 11-15: ECG Parameters Categorical Analysis - Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
QTcB Interval (msec)	Day 1	1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	1 (2.0)	0 (0.0)	1 (2.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	1 (2.0)	1 (1.7)	0 (0.0)
		4 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	2 (4.0)	0 (0.0)	1 (2.0)
		4 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	0 (0.0)	0 (0.0)	2 (4.0)
	Day 8	Pre dose	Absolute interval	> 450 msec and <= 480 msec	2 (4.0)	1 (1.7)	0 (0.0)
		Pre dose	Change from baseline	> 30 msec and <= 60 msec	4 (8.0)	1 (1.7)	1 (2.0)
		1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	1 (2.0)	0 (0.0)	0 (0.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	4 (8.0)	5 (8.3)	3 (6.0)
	Day 15		Absolute interval	> 450 msec and <= 480 msec	0 (0.0)	1 (1.7)	0 (0.0)
			Change from baseline	> 30 msec and <= 60 msec	1 (2.0)	2 (3.3)	1 (2.0)
	Day 29		Absolute interval	> 450 msec and <= 480 msec	2 (4.0)	0 (0.0)	1 (2.0)
			Change from baseline	> 30 msec and <= 60 msec	2 (4.0)	3 (5.0)	0 (0.0)
	Day 43		Absolute interval	> 450 msec and <= 480 msec	1 (2.0)	0 (0.0)	3 (6.0)
			Change from baseline	> 30 msec and <= 60 msec	2 (4.0)	3 (5.0)	1 (2.0)

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
QTcF Interval (msec)	Day 8	Pre dose	Absolute interval	> 450 msec and <= 480 msec	0 (0.0)	1 (1.7)	0 (0.0)
		Pre dose	Change from baseline	> 30 msec and <= 60 msec	0 (0.0)	0 (0.0)	1 (2.0)
		Pre dose	Change from baseline	> 60 msec	1 (2.0)	0 (0.0)	0 (0.0)
		1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	0 (0.0)	1 (1.7)	0 (0.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	2 (4.0)	1 (1.7)	1 (2.0)
	Day 15		Change from baseline	> 30 msec and <= 60 msec	0 (0.0)	1 (1.7)	0 (0.0)
	Day 29		Change from baseline	> 30 msec and <= 60 msec	2 (4.0)	2 (3.3)	1 (2.0)
	Day 43		Change from baseline	> 30 msec and <= 60 msec	3 (6.0)	2 (3.3)	1 (2.0)
QRS Duration (msec)	Day 8	Pre dose	Change from baseline	More than 25% change from baseline	1 (2.0)	0 (0.0)	0 (0.0)
	Day 43		Change from baseline	More than 25% change from baseline	0 (0.0)	0 (0.0)	1 (2.0)
PR Interval (msec)	Day 1	4 Hour Post dose	Absolute interval	> 200 msec	1 (2.0)	0 (0.0)	0 (0.0)
	Day 8	Pre dose	Absolute interval	> 200 msec	1 (2.0)	0 (0.0)	0 (0.0)
		Pre dose	Change from baseline	More than 25% change from baseline	0 (0.0)	1 (1.7)	0 (0.0)
		1 Hour Post dose	Absolute interval	> 200 msec	1 (2.0)	0 (0.0)	0 (0.0)
		1 Hour Post dose	Change from baseline	More than 25% change from baseline	0 (0.0)	1 (1.7)	0 (0.0)
	Day 15		Absolute interval	> 200 msec	1 (2.0)	0 (0.0)	1 (2.0)
			Change from baseline	More than 25% change from baseline	0 (0.0)	2 (3.3)	1 (2.0)
	Day 29		Absolute interval	> 200 msec	0 (0.0)	0 (0.0)	1 (2.0)
			Change from baseline	More than 25% change from baseline	0 (0.0)	0 (0.0)	1 (2.0)

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg *bid* (N=50) n (%)	Evenamide 15 mg *bid* (N=60) n (%)	Evenamide 30 mg *bid* (N=50) n (%)
	Day 43		Absolute interval	> 200 msec	0 (0.0)	0 (0.0)	1 (2.0)
			Change from baseline	More than 25% change from baseline	1 (2.0)	1 (1.7)	2 (4.0)

Abbreviations: 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.
Source: Listing 16.2.11.3; Table 14.3.5.4

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 (hallucinations and delusions) on the neurological examination conducted at Day 43, 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 Day 43 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 Day 43 compared to Baseline.

11.8.5 Calgary Depression Scale for Schizophrenia

The Calgary Depression Scale for Schizophrenia (CDSS) was used as a screening tool and to assess

changes in depressive symptoms during treatment. At Baseline, any patient with a CDSS total score of 7 or higher was excluded from the study. In addition to its use as a screening tool, the CDSS assessment was also performed at the final visit (Day 43 or at early discontinuation) to assess changes from baseline in depressive symptoms.

The change from baseline in CDSS score 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 Day 43 were 0.2 (0.78), 0.5 (1.26) and 0.6 (1.40) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The mean (SD) changes from baseline observed at Day 43 were -0.2 (0.72), -0.1 (0.56) and -0.2 (0.60) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, indicating a reduction in depressive symptoms in all groups (Table 11-16).

Table 11-16: Change from Baseline in Calgary Depression Scale for Schizophrenia Total Scores - Safety Population

			Evenamide 7.5 mg *bid* (N=50)		**Evenamide 15 mg *bid* (N=60)**		**Evenamide 30 mg *bid* (N=50)**	
Scale Category	**Visit**	**Statistics**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Total Score	Screening	n	50		60		50	
		Mean (SD)	0.5 (1.03)		0.8 (1.44)		0.9 (1.71)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Baseline	n	50		60		50	
		Mean (SD)	0.4 (0.97)		0.6 (1.29)		0.8 (1.65)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.2 (0.78)	-0.2 (0.72)	0.5 (1.26)	-0.1 (0.56)	0.6 (1.40)	-0.2 (0.60)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 4	-3, 1	0, 6	-2, 2	0, 6	-2, 1

Abbreviations: N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Source: Listing 16.2.15; Adapted from Table 14.3.9

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.

A clinically significant treatment-emergent post-baseline abnormal finding (visual field defect) on the eye examination was noted in 1 (2.0%) subject from evenamide 30 mg *bid* treated group. One subject (2.0%) each from evenamide 7.5 mg and 30 mg *bid* treated groups was noted to have a clinically non-significant treatment-emergent post-baseline abnormal finding (visual acuity defect) on the eye examination.

11.8.7 Seizure Checklist

Seizure Checklist abnormal findings for the Safety Population are provided in Table 14.3.10 and subject level data listing of findings reported on the Seizure Checklist is provided in Listing 16.2.16.

No seizure-like symptom was reported in any subject from any of the three treatment groups in the assessment of the Seizure Checklist.

11.9 Safety Conclusions

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

- A total of 41 subjects (25.6%) reported at least one TEAE, which included 13 (26.0%), 10 (16.7%) and 18 (36.0%) 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 ‘General disorders and administration site conditions’ and ‘Nervous system disorders’ by 10 subjects (6.3%) each. The most frequently reported TEAEs (those with a ≥1% incidence of events) by the PT were dizziness by 3 (1.9%) subjects; and asthenia, fatigue, postural dizziness, and hypersomnia by 2 (1.3%) subjects each.
- Of the 41 overall TEAEs reported, 32 (20.0%) were of mild severity and 9 (5.6%) were of moderate severity. None of the reported TEAE were of severe intensity.
- Medication errors, asymptomatic and not associated with adverse events, were reported in 7 (4.38%) subjects in the evenamide 30 mg *bid* treated group. None of the subjects in any of the 3 treatment groups reported a treatment-related SAE.
- A total of 15 subjects (9.4%) reported at least one treatment-related TEAE, which included 5 (10.0%), 4 (6.7%) and 6 (12.0%) 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’ by 6

subjects (3.8%), and 'General disorders and administration site conditions' by 3 subjects (1.9%). Out of the 15 overall treatment-related TEAEs reported, 11 (6.9%) were of mild severity and 4 (2.5%) were of moderate severity. None of the reported treatment-related TEAEs were of severe intensity.

- Overall, 2 (1.3%) subjects reported a TEAE leading to study drug discontinuation, which included 1 (2.0%) subject each from the evenamide 7.5 mg and 30 mg *bid* treated groups.
- No TEAE resulting in death was reported during the study.
- Very few clinical laboratory parameters (hematology and clinical chemistry) results 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 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. Low hemoglobin level (≤ 0.85 x lower limit of normal (LLN) g/L), was seen in 7 (14.0%), 10 (16.7%) and 6 (12.0%) subjects and low high density lipoprotein level (≤ 0.8 mmol/L) was seen in 19 (38.0%), 19 (31.7%) and 21 (42.0%) 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 significant 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 significant effects or trends were observed at the end of treatment compared to baseline for any of the three doses of evenamide on physical examination, neurological examination, extrapyramidal symptoms (assessed by the ESRS-A), changes in depressive symptoms (assessed by the CDSS), eye examination, and seizure-like symptoms reported on the Seizure Checklist.

Overall, the results for the safety parameters assessed in the study indicated that evenamide, given orally at three fixed doses (7.5, 15 and 30 mg *bid*) in patients with treatment-resistant schizophrenia, was well tolerated and without any major safety concern.

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 at the approximately the same time relative to the morning dose of study medication during the scheduled clinic visits on Days 8, 15, 29 and 43. 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 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 Screening, Baseline (Day 0), and at Days 8, 15, 29 and 43 (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

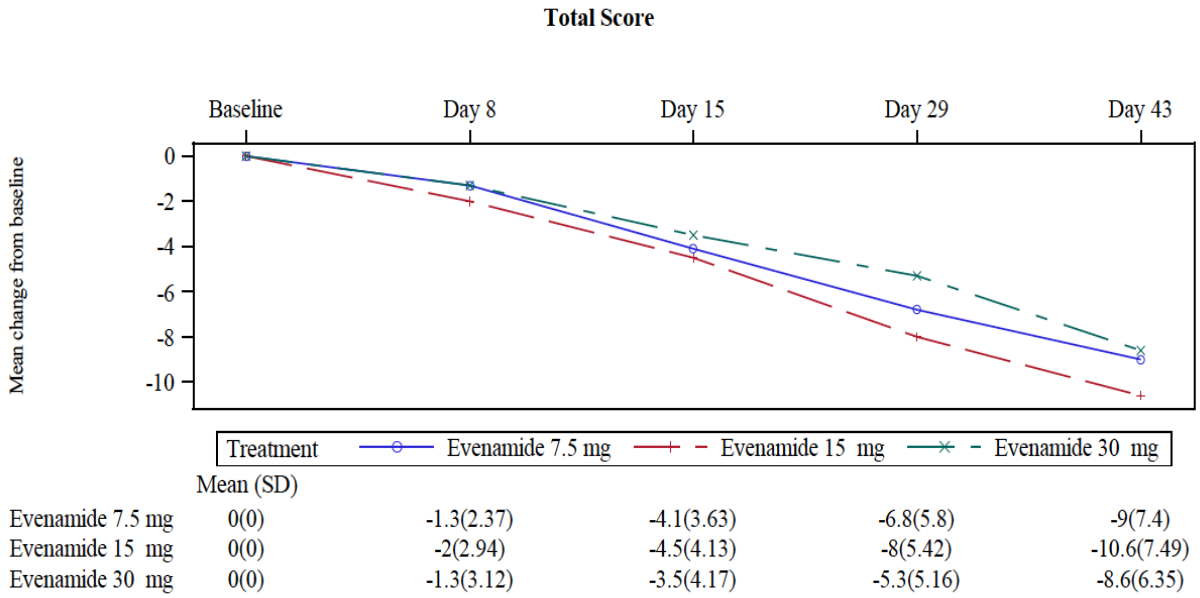
The mean change from baseline at Day 43 in PANSS Total Score using within group comparisons (*Primary Estimand: Effect of being randomized to an evenamide dose, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline in PANSS total score at Day 43*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.1, with by subject details in Listing 16.2.6.1.2. The estimand panel is presented in Table 9-6. Further details of the efficacy estimand analysis has been described in Section 9.7.1.5.5.

A steady improvement in the PANSS total score (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the 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, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.19), 79.2 (5.17) and 79.4 (4.77) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of PANSS total score, with a mean (SD) of 71.1 (9.56), 68.6 (8.07) and 70.6 (7.05), was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -9.0 (7.40) (95% CI: -11.13, -6.83; $p<0.001$), -10.6 (7.49) (95% CI: -12.63, -8.62; $p<0.001$) and -8.6 (6.35) (95% CI: -10.43, -6.74; $p<0.001$) 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.



Source: Listing 16.2.6.1.1, Table 14.2.1.1; 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=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Screening	n	48		59		49	
	Mean (SD)	80.1 (5.30)		79.2 (5.09)		79.7 (5.30)	
	Median	80		80		79	
	Min, Max	71, 89		70, 89		71, 89	
Baseline	n	48		59		49	
	Mean (SD)	80.1 (5.19)		79.2 (5.17)		79.4 (4.77)	
	Median	82		80		79	
	Min, Max	72, 89		70, 89		71, 89	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	78.8 (5.49)	-1.3 (2.37)	77.2 (5.61)	-2.0 (2.94)	77.8 (5.09)	-1.3 (3.12)
	Median	78.5	-0.5	78	-1	76	0
	Min, Max	69, 91	-10, 2	65, 89	-16, 2	70, 94	-13, 5

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Day 15	n	48	48	57	57	48	48
	Mean (SD)	76.0 (6.84)	-4.1 (3.63)	74.7 (6.54)	-4.5 (4.13)	75.8 (5.80)	-3.5 (4.17)
	Median	77	-4	74	-4	74.5	-2.5
	Min, Max	60, 89	-15, 0	60, 88	-17, 3	68, 91	-16, 2
Day 29	n	48	48	56	56	49	49
	Mean (SD)	73.3 (8.64)	-6.8 (5.80)	71.3 (7.37)	-8.0 (5.42)	74.1 (6.35)	-5.3 (5.16)
	Median	73	-5	72	-8.5	74	-4
	Min, Max	54, 88	-28, 2	55, 88	-22, 4	64, 90	-20, 3
Day 43	n	48	48	56	56	48	48
	Mean (SD)	71.1 (9.56)	-9.0 (7.40)	68.6 (8.07)	-10.6 (7.49)	70.6 (7.05)	-8.6 (6.35)
	Median	70.5	-8	68.5	-10	70.5	-8.5
	Min, Max	48, 91	-34, 3	49, 87	-28, 12	58, 85	-25, 1
	95% CI		(-11.13, -6.83)		(-12.63, -8.62)		(-10.43, -6.74)
	p-value		<.001		<.001		<.001

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.
p-Value = Paired t-test.
Source: Listing 16.2.6.1.2; Table 14.2.1.1

Mixed-effects repeated measures model approach (MMRM)

Mean changes from baseline to endpoint (Day 43 or early discontinuation) on the PANSS total score were compared between the evenamide dose groups using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate for the mITT Population. The results are presented in Table 14.2.1.1a, with by subject details in Listing 16.2.6.1.2. The repeated measures were the change from baseline in the PANSS total score obtained at the scheduled visits at Days 8, 15, 29 and 43.

A steady improvement in the PANSS total score (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the 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, reflecting a continuation of improvement in the symptoms of schizophrenia.

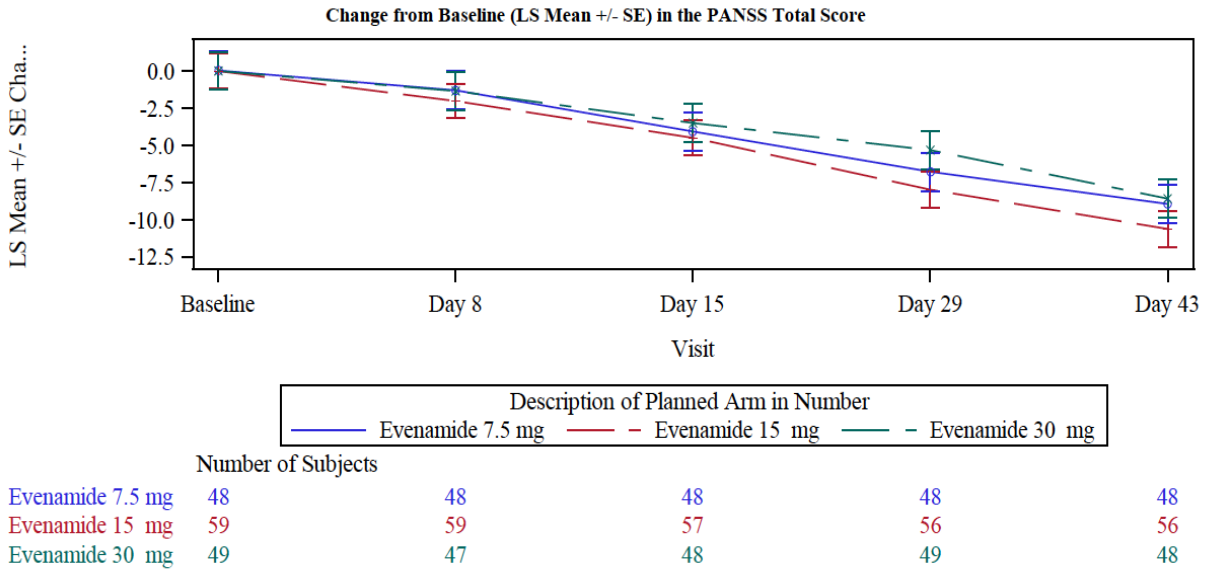
At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.19), 79.2 (5.17) and 79.4

(4.77) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of PANSS total score, with a mean (SD) of 71.1 (9.56), 68.6 (8.07) and 70.6 (7.05), was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of -9.0 (7.40), -10.6 (7.49) and -8.6 (6.35) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

A similar trend was seen in the analysis of LS mean (SE) values of PANSS total score, with change from baseline at Week 43 of -8.9 (1.02) (95% CI: -10.96, -6.92), -9.6 (0.69) (95% CI: -11.01, -8.27) and -8.5 (1.01) (95% CI: -10.46, -6.45) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The LS mean difference (SE) in PANSS total score between the combined evenamide (15 + 30 mg *bid*) versus evenamide low dose (7.5 mg *bid*) groups was found to be statistically non-significant [-0.7 (1.24) (95% CI: -3.16, 1.74; p=0.569) (Table 12-2, Figure 12-2). Therefore, no further testing of between-group differences was performed.

Figure 12-2: Change from Baseline (LS Mean + SE) in the PANSS Total Score Mixed Model - mITT Population.



Source: Listing 16.2.6.1.1, Table 14.2.1.1a; Figure 14.2.1.2

Table 12-2: Summary of Mean Value and Change from Baseline in PANSS Total Score by Visit Between Dose Group Comparisons - MMRM - mITT Population.

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Mean (SD)	80.1 (5.19)		79.2 (5.17)		79.4 (4.77)	
	Median	82		80		79	
	Min, Max	72, 89		70, 89		71, 89	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	78.8 (5.49)	-1.3 (2.37)	77.2 (5.61)	-2.0 (2.94)	77.8 (5.09)	-1.3 (3.12)
	Median	78.5	-0.5	78	-1	76	0
	Min, Max	69, 91	-10, 2	65, 89	-16, 2	70, 94	-13, 5
Day 15	n	48	48	57	57	48	48
	Mean (SD)	76.0 (6.84)	-4.1 (3.63)	74.7 (6.54)	-4.5 (4.13)	75.8 (5.80)	-3.5 (4.17)
	Median	77	-4	74	-4	74.5	-2.5
	Min, Max	60, 89	-15, 0	60, 88	-17, 3	68, 91	-16, 2
Day 29	n	48	48	56	56	49	49
	Mean (SD)	73.3 (8.64)	-6.8 (5.80)	71.3 (7.37)	-8.0 (5.42)	74.1 (6.35)	-5.3 (5.16)
	Median	73	-5	72	-8.5	74	-4
	Min, Max	54, 88	-28, 2	55, 88	-22, 4	64, 90	-20, 3
Day 43	n	48	48	56	56	48	48
	Mean (SD)	71.1 (9.56)	-9.0 (7.40)	68.6 (8.07)	-10.6 (7.49)	70.6 (7.05)	-8.6 (6.35)
	Median	70.5	-8	68.5	-10	70.5	-8.5
	Min, Max	48, 91	-34, 3	49, 87	-28, 12	58, 85	-25, 1
	LS Mean (SE)		-8.9 (1.02)		-9.6 (0.69)		-8.5 (1.01)
	95% CI		(-10.96, -6.92)		(-11.01, -8.27)		(-10.46, -6.45)
	LS Mean Diff (SE)				-0.7(1.24) [a]		
	95% CI				(-3.16, 1.74)		
	p-value				0.569		

Abbreviations: MMRM = Mixed Model Repeated Measure, N – Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, Min = Minimum, Max = Maximum
[a] Results are for 15 mg bid + 30 mg bid combined. [b] If combined 15 mg bid + 30 mg bid result was significant then 30 mg would be compared with 7.5 mg bid.
A mixed model repeated measures (MMRM) linear regression model was fitted, with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline PANSS total score obtained at the scheduled visits Days 8, 15, 29 and 43(Endpoint), respectively. LS Mean Difference and p-value correspond to the difference between dose groups.
Source: Listing 16.2.6.1.2; Table 14.2.1.1a

12.1.1.2 PANSS Subscales

PANSS Positive Syndrome subscale scores

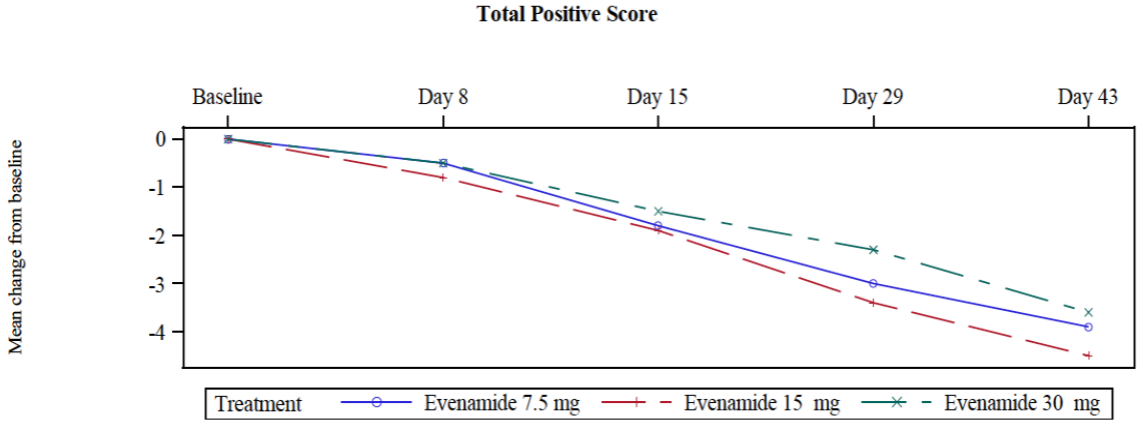
The mean change from baseline at Day 43 in PANSS Positive Syndrome subscale scores using within group comparisons was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.2, with by subject details in Listing 16.2.6.1.1.

A steady improvement in the PANSS Positive Syndrome subscale scores (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS Positive Syndrome subscale scores recorded was 24.0 (3.61), 23.8 (3.35) and 23.1 (2.90) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a significant mean (SD) change from baseline in the PANSS Positive Syndrome subscale scores of -3.9 (3.52) (95% CI: -4.94, -2.89; *p<0.001*), -4.5 (3.75) (95% CI: -5.49, -3.48; *p<0.001*) and -3.6 (2.77) (95% CI: -4.41, -2.80); *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 Positive Syndrome Subscale Score - mITT Population.



	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.5(1.25)	-1.8(1.81)	-3(2.9)	-3.9(3.52)
Evenamide 15 mg	0(0)	-0.8(1.21)	-1.9(2.23)	-3.4(2.8)	-4.5(3.75)
Evenamide 30 mg	0(0)	-0.5(1.16)	-1.5(2)	-2.3(2.5)	-3.6(2.77)

Source: Listing 16.2.6.1.1, Table 14.2.1.2; Figure 14.2.1.1

Table 12-3: 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=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Visit	**Statistic**	**Change from Baseline**	**Change from Baseline**	**Change from Baseline**
Baseline	n	48	59	49
	Mean (SD)	24.0 (3.61)	23.8 (3.35)	23.1 (2.90)
	Median	24.5	24	23
	Min, Max	17, 36	17, 30	17, 29
Day 8	n	48	59	47
	Mean (SD)	-0.5 (1.25)	-0.8 (1.21)	-0.5 (1.16)
	Median	0	0	0
	Min, Max	-5, 2	-4, 1	-5, 1
Day 15	n	48	57	48
	Mean (SD)	-1.8 (1.81)	-1.9 (2.23)	-1.5 (2.00)
	Median	-2	-1	-1
	Min, Max	-9, 1	-9, 2	-7, 1
Day 29	n	48	56	49
	Mean (SD)	-3.0 (2.90)	-3.4 (2.80)	-2.3 (2.50)
	Median	-2.5	-3	-2
	Min, Max	-15, 1	-9, 3	-7, 2
Day 43	n	48	56	48
	Mean (SD)	-3.9 (3.52)	-4.5 (3.75)	-3.6 (2.77)
	Median	-3	-4	-4
	Min, Max	-15, 3	-13, 2	-10, 1
	95% CI	(-4.94, -2.89)	(-5.49, -3.48)	(-4.41, -2.80)
	P-Value	<.001	<.001	<.001

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. P-Value = Paired t-test. Source: Listing 16.2.6.1.1; Table 14.2.1.2

PANSS Negative Syndrome scores

The mean change from Baseline at Day 43 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 14.2.1.2, with by subject details in Listing 16.2.6.1.1.

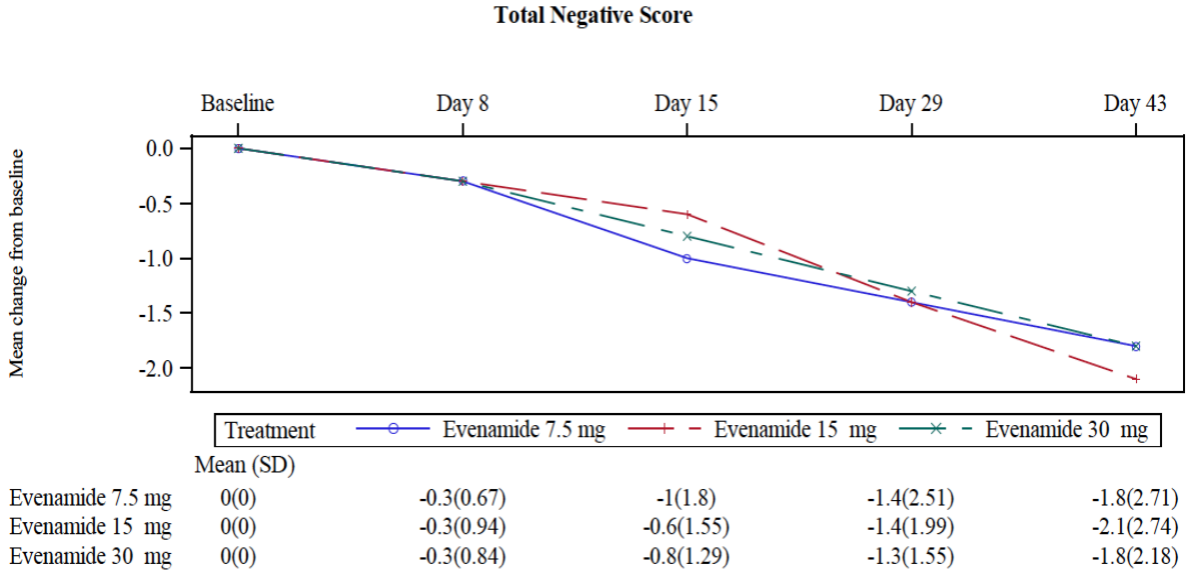
A steady improvement in the PANSS Negative Syndrome subscale scores (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS Negative Syndrome subscale scores recorded was 20.1

(3.27), 19.6 (3.72) and 19.6 (3.05) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a significant mean (SD) change from baseline in the PANSS Negative Syndrome subscale scores of -1.8 (2.71) (95% CI: -2.62, -1.05; *p<0.001*), -2.1 (2.74) (95% CI: -2.86, -1.39; *p<0.001*) and -1.8 (2.18) (95% CI: -2.47, -1.20; *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 Negative Syndrome Subscale Score - mITT Population.



	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.3(0.67)	-1(1.8)	-1.4(2.51)	-1.8(2.71)
Evenamide 15 mg	0(0)	-0.3(0.94)	-0.6(1.55)	-1.4(1.99)	-2.1(2.74)
Evenamide 30 mg	0(0)	-0.3(0.84)	-0.8(1.29)	-1.3(1.55)	-1.8(2.18)

Source: Listing 16.2.6.1.1, Table 14.2.1.2; Figure 14.2.1.1

Table 12-4: 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=48)	**Evenamide 15 mg *bid* (N=59)**	**Evenamide 30 mg *bid* (N=49)**
Visit	**Statistic**	**Change from Baseline**	**Change from Baseline**	**Change from Baseline**
Baseline	n	48	59	49
	Mean (SD)	20.1 (3.27)	19.6 (3.72)	19.6 (3.05)
	Median	20	20	20
	Min, Max	12, 31	10, 29	12, 26
Day 8	n	48	59	47
	Mean (SD)	-0.3 (0.67)	-0.3 (0.94)	-0.3 (0.84)
	Median	0	0	0
	Min, Max	-2, 1	-6, 1	-3, 1
Day 15	n	48	57	48
	Mean (SD)	-1.0 (1.80)	-0.6 (1.55)	-0.8 (1.29)
	Median	0	0	0

		Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Visit	**Statistic**	**Change from Baseline**	**Change from Baseline**	**Change from Baseline**
	Min, Max	-7, 1	-6, 4	-5, 1
Day 29	n	48	56	49
	Mean (SD)	-1.4 (2.51)	-1.4 (1.99)	-1.3 (1.55)
	Median	-1	-1	-1
	Min, Max	-10, 2	-7, 6	-5, 1
Day 43	n	48	56	48
	Mean (SD)	-1.8 (2.71)	-2.1 (2.74)	-1.8 (2.18)
	Median	-1	-1.5	-1.5
	Min, Max	-11, 3	-10, 7	-9, 1
	95% CI	(-2.62, -1.05)	(-2.86, -1.39)	(-2.47, -1.20)
	P-Value	<.001	<.001	<.001

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. P-Value = Paired t-test. Source: Listing 16.2.6.1.1; Table 14.2.1.2

PANSS General Psychopathology scores

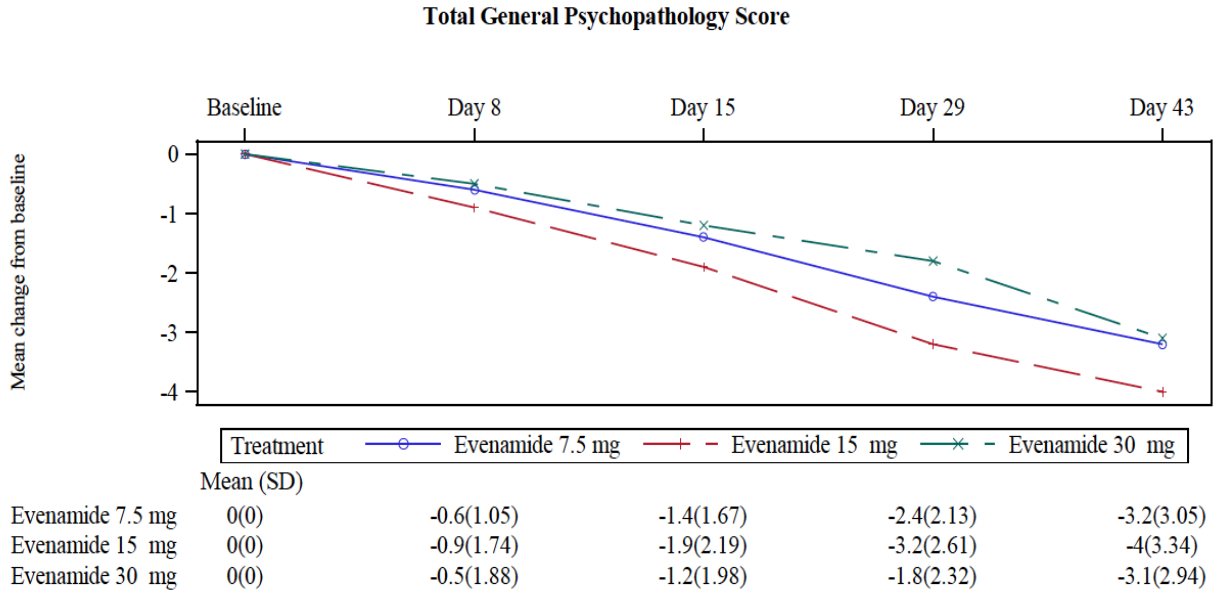
The mean change from Baseline at Day 43 in PANSS General Psychopathology subscale scores using within group comparisons was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.2, with by subject details in Listing 16.2.6.1.1.

A steady improvement in the PANSS General Psychopathology subscale scores (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups.

At baseline, the mean (SD) of PANSS General Psychopathology subscale scores recorded was 35.9 (3.93), 35.8 (3.48) and 36.7 (3.77) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a significant mean (SD) change from baseline in the PANSS General Psychopathology subscale scores of -3.2 (3.05) (95% CI: -4.12, -2.34; *p<0.001*), -4.0 (3.34) (95% CI: -4.91, -3.12; *p<0.001*) and -3.1 (2.94) (95% CI: -4.00, -2.29; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. (Table 12-5, Figure 12-5).

Figure 12-5: Mean Change from Baseline by Visit in PANSS General Psychopathology Subscale Score - mITT Population



	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.6(1.05)	-1.4(1.67)	-2.4(2.13)	-3.2(3.05)
Evenamide 15 mg	0(0)	-0.9(1.74)	-1.9(2.19)	-3.2(2.61)	-4(3.34)
Evenamide 30 mg	0(0)	-0.5(1.88)	-1.2(1.98)	-1.8(2.32)	-3.1(2.94)

Source: Listing 16.2.6.1.1, Table 14.2.1.2; Figure 14.2.1.1

Table 12-5: 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=48)	**Evenamide 15 mg *bid* (N=59)**	**Evenamide 30 mg *bid* (N=49)**
Visit	**Statistic**	**Change from Baseline**	**Change from Baseline**	**Change from Baseline**
Baseline	n	48	59	49
	Mean (SD)	35.9 (3.93)	35.8 (3.48)	36.7 (3.77)
	Median	36	35	37
	Min, Max	28, 49	29, 46	30, 44
Day 8	n	48	59	47
	Mean (SD)	-0.6 (1.05)	-0.9 (1.74)	-0.5 (1.88)
	Median	0	0	0
	Min, Max	-5, 1	-9, 2	-8, 3
Day 15	n	48	57	48
	Mean (SD)	-1.4 (1.67)	-1.9 (2.19)	-1.2 (1.98)
	Median	-1.5	-2	-1
	Min, Max	-7, 2	-10, 3	-8, 2
Day 29	n	48	56	49
	Mean (SD)	-2.4 (2.13)	-3.2 (2.61)	-1.8 (2.32)
	Median	-2	-2.5	-2
	Min, Max	-8, 2	-12, 0	-9, 2
Day 43	n	48	56	48

		Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Visit	**Statistic**	**Change from Baseline**	**Change from Baseline**	**Change from Baseline**
	Mean (SD)	-3.2 (3.05)	-4.0 (3.34)	-3.1 (2.94)
	Median	-2.5	-3	-3
	Min, Max	-11, 4	-14, 4	-10, 2
	95% CI	(-4.12, -2.34)	(-4.91, -3.12)	(-4.00, -2.29)
	P-Value	<.001	<.001	<.001

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.
P-Value = Paired t-test.
Source: Listing 16.2.6.1.1; Table 14.2.1.2

12.1.1.3 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 14.2.1.3, 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) or had a 4-point change (improvement) on the PANSS Positive Syndrome sub-scale score from baseline.

At Day 8, none of the subjects in the three treatment groups could be termed as responders based on the PANSS total score. At Day 15, one (1.7%) subject in evenamide 15 mg *bid* treated group was a responder based on the PANSS total score. At Day 29, 4 (8.3%), 4 (6.8%) and 2 (4.0%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, were responders based on the PANSS total score. By Day 43, 9 (18.8%), 11 (18.6%) and 4 (8.2%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, were responders based on the PANSS total score. The proportion of responders was higher in evenamide 7.5 mg and 15 mg *bid* treated groups, compared to the 30 mg *bid* treated group (Table 12-6).

At Day 8, 2 (4.2%), 3 (5.0%) and 1 (2.0%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, could be termed as responders based on the PANSS Positive Syndrome sub-scale. At Day 15, 5 (10.4%), 13 (22.0%) and 9 (18.4%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, were responders based on the PANSS Positive Syndrome sub-scale. At Day 29, 19 (39.6%), 24 (40.7%) and 16 (32.7%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, were responders based on the PANSS Positive Syndrome sub-scale score. By Day 43, 23 (47.9%), 31 (52.5%) and 25 (51.0%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively, were responders based on the PANSS Positive Syndrome sub-scale score. Similar proportion of

responders were seen in all the three treatment groups (Table 12-6).

An increase in the proportion of responders based on the PANSS total score and Positive Syndrome sub-scale score was observed between Day 8 and Day 43, indicating continuing improvement in the proportion of patients experiencing clinically significant improvement in symptoms of schizophrenia.

Table 12-6: 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=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)	Total [a] (N=156)
Day 8	Total Score	Change >=20%	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total Positive Score	>=4-Point Improvement	n (%)	2 (4.2)	3 (5.1)	1 (2.0)	6 (3.9)
Day 15	Total Score	Change >=20%	n (%)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
	Total Positive Score	>=4-Point Improvement	n (%)	5 (10.4)	13 (22.0)	9 (18.4)	27 (17.3)
Day 29	Total Score	Change >=20%	n (%)	4 (8.3)	4 (6.8)	2 (4.0)	10 (6.4)
	Total Positive Score	>=4-Point Improvement	n (%)	19 (39.6)	24 (40.7)	16 (32.7)	59 (37.8)
Day 43	Total Score	Change >=20%	n (%)	9 (18.8)	11 (18.6)	4 (8.2)	24 (15.4)
	Total Positive Score	>=4-Point Improvement	n (%)	23 (47.9)	31 (52.5)	25 (51.0)	79 (50.6)

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat. Responder analyses were 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 Syndrome sub-scale.
Source: Listing 16.2.6.1.2; Table 14.2.1.3

12.1.1.4 Sensitivity Analysis on Change from Baseline in PANSS Total Score

Paired t-test Using Multiple Imputation

The mean change from Baseline at Day 43 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 Day 43 compared to baseline in all the three treatment groups. Mean (SD) values of the PANSS total score showed a decreasing trend at all the time points during the study in all the three treatment groups, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.19), 79.2 (5.17) and 79.4 (4.77) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of PANSS total score, with a mean (SD) of 71.1 (9.56), 68.6 (7.92) and 70.9 (7.29) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -9.0 (7.40) (95% CI: -11.13, -6.83; *p<0.001*), -10.6 (7.33) (95% CI: -12.52, -8.67; *p<0.001*) and -8.5 (6.32) (95% CI: -10.27, -6.69; *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 PANSS Total Score at Day 43 - Paired t-test Using Multiple Imputation - mITT Population.

		Evenamide 7.5 mg *bid* (N=48)	**Evenamide 15 mg *bid* (N=59)**	**Evenamide 30 mg *bid* (N=49)**
Visit	**Statistic**			
Baseline	n	48	59	49
	Mean (SD)	80.1 (5.19)	79.2 (5.17)	79.4 (4.77)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 89
Day 43	n	48	59	49
	Mean (SD)	71.1 (9.56)	68.6 (7.92)	70.9 (7.29)
	Median	70.5	68	71
	Min, Max	48, 91	49, 87	58, 85
	Mean change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.33)	-8.5 (6.32)
	95% CI	(-11.13, -6.83)	(-12.52, -8.67)	(-10.27, -6.69)
	p-value	<.001	<.001	<.001

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, 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.
Source: Listing 16.2.6.1.2; Table 14.2.1.4

Paired t-test Using LOCF Supportive Estimand

The mean change from Baseline at Day 43 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 Day 43 compared to baseline in all the three treatment groups. Mean (SD) values of the PANSS total score showed a decreasing trend at each visit, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of PANSS total score recorded was 80.1 (5.19), 79.2 (5.17) and 79.4 (4.77) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of PANSS total score with a mean (SD) of 71.1 (9.56), 69.0 (8.03) and 71.0 (7.51) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -9.0 (7.40) (95% CI: -11.13, -6.83; *p<0.001*), -10.2 (7.49) (95% CI: -12.19, -8.29; *p<0.001*) and -8.4 (6.43) (95% CI: -10.23, -6.54; *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 Day 43 - Paired t-test Using LOCF Supportive Estimand - mITT Population.

		Evenamide 7.5 mg *bid* (N=48)	**Evenamide 15 mg *bid* (N=59)**	**Evenamide 30 mg *bid* (N=49)**
Visit	**Statistic**			
Baseline	n	48	59	49
	Mean (SD)	80.1 (5.19)	79.2 (5.17)	79.4 (4.77)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 89
Day 43	n	48	59	49
	Mean (SD)	71.1 (9.56)	69.0 (8.03)	71.0 (7.51)
	Median	70.5	70.0	71.0
	Min, Max	48, 91	49, 87	58, 90
	Mean change from Baseline (SD)	-9.0 (7.40)	-10.2 (7.49)	-8.4 (6.43)
	95% CI	(-11.13, -6.83)	(-12.19, -8.29)	(-10.23, -6.54)
	p-value	<.001	<.001	<.001

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. The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data was not carried forward to post baseline visit.

		Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Visit	**Statistic**			

p-value = Paired t-test.
Source: Listing 16.2.6.1.2; Table 14.2.1.5

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 Day 43 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, LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in PANSS total score at Day 43 (Table 12-9). A significant mean (SD) change from baseline (*p<0.001*) was observed in all the three treatment groups with all models.

Table 12-9: Sensitivity Analysis on Change from Baseline in PANSS Total Score at Day 43 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Primary Estimand	Mean Change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.49)	-8.6 (6.35)
	95% CI	(-11.13, -6.83)	(-12.63, -8.62)	(-10.43, -6.74)
	p-value	<.001	<.001	<.001
LOCF@	Mean Change from Baseline (SD)	-9.0 (7.40)	-10.2 (7.49)	-8.4 (6.43)
	95% CI	(-11.13, -6.83)	(-12.19, -8.29)	(-10.23, -6.54)
	p-value	<.001	<.001	<.001
MI	Mean change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.33)	-8.5 (6.32)
	95% CI	(-11.13, -6.83)	(-12.52, -8.67)	(-10.27, -6.69)
	p-value	<.001	<.001	<.001

Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test; LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, Min=Minimum, Max=Maximum, n - number of subjects in the specified category, the results obtained in each model are compared in this table.
@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF would be considered as supportive.
Source: Listing 16.2.6.1.2; Table 14.2.1.6

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 assessment was conducted at Screening, Baseline (Day 0), and Days 8, 15, 29 and 43 (or at early discontinuation), while the CGI-C was assessed on Days 8, 15, 29 and 43 (or at early discontinuation).

12.1.2.1 Clinical Global Impression – Severity of Illness (CGI-S) score

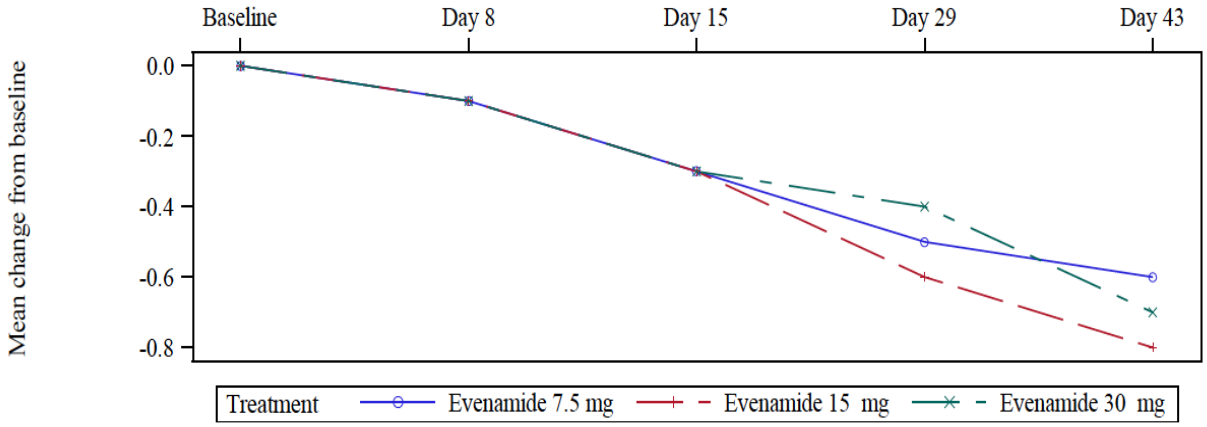
The mean change from Baseline at Day 43 on the CGI-S was summarized by visit and is presented in Table 14.2.2.1, with by subject details are presented Listing 16.2.6.2. Paired *t-test* was also performed at post-dose visits to analyze CGI-S change from baseline within each dose group.

A significant ($p<0.001$) improvement (lowering of scores) in the CGI-S was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups, indicating improvement in severity of illness.

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.65), 4.5 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of CGI-S scores with a mean (SD) of 3.9 (0.87), 3.7 (0.70) and 3.8 (0.64) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -0.6 (0.79) (95% CI: -0.87, -0.42; $p<0.001$), -0.8 (0.72) (95% CI: -1.01, -0.63; $p<0.001$) and -0.7 (0.62) (95% CI: -0.87, -0.51; $p<0.001$) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-10 and Figure 12-6).

Figure 12-6: Mean Change from Baseline by Visit in Clinical Global Impression - Severity of Illness (CGI-S) - mITT Population.



	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.1(0.35)	-0.3(0.49)	-0.5(0.65)	-0.6(0.79)
Evenamide 15 mg	0(0)	-0.1(0.33)	-0.3(0.57)	-0.6(0.62)	-0.8(0.72)
Evenamide 30 mg	0(0)	-0.1(0.31)	-0.3(0.49)	-0.4(0.58)	-0.7(0.62)

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=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Screening	n	48		59		49	
	Mean (SD)	4.5 (0.65)		4.5 (0.60)		4.4 (0.49)	
	Median	4		4		4	
	Min, Max	4, 6		4, 6		4, 5	
Baseline	n	48		59		49	
	Mean (SD)	4.6 (0.65)		4.5 (0.60)		4.4 (0.50)	
	Median	4		4		4	
	Min, Max	4, 6		4, 6		4, 5	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	4.5 (0.68)	-0.1 (0.35)	4.4 (0.59)	-0.1 (0.33)	4.3 (0.52)	-0.1 (0.31)
	Median	4	0	4	0	4	0
	Min, Max	3, 6	-2, 0	3, 6	-1, 0	3, 5	-1, 0
Day 15	n	48	48	57	57	48	48

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Mean (SD)	4.3 (0.74)	-0.3 (0.49)	4.2 (0.69)	-0.3 (0.57)	4.2 (0.48)	-0.3 (0.49)
	Median	4	0	4	0	4	0
	Min, Max	3, 6	-2, 0	2, 6	-3, 0	3, 5	-2, 0
Day 29	n	48	48	56	56	49	49
	Mean (SD)	4.0 (0.81)	-0.5 (0.65)	3.9 (0.75)	-0.6 (0.62)	4.0 (0.54)	-0.4 (0.58)
	Median	4	0	4	-1	4	0
	Min, Max	2, 6	-3, 0	2, 6	-3, 0	3, 5	-2, 0
Day 43	n	48	48	56	56	48	48
	Mean (SD)	3.9 (0.87)	-0.6 (0.79)	3.7 (0.70)	-0.8 (0.72)	3.8 (0.64)	-0.7 (0.62)
	Median	4	-1	4	-1	4	-1
	Min, Max	2, 6	-3, 1	2, 6	-3, 0	3, 5	-2, 0
	95% CI		(-0.87, -0.42)		(-1.01, -0.63)		(-0.87, -0.51)
	p-value		<.001		<.001		<.001

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.
Source: Listing 16.2.6.2; Table 14.2.2.1

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 Day 43 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 Day 43 compared to baseline in all the three treatment groups. Mean (SD) values of the CGI-S score showed a decreasing trend at all the time points during the study in all the three treatment groups, reflecting a continuation of improvement in severity of illness.

A significant ($p<0.001$) improvement (lowering of scores) in the CGI-S was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups, indicating improvement in severity of illness (Table 12-11).

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.65), 4.5 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of CGI-S scores with a mean (SD) of 3.9 (0.87), 3.7 (0.69) and 3.8 (0.64) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -0.6 (0.79) (95% CI: -0.87, -0.42; *p<0.001*), -0.8 (0.70) (95% CI: -1.00, -0.63; *p<0.001*) and -0.7 (0.62) (95% CI: -0.86, -0.51; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Table 12-11: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 - Paired t-test Using Multiple Imputation - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Baseline	n	48	59	49
	Mean (SD)	4.6 (0.65)	4.5 (0.60)	4.4 (0.50)
	Median	4.0	4.0	4.0
	Min, Max	4, 6	4, 6	4, 5
Day 43	n	48	59	49
	Mean (SD)	3.9 (0.87)	3.7 (0.69)	3.8 (0.64)
	Median	4.0	4.0	4.0
	Min, Max	2, 6	2, 6	3, 5
	Mean change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.70)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.00, -0.63)	(-0.86, -0.51)
	p-value	<.001	<.001	<.001

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min=Minimum, Max=Maximum.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. p-value = Paired t-test.
Source: Listing 16.2.6.2; Table 14.2.2.2

Paired t-test Using LOCF

The mean change from Baseline at Day 43 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 and 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 Day 43 compared to baseline in all the three treatment groups. Mean (SD) values of

the CGI-S score showed a decreasing trend at the time points during the study, reflecting a continuation of improvement in severity of illness (Table 12-12).

At baseline, the mean (SD) of CGI-S scores recorded was 4.6 (0.65), 4.5 (0.60) and 4.4 (0.50) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, a reduction of CGI-S scores with a mean (SD) of 3.9 (0.87), 3.8 (0.70) and 3.8 (0.65) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of -0.6 (0.79) (95% CI: -0.87, -0.42; *p<0.001*), -0.8 (0.72) (95% CI: -0.97, -0.59; *p<0.001*) and -0.7 (0.63) (95% CI: -0.85, -0.49; *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 Day 43 - Paired t-test Using LOCF - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Baseline	n	48	59	49
	Mean (SD)	4.6 (0.65)	4.5 (0.60)	4.4 (0.50)
	Median	4.0	4.0	4.0
	Min, Max	4, 6	4, 6	4, 5
Day 43	n	48	59	49
	Mean (SD)	3.9 (0.87)	3.8 (0.70)	3.8 (0.65)
	Median	4.0	4.0	4.0
	Min, Max	2, 6	2, 6	3, 5
	Mean change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.63)
	95% CI	(-0.87, -0.42)	(-0.97, -0.59)	(-0.85, -0.49)
	p-value	<.001	<.001	<.001

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.
The LOCF approach imputes the missing data for the post dose scheduled visits to the Last value observed in previous scheduled visits. Baseline data was not carried forward to post baseline visit. p-value = Paired t-test.
Source: Listing 16.2.6.2; Table 14.2.2.3

Comparison Analysis of Different Models

A comparison of the different models used for the Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 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 different models (*Primary estimand, LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in CGI-S

score at Day 43. A significant mean (SD) change from baseline (*p<0.001*) was observed in all the three treatment groups with all models (Table 12-13).

Table 12-13: Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Primary Estimand	Mean Change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.01, -0.63)	(-0.87, -0.51)
	p-value	<.001	<.001	<.001
LOCF@	Mean Change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.63)
	95% CI	(-0.87, -0.42)	(-0.97, -0.59)	(-0.85, -0.49)
	p-value	<.001	<.001	<.001
MI	Mean change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.70)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.00, -0.63)	(-0.86, -0.51)
	p-value	<.001	<.001	<.001

Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test; LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, Min=Minimum, Max=Maximum, n - number of subjects in the specified category, the results obtained in each model are compared in this table.
@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF would be considered as supportive.
Source: Listing 16.2.6.2; Table 14.2.2.4

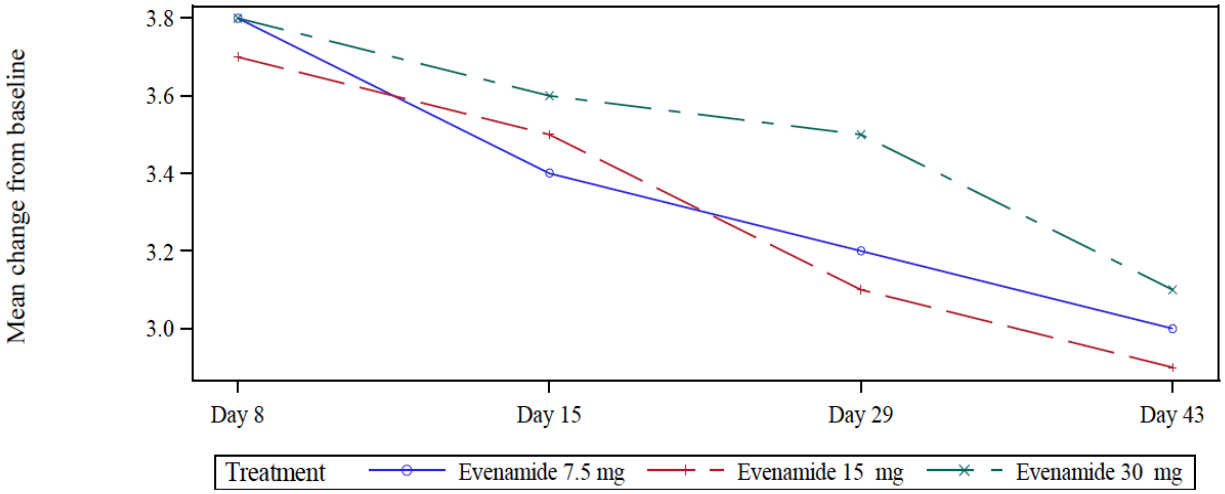
12.1.2.3 Clinical Global Impression - Change (CGI-C)

The change from baseline of Clinical Global Impression – Change (CGI-C) Score at Days 8, 15, 29 and 43 (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 Day 8, the mean (SD) of CGI-C scores recorded were 3.8 (0.43), 3.7 (0.49) and 3.8 (0.51) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, indicating improvement from baseline. By Day 43, the mean (SD) of CGI-C scores recorded were 3.0 (0.80), 2.9 (0.72) and 3.1 (0.65) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-14, Figure 12-7).

A reduction in the mean CGI-C score was observed between Day 8 and Day 43, from 3.8 to 3.0 in evenamide 7.5 mg, from 3.7 to 2.9 in evenamide 15 mg, and from 3.8 to 3.1 in evenamide 30 mg *bid* treated groups, indicating continuing improvement in overall severity of illness.

Figure 12-7: Mean Change from Baseline by Visit in Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population.



	Mean (SD)			
Evenamide 7.5 mg	3.8(0.43)	3.4(0.5)	3.2(0.62)	3(0.8)
Evenamide 15 mg	3.7(0.49)	3.5(0.6)	3.1(0.63)	2.9(0.72)
Evenamide 30 mg	3.8(0.51)	3.6(0.57)	3.5(0.62)	3.1(0.65)

Source: Listing 16.2.6.3; Table 14.2.3.1; Figure 14.2.3.1

Table 12-14: Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population.

Visit	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
Day 8	n	48	59	47
	Mean (SD)	3.8 (0.43)	3.7 (0.49)	3.8 (0.51)
	Median	4	4	4
	Min, max	2, 4	3, 5	2, 5
Day 15	n	48	57	48
	Mean (SD)	3.4 (0.50)	3.5 (0.60)	3.6 (0.57)
	Median	3	3	4
	Min, max	3, 4	2, 5	2, 5
Day 29	n	48	56	49
	Mean (SD)	3.2 (0.62)	3.1 (0.63)	3.5 (0.62)
	Median	3	3	4
	Min, max	2, 4	2, 4	2, 5
Day 43	n	48	56	48
	Mean (SD)	3.0 (0.80)	2.9 (0.72)	3.1 (0.65)
	Median	3	3	3
	Min, max	2, 5	2, 5	2, 4

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients,

Visit	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)
SD = Standard Deviation, Min = Minimum, Max = Maximum, mITT = Modified intent-to-treat *Source: Listing 16.2.6.3; Table 14.2.3.1*				

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 Days 8, 15, 29 and 43 (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.

The responder analysis was done considering change in the subject's condition from baseline, as indicated by the CGI-C score (CGI-C score change ≤ 3 [indicating improvement]) and (CGI-C score change >3 [indicating no change or worsening]).

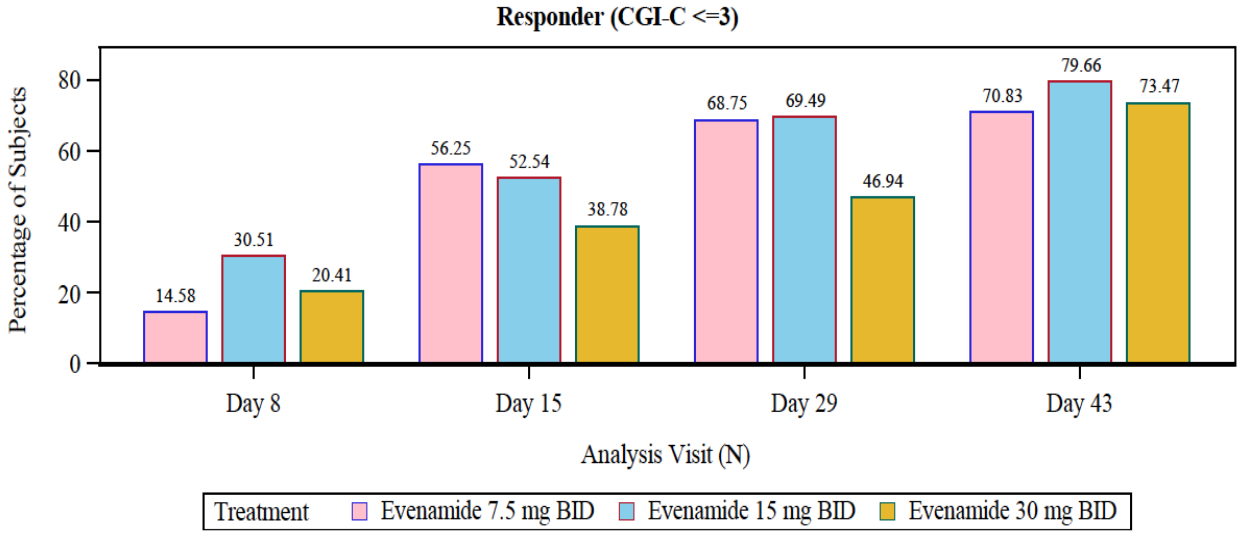
Responders

An increase in the proportion of responders (CGI-C score change ≤ 3 [indicating improvement]) was observed at all the timepoints from Day 8 to Day 43 (from 22.44% to 75.00% in overall subjects) in all the three treatment groups, indicating that more subjects were experiencing meaningful benefit. The highest proportion of responders were seen in the evenamide 15 mg *bid* treated group.

At Day 8, the proportion of subjects rated as at least "minimally improved" (CGI score ≤ 3) in the severity of illness was 22.4% overall, including 14.6%, 30.5% and 20.4% in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, the proportion of subjects rated as at least "minimally improved" (CGI score ≤ 3) in the severity of illness increased to 75.0% overall, including 70.8%, 79.7% and 73.5% in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively (Table 12-15; Figure 12-8).

Figure 12-8: Bar Chart for Clinical Global Impression – Change from Baseline (CGI-C) Responder Analysis - mITT Population



Source: Listing 16.2.6.3; Table 14.2.3.2; Figure 14.2.3.2

Table 12-15: Responder Analysis - Clinical Global Impression - Change (CGI-C) - mITT Population

Visit	Category	Statistic	Evenamide 7.5 mg *bid* (N=48)	Evenamide 15 mg *bid* (N=59)	Evenamide 30 mg *bid* (N=49)	Total [a] (N=156)
Day 8	CGI-C score <= 3	n (%)	7 (14.6)	18 (30.5)	10 (20.4)	35 (22.4)
	CGI-C score > 3	n (%)	41 (85.4)	41 (69.5)	37 (75.5)	119 (76.3)
Day 15	CGI-C score <= 3	n (%)	27 (56.3)	31 (52.5)	19 (38.8)	77 (49.4)
	CGI-C score > 3	n (%)	21 (43.8)	26 (44.1)	29 (59.2)	76 (48.7)
Day 29	CGI-C score <= 3	n (%)	33 (68.8)	41 (69.5)	23 (46.9)	97 (62.2)
	CGI-C score > 3	n (%)	15 (31.3)	15 (25.4)	26 (53.1)	56 (35.9)
Day 43	CGI-C score <= 3	n (%)	34 (70.8)	47 (79.7)	36 (73.5)	117 (75.0)
	CGI-C score > 3	n (%)	14 (29.2)	9 (15.3)	12 (24.5)	35 (22.4)

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat
Responder analysis was performed by summarizing the proportion of patients in each of the evenamide groups and overall, with different categories of improvement at each visit on the CGI-C Score.
Responders: Patients with CGI-C Score of 1, 2 or 3.
[a] Total was the total number of subjects taking the active treatment evenamide included in each category.
Source: Listing 16.2.6.3; Table 14.2.3.2

12.1.3 Strauss-Carpenter Level of Functioning (LOF) Scale Results

The Strauss-Carpenter Level of Functioning (LOF) scale was used as an instrument to evaluate

clinical outcomes in patients with schizophrenia. 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). A total score was calculated as the sum of the raw scores across the nine items. The LOF was conducted at Baseline (Day 0) and on Day 43 (or at early discontinuation).

The Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score and Sub-scale Scores at Day 43 – Within Group Comparisons for the mITT Population is presented in Table 14.2.4 and by Subject details in Listing 16.2.6.4 and 16.2.6.4a.

Total Score

An increase in the LOF total score was observed at Day 43 compared to baseline in all the three treatment groups, indicating improvement in functionality of subjects after treatment (Table 12-16).

At baseline, the mean (SD) of LOF total scores recorded were 18.0 (4.11), 18.2 (3.87) and 17.6 (4.27) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, an increase of LOF total score, with a mean (SD) of 18.9 (3.75), 19.4 (3.44) and 19.5 (5.26), was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively. A significant mean (SD) change from baseline of 0.9 (1.73) (95% CI: 0.37, 1.38; *p=0.001*), 1.3 (2.82) (95% CI: 0.53, 2.04; *p=0.001*) and 1.8 (3.35) (95% CI: 0.84, 2.79; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Table 12-16: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score at Day 43 – Within Group Comparisons - mITT Population.

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	18.0 (4.11)		18.2 (3.87)		17.6 (4.27)	
	Median	19		19		19	
	Min, Max	6, 26		9, 30		3, 28	
Day 43	n	48	48	56	56	48	48
	Mean (SD)	18.9 (3.75)	0.9 (1.73)	19.4 (3.44)	1.3 (2.82)	19.5 (5.26)	1.8 (3.35)
	Median	19.5	0	20	1	19.5	1

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Min, Max	9, 24	-4, 6	9, 26	-11, 8	3, 35	-1, 13
	95% CI		(0.37, 1.38)		(0.53, 2.04)		(0.84, 2.79)
	p-value		0.001		0.001		<.001

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 was calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4

Subscale: Social Contacts

An increase in the LOF Social Contacts Sub-scale scores was observed at Day 43 compared to baseline in all the three treatment groups, indicating improvement in frequency and quality of social contacts in subjects after treatment (Table 12-17).

At baseline, the mean (SD) of LOF Social Contacts Sub-scale scores recorded was 1.3 (0.83), 1.3 (0.94) and 1.4 (1.03) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, an increase of LOF Social Contacts Sub-scale scores with a mean (SD) of 1.5 (0.81), 1.5 (0.99) and 1.7 (1.20) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.2 (0.51) in evenamide 7.5 mg and 15 mg and 0.2 (0.65) in evenamide 30 mg *bid* treated groups was observed.

Table 12-17: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Social Contacts) Scores at Day 43 – Within Group Comparisons - mITT Population

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	1.3 (0.83)		1.3 (0.94)		1.4 (1.03)	
	Median	1.5		1.5		2	
	Min, Max	0, 3		0, 4		0, 4	
Day 43	n	48	48	56	56	48	48
	Mean (SD)	1.5 (0.81)	0.2 (0.51)	1.5 (0.99)	0.2 (0.51)	1.7 (1.20)	0.2 (0.65)
	Median	1.75	0	1.5	0	2	0
	Min, Max	0, 3	-0.5, 2.5	0, 4	-1, 1.5	0, 4	-2, 2

Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients,

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat *Subscale scores were calculated as the mean scores for items in each scale.* *Change from Baseline = Post Dose – Baseline.* *P-Value = Paired t-test.* *Source: Listing 16.2.6.4; Adapted from Table 14.2.4*							

Subscale: Work

A minor increase in the LOF Work Sub-scale scores was observed at Day 43 compared to baseline in the evenamide 15 mg and 30 mg *bid* groups, indicating improvement in quantity and quality of useful work in subjects after treatment (Table 12-18).

At baseline, the mean (SD) of LOF Work Sub-scale scores recorded was 1.3 (0.97), 1.2 (0.97) and 1.1 (1.01) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively.

At Day 43, an increase of LOF Sub-scale (Work) scores with a mean (SD) of 1.3 (0.93), 1.2 (0.97) and 1.1 (1.01) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.0 (0.33), 0.2 (0.71) and 0.2 (0.62) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, was observed.

Table 12-18: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Work) Scores at Day 43 – Within Group Comparisons - mITT Population

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	1.3 (0.97)		1.2 (0.97)		1.1 (1.01)	
	Median	2		2		1	
	Min, Max	0, 3		0, 3		0, 3	
Day 43	n	48	48	56	56	48	48
	Mean (SD)	1.3 (0.93)	0.0 (0.33)	1.3 (0.94)	0.2 (0.71)	1.3 (1.10)	0.2 (0.62)
	Median	2	0	2	0	2	0
	Min, Max	0,3	-1,1	0,3	-2,2	0, 4	-1,2
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* *Subscale scores were calculated as the mean scores for items in each scale.* *Change from Baseline = Post Dose – Baseline.* *P-Value = Paired t-test.* *Source: Listing 16.2.6.4; Adapted from Table 14.2.4*							

Subscale: Symptomatology

An increase in the LOF Symptomatology Sub-scale scores was observed at Day 43 compared to baseline in all three treatment groups, indicating improvement in absence of symptoms and recent hospitalization in subjects after treatment (Table 12-19).

At baseline, the mean (SD) of LOF Symptomatology Sub-scale scores recorded was 2.8 (0.32), 2.8 (0.38) and 2.7 (0.60) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, an increase of LOF Symptomatology Sub-scale scores with a mean (SD) of 3.0 (0.40), 3.0 (0.48) and 3.0 (0.57) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A mean (SD) change from baseline of 0.2 (0.33), 0.2 (0.53) and 0.3 (0.51) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated group, respectively, was observed.

Table 12-19: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Symptomatology) Scores at Day 43 – Within Group Comparisons - mITT Population

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	2.8 (0.32)		2.8 (0.38)		2.7 (0.60)	
	Median	3		3		3	
	Min, Max	2, 4		1, 4		0.5, 3.5	
Day 43	n	48	48	56	56	48	48
	Mean (SD)	3.0 (0.40)	0.2 (0.33)	3.0 (0.48)	0.2 (0.53)	3.0 (0.57)	0.3 (0.51)
	Median	3	0	3	0	3	0
	Min, Max	2.5, 3.5	-1, 1	1, 3.5	-2, 2	0.5, 3.5	-1, 2.5

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4

Subscale: Function

A minor increase in the LOF Function Sub-scale scores was observed at Day 43 compared to baseline in all three treatment groups, indicating improvement in ability to meet basic needs, fullness of life, and overall level of function in subjects after treatment (Table 12-20).

At baseline, the mean (SD) of LOF Function Sub-scale scores recorded was 2.4 (0.50), 2.5 (0.42) and 2.4 (0.52) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, an increase of LOF Function Sub-scale scores with a mean (SD) of 2.5 (0.48), 2.6 (0.33) and 2.5 (0.58) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively A mean (SD) change from baseline of 0.0 (0.10), 0.1 (0.29) and 0.1 (0.34) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, was observed.

Table 12-20: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Function) Scores at Day 43 – Within Group Comparisons - mITT Population

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	2.4 (0.50)		2.5 (0.42)		2.4 (0.52)	
	Median	2.7		2.7		2.7	
	Min, Max	0.7, 3.3		1.3, 4		0.7, 3.3	
Day 43	n	48	48	56	56	48	48
	Mean (SD)	2.5 (0.48)	0.0 (0.10)	2.6 (0.33)	0.1 (0.29)	2.5 (0.58)	0.1 (0.34)
	Median	2.7	0	2.7	0	2.7	0
	Min, Max	0.7, 3.3	0, 0.7	1.3, 3.3	-0.7, 1.4	0.7, 4	-0.6, 1.3

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4

12.1.4 Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, 7-point Likert-type scale for patients with schizophrenia to rate their satisfaction with their antipsychotic medication. The MSQ was assessed at Baseline (Day 0), Day 15 and Day 43 (or at early discontinuation).

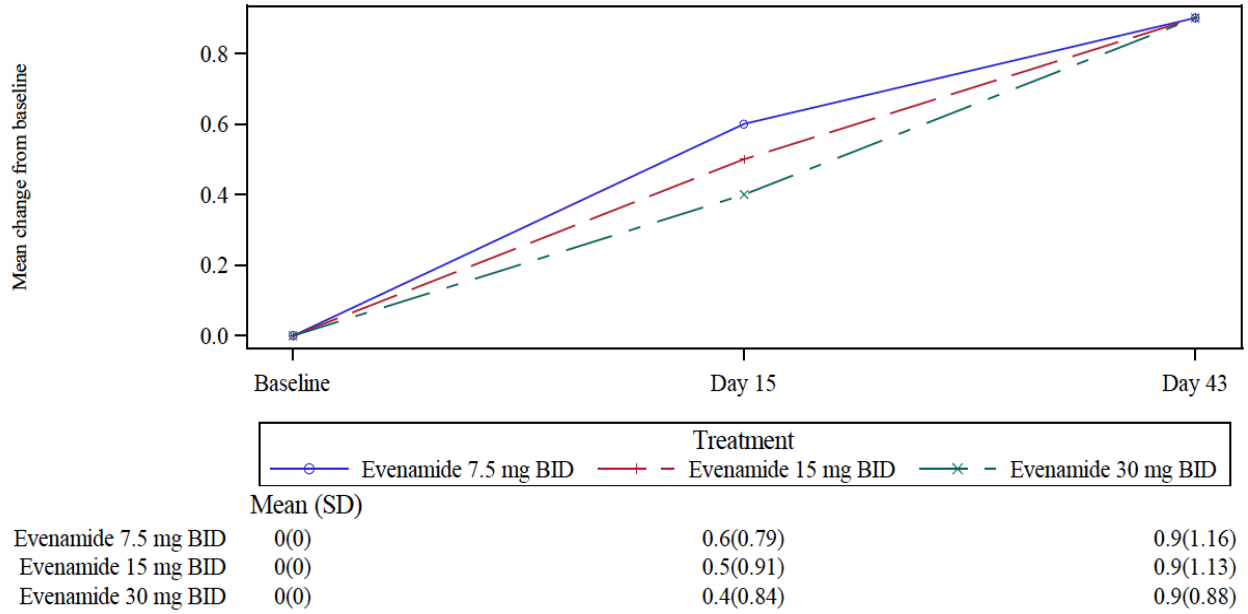
The change from baseline to endpoint on MSQ was summarized and analyzed by using a paired *t-test* within each dose group and presented in Table 14.2.5, with by subject details in Listing 16.2.6.5.

An improvement in the MSQ score was observed at Day 15 and Day 43 compared to baseline in all the three treatment groups, indicating patient's greater satisfaction with the current antipsychotic treatment compared to their previous treatment.

At baseline, the mean (SD) of MSQ scores recorded was 3.8 (0.73), 4.1 (0.76) and 4.1 (0.83) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

At Day 43, an increase of MSQ scores with a mean (SD) of 4.6 (0.94), 5.0 (0.71) and 4.9 (0.71) was recorded in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. A significant mean (SD) change from baseline of 0.9 (1.16) (95% CI: 0.54, 1.21; *p<0.001*), 0.9 (1.13) (95% CI: 0.57, 1.18; *p<0.001*) and 0.9 (0.88) (95% CI: 0.64, 1.15; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively (Table 12-21, Figure 12-9).

Figure 12-9: Mean Change from Baseline by Visit in Medication Satisfaction Questionnaire (MSQ) - mITT Population



	Mean (SD)		
Evenamide 7.5 mg BID	0(0)	0.6(0.79)	0.9(1.16)
Evenamide 15 mg BID	0(0)	0.5(0.91)	0.9(1.13)
Evenamide 30 mg BID	0(0)	0.4(0.84)	0.9(0.88)

Source: Listing 16.2.6.4; Table 14.2.5; Figure 14.2.4.1

Table 12-21: Change from Baseline in Medication Satisfaction Questionnaire (MSQ) – Within Group Comparison - mITT Population

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	48		59		49	
	Mean (SD)	3.8 (0.73)		4.1 (0.76)		4.1 (0.83)	
	Median	4		4		4	
	Min, Max	3, 6		2, 6		2, 6	
Day 15	n	48	48	57	57	49	49
	Mean (SD)	4.4 (0.79)	0.6 (0.79)	4.6 (0.76)	0.5 (0.91)	4.4 (0.82)	0.4 (0.84)
	Median	4	1	5	0	4	0
	Min, Max	3, 7	-1, 2	2, 6	-2, 3	3, 7	-1, 2
Day 43	n	48	48	56	56	48	48

		Evenamide 7.5 mg *bid* (N=48)		Evenamide 15 mg *bid* (N=59)		Evenamide 30 mg *bid* (N=49)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
	Mean (SD)	4.6 (0.94)	0.9 (1.16)	5.0 (0.71)	0.9 (1.13)	4.9 (0.71)	0.9 (0.88)
	Median	5	1	5	1	5	1
	Min, Max	2, 6	-4, 3	3, 6	-3, 3	3, 6	-1, 3
	95% CI		(0.54, 1.21)		(0.57, 1.18)		(0.64, 1.15)
	p-value		<.001		<.001		<.001

Abbreviations: N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
P-Value = Paired t-test, Change from Baseline = Post Dose – Baseline
Source: Listing 16.2.6.4; Table 14.2.5

12.2 Additional Analysis

Additional efficacy analyses were conducted using combined evenamide group data.

12.2.1 Positive and Negative Syndrome Scale Results

12.2.1.1 PANSS Total Scores

Primary Efficacy Estimand Analysis

The mean change from baseline at Day 43 in PANSS Total Score using the overall evenamide group comparison (*Primary Estimand*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.1c and by subject details in Listing 16.2.6.1.2.

A steady improvement in the PANSS total score (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) 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 43, a reduction of PANSS total score with a mean (SD) of 70.0 (8.30) was recorded, with the statistically significant mean (SD) change from baseline of -9.5 (7.13) (95% CI: -10.60, -8.32; $p<0.001$) was observed in the overall evenamide group (Table 12-22).

Table 12-22: Summary of Mean Value and Change from Baseline in PANSS Total Score by Visit Using Overall Comparison (Primary Estimand) - mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Screening	n	156	
	Mean (SD)	79.6 (5.20)	

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
	Median	79.5	
	Min, Max	70, 89	
Baseline	n	156	
	Mean (SD)	79.5 (5.04)	
	Median	80	
	Min, Max	70, 89	
Day 8	n	154	154
	Mean (SD)	77.9 (5.42)	-1.6 (2.84)
	Median	78	-1
	Min, Max	65, 94	-16, 5
Day 15	n	153	153
	Mean (SD)	75.4 (6.40)	-4.1 (3.99)
	Median	75	-3
	Min, Max	60, 91	-17, 3
Day 29	n	153	153
	Mean (SD)	72.8 (7.54)	-6.8 (5.54)
	Median	73	-6
	Min, Max	54, 90	-28, 4
Day 43	n	152	152
	Mean (SD)	70.0 (8.30)	-9.5 (7.13)
	Median	70	-9
	Min, Max	48, 91	-34, 12
	95% CI		(-10.60, -8.32)
	p-value		<.001

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.
p-Value = Paired t-test.
Source: Listing 16.2.6.1.2; Table 14.2.1.1c

12.2.1.2 PANSS Subscales

PANSS Positive Syndrome subscale scores

The mean change from baseline at Day 43 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 14.2.1.2c and by subject details in Listing 16.2.6.1.1.

A steady improvement in the PANSS Positive Syndrome subscale scores (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in the overall evenamide group. At Day 43, a significant mean (SD) change from baseline in the PANSS Positive Syndrome subscale scores of -4.0 (3.39) (95% CI: -4.57, -3.48; *p<0.001*) was observed in the overall evenamide group. (Table 12-23).

Table 12-23: Summary of Change from Baseline in PANSS (Positive Syndrome subscale) score by Visit Using Overall Comparison - mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	23.7 (3.30)	
	Median	24	
	Min, Max	17, 36	
Day 8	n	154	154
	Mean (SD)	23.1 (3.40)	-0.6 (1.21)
	Median	23	0
	Min, Max	14, 32	-5, 2
Day 15	n	153	153
	Mean (SD)	21.9 (3.74)	-1.8 (2.03)
	Median	22	-1
	Min, Max	11, 35	-9, 2
Day 29	n	153	153
	Mean (SD)	20.7 (4.06)	-2.9 (2.76)
	Median	21	-2
	Min, Max	10, 35	-15, 3
Day 43	n	152	152
	Mean (SD)	19.6 (4.39)	-4.0 (3.39)
	Median	19.5	-4
	Min, Max	10, 35	-15, 3
	95% CI		(-4.57, -3.48)
	p-value		<.001

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.
p-Value = Paired t-test.
Source: Listing 16.2.6.1.2; Table 14.2.1.2c

PANSS Negative Syndrome subscale scores

The mean change from baseline at Day 43 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 14.2.1.2c and by subject details in Listing 16.2.6.1.1.

A steady improvement in the PANSS Negative Syndrome subscale scores (lowering of score) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in the overall evenamide group. At Day 43, a significant mean (SD) change from baseline in the PANSS Negative Syndrome subscale scores of -1.9 (2.55) (95% CI: -2.35, -1.53; *p<0.001*) was observed in the overall evenamide group. (Table 12-24).

Table 12-24: Summary of Change from Baseline in PANSS (Positive Syndrome subscale) score by Visit Using Overall Comparison - mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	19.7 (3.37)	
	Median	20	
	Min, Max	10, 31	
Day 8	n	154	154
	Mean (SD)	19.4 (3.31)	-0.3 (0.83)
	Median	20	0
	Min, Max	10, 29	-6, 1
Day 15	n	153	153
	Mean (SD)	19.0 (3.20)	-0.8 (1.55)
	Median	19	0
	Min, Max	10, 28	-7, 4
Day 29	n	153	153
	Mean (SD)	18.5 (3.09)	-1.4 (2.04)
	Median	19	-1
	Min, Max	11, 26	-10, 6
Day 43	n	152	152
	Mean (SD)	17.9 (3.20)	-1.9 (2.55)
	Median	18	-1
	Min, Max	10, 26	-11, 7
	95% CI		(-2.35, -1.53)
	p-value		<.001

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.
p-Value = Paired t-test.
Source: Listing 16.2.6.1.2; Table 14.2.1.2c

PANSS General Psychopathology scores

The mean change from baseline at Day 43 in PANSS General Psychopathology subscale scores using the overall evenamide group comparison was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.2c and 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 study visits (Days 8, 15, 29 and 43) compared to baseline in overall evenamide group. At Day 43, a significant mean (SD) change from baseline in the PANSS general psychopathology subscale scores of -3.5 (3.13) (95% CI: -4.00, -2.99; *p<0.001*) was observed in the overall evenamide group. (Table 12-25).

Table 12-25: Summary of Change from Baseline in PANSS (General Psychopathology subscale) score by Visit Overall Comparison - mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	36.1 (3.71)	
	Median	36	
	Min, Max	28, 49	
Day 8	n	154	154
	Mean (SD)	35.3 (3.73)	-0.7 (1.61)
	Median	35	0
	Min, Max	27, 49	-9, 3
Day 15	n	153	153
	Mean (SD)	34.5 (4.07)	-1.5 (1.99)
	Median	34	-1
	Min, Max	23, 49	-10, 3
Day 29	n	153	153
	Mean (SD)	33.6 (4.36)	-2.5 (2.44)
	Median	33	-2
	Min, Max	24, 48	-12, 2
Day 43	n	152	152
	Mean (SD)	32.5 (4.27)	-3.5 (3.13)
	Median	32	-3
	Min, Max	23, 46	-14, 4
	95% CI		(-4.00, -2.99)
	p-value		<.001

Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients,

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
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.* *Source: Listing 16.2.6.1.2; Table 14.2.1.2c*			

12.2.1.3 Sensitivity Analysis on Change from Baseline in PANSS Total Score

Paired t-test Using Multiple Imputation

The mean change from baseline at Day 43 in Positive and Negative Syndrome Scale (PANSS) Total Score in overall evenamide group comparison (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.1.4c and 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 Day 43 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 PANSS total score recorded was 79.5 (5.04) in overall evenamide group. At Day 43, a reduction of PANSS total score with a mean (SD) of 70.1 (8.30) was recorded with a statistically significant mean (SD) change from baseline of -9.4 (7.07) (95% CI: -10.56, -8.31; *p<0.001*) was observed in the overall evenamide group (Table 12-26).

Table 12-26: Sensitivity Analysis on Change from Baseline in PANSS Total Score Overall Comparison at Day 43 - Paired t-test Using Multiple Imputation- - mITT Population.

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Day 43	n	156
	Mean (SD)	70.1 (8.30)
	Median	70
	Min, Max	48, 91
	Mean change from Baseline (SD)	-9.4 (7.07)
	95% CI	(-10.56, -8.31)
	p-value	<.001
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min=Minimum, Max=Maximum, p-value = Paired t-test.		

Visit	Statistic	Evenamide (N=156)
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. *Source: Listing 16.2.6.1.2; Table 14.2.1.4c*		

Paired t-test Using LOCF Supportive Estimand

The mean change from baseline at Day 43 in PANSS Total Score using overall evenamide group comparison (*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 and by subject details in Listing 16.2.6.1.2. The sensitivity analysis was performed using the LOCF (Last-observation-carried forward). 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 Day 43 compared to baseline in the overall evenamide group. Mean (SD) values of the PANSS total score showed a decreasing trend at each visit, reflecting a continuation of improvement in the symptoms of schizophrenia.

At baseline, the mean (SD) of PANSS total score recorded was 79.5 (5.04) in overall evenamide group. At Day 43, a reduction of PANSS total score with a mean (SD) of 70.3 (8.39) was recorded with a statistically significant mean (SD) change from baseline of -9.3 (7.14) (95% CI: -10.40, -8.14; *p<0.001*) was observed in the overall evenamide group (Table 12-27).

Table 12-27: Sensitivity Analysis on Change from Baseline in PANSS Total Score Overall Comparison at Day 43 - Paired t-test Using LOCF Supportive Estimand mITT Population.

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Day 43	n	156
	Mean (SD)	70.3 (8.39)
	Median	70.0
	Min, Max	48, 91
	Mean change from Baseline (SD)	-9.3 (7.14)
	95% CI	(-10.40, -8.14)
	p-value	<.001
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. The LOCF		

Visit	Statistic	Evenamide (N=156)
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.* *Source: Listing 16.2.6.1.2; Table 14.2.1.5c*		

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 Day 43 using the overall evenamide group comparison for the mITT Population is presented in Table 14.2.1.6c and by subject details in Listing 16.2.6.1.2.

Similar decreasing trends (improvement) were observed in the different models (*Primary estimand, LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in PANSS total score at Day 43 using overall evenamide group comparison (Table 12-28). A statistically significant mean (SD) change from baseline (*p<0.001*) in all the three models was observed in the overall evenamide group analysis.

Table 12-28: Sensitivity Analysis on Change from Baseline in PANSS Total Score at Day 43 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide (N=156)
Primary Estimand	Mean Change from Baseline (SD)	-9.5 (7.13)
	95% CI	(-10.60, -8.32)
	p-value	<.001
LOCF@	Mean Change from Baseline (SD)	-9.3 (7.14)
	95% CI	(-10.40, -8.14)
	p-value	<.001
MI	Mean change from Baseline (SD)	-9.4 (7.07)
	95% CI	(-10.56, -8.31)
	p-value	<.001
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test; LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, Min=Minimum, Max=Maximum, n - number of subjects in the specified category, the results obtained in each model are compared in this table. *@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF would be considered as supportive.* *Source: Listing 16.2.6.1.2; Table 14.2.1.6c*		

12.2.2 Clinical Global Impression – Severity of Illness (CGI-S) score

The mean change from baseline at Day 43 on the CGI-S using the overall evenamide group comparison was summarized by visit and is presented in Table 14.2.2.1c and by subject details are presented Listing 16.2.6.2.

A significant (*p<0.001*) improvement (lowering of scores) in the CGI-S was observed at study

visits (Days 8, 15, 29 and 43) 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 (0.58) was recorded in the overall evenamide group. At Day 43, a reduction of CGI-S scores with a mean (SD) of 3.8 (0.74) was recorded. A statistically significant mean (SD) change from baseline of -0.7 (0.71) (95% CI: -0.84, -0.61; *p<0.001*) was observed in the overall evenamide group (Table 12-29).

Table 12-29: Summary of Mean Value and Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Overall Comparison -mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Screening	n	156	
	Mean (SD)	4.5 (0.58)	
	Median	4	
	Min, Max	4, 6	
Baseline	n	156	
	Mean (SD)	4.5 (0.58)	
	Median	4	
	Min, Max	4, 6	
Day 8	n	154	154
	Mean (SD)	4.4 (0.60)	-0.1 (0.33)
	Median	4	0
	Min, Max	3, 6	-2, 0
Day 15	n	153	153
	Mean (SD)	4.2 (0.65)	-0.3 (0.52)
	Median	4	0
	Min, Max	2, 6	-3, 0
Day 29	n	153	153
	Mean (SD)	4.0 (0.71)	-0.5 (0.62)
	Median	4	0
	Min, Max	2, 6	-3, 0
Day 43	n	152	152
	Mean (SD)	3.8 (0.74)	-0.7 (0.71)
	Median	4	-1
	Min, Max	2, 6	-3, 1
	95% CI		(-0.84, -0.61)
	p-value		<.001

Abbreviations: N - Total number of subjects in the mITT Population, n - number of patients,

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
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.* *Source: Listing 16.2.6.2; Table 14.2.2.1c*			

12.2.2.1 Sensitivity Analysis on Change from Baseline in CGI-S Score

Paired t-test Using Multiple Imputation

The mean change from baseline at Day 43 in the CGI-S score using the overall evenamide group comparison (*sensitivity analysis: Multiple imputation*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.2.2c and 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 Day 43 compared to baseline in the overall evenamide group. Mean (SD) values of the CGI-S score showed a decreasing trend at all the time points during the study, reflecting a continuation of improvement in severity of illness.

At baseline, the mean (SD) of CGI-S score of 4.5 (0.58) was recorded. At Day 43, a reduction of CGI-S score with a mean (SD) of 3.8 (0.74) was recorded with a statistically significant mean (SD) change from baseline of -0.7 (0.70) (95% CI: -0.83, -0.61; *p<0.001*) in the overall evenamide group (Table 12-30).

Table 12-30: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) using Overall Evenamide Group Comparison at Day 43 - Paired t-test Using Multiple Imputation- - mITT Population.

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	4.5 (0.58)
	Median	4.0
	Min, Max	4, 6
Day 43	n	156
	Mean (SD)	3.8 (0.74)
	Median	4.0
	Min, Max	2, 6
	Mean change from Baseline (SD)	-0.7 (0.70)
	95% CI	(-0.83, -0.61)
	p-value	<.001
Abbreviations: N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min=Minimum, Max=Maximum, p-value = Paired t-test.		

Visit	Statistic	Evenamide (N=156)
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. *Source: Listing 16.2.6.1.2; Table 14.2.2.2c*		

Paired t-test Using LOCF

The mean change from baseline at Day 43 in CGI-S score using the overall evenamide group comparison (*sensitivity analysis: LOCF*) was analyzed by using a paired *t-test* for the mITT Population and presented in Table 14.2.2.3c and by subject details in Listing 16.2.6.2. The sensitivity analysis was performed using the LOCF (Last-observation-carried forward). 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 Day 43 compared to baseline in the overall evenamide group. Mean (SD) values of the CGI-S score showed a decreasing trend at, reflecting a continuation of improvement in severity of illness.

At baseline, the mean (SD) of CGI-S score of 4.5 (0.58) was recorded. At Day 43, a reduction of CGI-S score with a mean (SD) of 3.8 (0.74) was recorded with a statistically significant mean (SD) change from baseline of -0.7 (0.71) (95% CI: -0.82, -0.59; *p<0.001*) in the overall evenamide group (Table 12-31).

Table 12-31: Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) using Overall evenamide group Comparison at Day 43 - Paired t-test Using LOCF - mITT Population.

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	4.5 (0.58)
	Median	4.0
	Min, Max	4, 6
Day 43	n	156
	Mean (SD)	3.8 (0.74)
	Median	4.0
	Min, Max	2, 6
	Mean change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.82, -0.59)
	p-value	<.001
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.		

Visit	Statistic	Evenamide (N=156)
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. *Source: Listing 16.2.6.1.2; Table 14.2.2.3c*		

Comparison Analysis of Different Models

A comparison of the different models used for the Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 for the mITT Population is presented in Table 14.2.2.4c and by subject details in Listing 16.2.6.2.

Similar decreasing trends (improvement) were observed in different models (*Primary estimand, LOCF and Multiple imputations*) for the Sensitivity Analysis on change from baseline in CGI-S score at Day 43. A significant mean (SD) change from baseline (*p<0.001*) was observed in the overall evenamide group with all models (Table 12-32).

Table 12-32: Sensitivity Analysis on Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 – Comparison of Different Models - mITT Population.

Models	Statistic	Evenamide (N=156)
Primary Estimand	Mean Change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.84, -0.61)
	p-value	<.001
LOCF@	Mean Change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.82, -0.59)
	p-value	<.001
MI	Mean change from Baseline (SD)	-0.7 (0.70)
	95% CI	(-0.83, -0.61)
	p-value	<.001
Abbreviations: N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test; LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, Min=Minimum, Max=Maximum, n - number of subjects in the specified category, the results obtained in each model are compared in this table. *@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF would be considered as supportive.* *Source: Listing 16.2.6.2; Table 14.2.2.4c*		

12.2.2.2 Clinical Global Impression - Change (CGI-C)

The change from baseline of Clinical Global Impression – Change (CGI-C) Score at Days 8, 15, 29 and 43 (or at early discontinuation) for the combined evenamide group for the mITT Population is presented in Table 14.2.3.1c and by subject details in Listing 16.2.6.3.

At Day 8, the mean (SD) of CGI-C scores recorded were 3.8 (0.48), which reduced to 3.0 (0.72)

by Day 43 in the overall evenamide group. (Table 12-33).

A reduction in the mean CGI-C score was observed between Day 8 and Day 43, from 3.8 to 3.0, indicating continuing improvement in overall severity of illness.

Table 12-33: Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population.

Visit	Statistic	Evenamide (N=156)
Day 8	n	154
	Mean (SD)	3.8 (0.48)
	Median	4
	Min, max	2, 5
Day 15	n	153
	Mean (SD)	3.5 (0.56)
	Median	3
	Min, max	2, 5
Day 29	n	153
	Mean (SD)	3.3 (0.64)
	Median	3
	Min, max	2, 5
Day 43	n	152
	Mean (SD)	3.0 (0.72)
	Median	3
	Min, max	2, 5

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
Source: Listing 16.2.6.3; Table 14.2.3.1c

12.2.3 Strauss-Carpenter Level of Functioning (LOF) Scale Results

The Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score and Sub-scale Scores at Day 43 – overall evenamide group comparisons for the mITT Population is presented in Table 14.2.4c and by subject details in Listing 16.2.6.4 and 16.2.6.4a.

Total Score

An increase in the LOF total score was observed at Day 43 compared to baseline for the combined evenamide group, indicating improvement in functionality of subjects after treatment.

At baseline, the mean (SD) of LOF total score recorded was 17.9 (4.05) in the overall evenamide group. At Day 43, an increase of LOF total score with a mean (SD) of 19.3 (4.17). A significant mean (SD) change from baseline of 1.3 (2.73) (95% CI: 0.88, 1.76; $p<0.001$) was observed in the overall evenamide group (Table 12-34).

Table 12-34: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score at Day 43 – Overall Comparisons - mITT Population.

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	17.9 (4.05)	
	Median	19	
	Min, Max	3, 30	
Day 43	n	152	152
	Mean (SD)	19.3 (4.17)	1.3 (2.73)
	Median	20	1
	Min, Max	3, 35	-11, 13
	95% CI		(0.88, 1.76)
	p-value		<.001

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 was calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4c

Subscale: Social Contacts

An increase in the LOF Social Contacts Sub-scale scores was observed at Day 43 compared to baseline in the overall evenamide group, indicating improvement in frequency and quality of social contacts in subjects after treatment (Table 12-35).

At baseline, the mean (SD) of LOF Social Contacts Sub-scale scores recorded was 1.3 (0.93) in the overall evenamide group. At Day 43, an increase of LOF Social Contacts Sub-scale scores with a mean (SD) of 1.6 (1.01) and the mean (SD) change from baseline of 0.2 (0.56) in the overall evenamide group was observed.

Table 12-35: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Social Contacts) Scores at Day 43 – Overall Comparisons - mITT Population

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	1.3 (0.93)	
	Median	1.5	
	Min, Max	0, 4	
Day 43	n	152	152
	Mean (SD)	1.6 (1.01)	0.2 (0.56)

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
	Median	1.75	0
	Min, Max	0, 4	-2, 2.5

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4c

Subscale: Work

A minor increase in the LOF Work Sub-scale scores was observed at Day 43 compared to baseline in the overall evenamide group, indicating improvement in quantity and quality of useful work in subjects after treatment (Table 12-36).

At baseline, the mean (SD) of LOF Work Sub-scale scores recorded was 1.2 (0.98) in the overall evenamide group. At Day 43, an increase of LOF Work Sub-scale scores with a mean (SD) of 1.3 (0.98) and the mean (SD) change from baseline of 0.1 (0.58) in the overall evenamide group was observed.

Table 12-36: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Work) Scores at Day 43 – Overall Comparisons - mITT Population

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	1.2 (0.98)	
	Median	2	
	Min, Max	0, 3	
Day 43	n	152	152
	Mean (SD)	1.3 (0.98)	0.1 (0.58)
	Median	2	0
	Min, Max	0, 4	-2, 2

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4c

Subscale: Symptomatology

An increase in the LOF Symptomatology Sub-scale scores was observed at Day 43 compared to baseline in the overall evenamide group, indicating improvement in absence of symptoms and recent hospitalization in subjects after treatment (Table 12-37).

At baseline, the mean (SD) of LOF Symptomatology Sub-scale scores recorded was 2.8 (0.45) in the overall evenamide group. At Day 43, an increase of LOF Symptomatology Sub-scale scores with a mean (SD) of 3.0 (0.49) and the mean (SD) change from baseline of 0.2 (0.47) in the overall evenamide group was observed.

Table 12-37: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Symptomatology) Scores at Day 43 – Overall Comparisons - mITT Population

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	2.8 (0.45)	
	Median	3	
	Min, Max	0.5, 4	
Day 43	n	152	152
	Mean (SD)	3.0 (0.49)	0.2 (0.47)
	Median	3	0
	Min, Max	0.5, 3.5	-2, 2.5

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4c

Subscale: Function

A minor increase in the LOF Function Sub-scale scores was observed at Day 43 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 12-38).

At baseline, the mean (SD) of LOF Function Sub-scale scores recorded was 2.4 (0.48) in the overall evenamide group. At Day 43, an increase of LOF Function Sub-scale scores with a mean (SD) of 2.5 (0.47) and the mean (SD) change from baseline of 0.1 (0.27) in the overall evenamide group was observed.

Table 12-38: Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-scale (Function) Scores at Day 43 – Overall Comparisons - mITT Population

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	2.4 (0.48)	
	Median	2.7	
	Min, Max	0.7, 4	
Day 43	n	152	152
	Mean (SD)	2.5 (0.47)	0.1 (0.27)
	Median	2.7	0
	Min, Max	0.7, 4	-0.7, 1.4

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
Subscale scores were calculated as the mean scores for items in each scale.
Change from Baseline = Post Dose – Baseline.
P-Value = Paired t-test.
Source: Listing 16.2.6.4; Adapted from Table 14.2.4c

12.2.4 Medication Satisfaction Questionnaire (MSQ)

The change from baseline to endpoint on MSQ was summarized and analysed by using a paired *t-test* in overall evenamide combined group and presented in Table 14.2.5c and by subject details in Listing 16.2.6.5.

An improvement in the MSQ score was observed at Day 15 and Day 43 compared to baseline in the overall evenamide group, indicating patient's greater satisfaction with the current antipsychotic treatment compared to their previous treatment.

At baseline, the mean (SD) of MSQ scores recorded was 4.0 (0.78) in the overall evenamide group. At Day 43, an increase of MSQ scores with a mean (SD) of 4.8 (0.8) was recorded. A significant mean (SD) change from baseline of 0.9 (1.06) (95% CI: 0.71, 1.05; $p<0.001$) was observed in the overall evenamide group (Table 12-39).

Table 12-39: Change from Baseline in Medication Satisfaction Questionnaire (MSQ) – Overall Comparison - mITT Population

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
Baseline	n	156	
	Mean (SD)	4.0 (0.78)	
	Median	4	

		Evenamide (N=156)	
Visit	**Statistic**	**Observed**	**Change from Baseline**
	Min, Max	2, 6	
Day 15	n	153	153
	Mean (SD)	4.5 (0.78)	0.5 (0.84)
	Median	5	0
	Min, Max	2, 7	-2, 3
Day 43	n	152	152
	Mean (SD)	4.8 (0.8)	0.9 (1.06)
	Median	5	1
	Min, Max	2, 6	-4, 3
	95% CI		(0.71, 1.05)
	p-value		<.001

Abbreviations: N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
P-Value = Paired t-test, Change from Baseline = Post Dose – Baseline
Source: Listing 16.2.6.5; Table 14.2.5c

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.

12.3.1.1 Adjustments for Covariates

The details of the covariate analyses performed have been described in Section 9.7.1.5.6.

12.3.1.2 Handling of Dropouts or Missing Data

Handling of missing data is described in Section 9.7.1.2.3.

12.3.1.3 Interim Analyses and Data Monitoring

An interim safety analysis was performed at the request of the ISMB after 50 patients were randomized to the 7.5 mg (n=26) and 15 mg (n=24) *bid* doses and completed their participation in this study, to determine the safety of the doses administered. An interim efficacy analysis was performed after the first 100 patients completed their participation in the trial. 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 9.5.1.1.14.

12.3.1.4 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.

12.3.1.5 Multiple Comparisons/Multiplicity

Multiplicity adjustment is detailed in Section 9.7.1.5.7.

12.3.2 Tabulation of Individual Response Data

Individual efficacy response data are provided in Appendix 16.2.6.

12.3.3 Drug Dose, Drug Concentration, and Relationships to Response

The MMRM analysis was conducted to compare the combined evenamide 15+30 mg *bid* doses vs the 7.5 mg *bid* dose.

12.3.4 Drug-Drug and Drug-Disease Interactions

Not applicable

12.3.5 By-Subject Displays

Not applicable

12.4 Efficacy Conclusions

The secondary objectives of the study were to evaluate preliminary efficacy of the three fixed doses of evenamide, based on symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression - Change from baseline (CGI-C) and CGI - Severity of illness (CGI-S). Secondarily, efficacy was determined by the effect of evenamide on daily functioning, based on changes on the Strauss-Carpenter Level of Functioning (LOF) scale and patient's satisfaction with the current antipsychotic treatment compared to their previous treatment, based on ratings of the Medication Satisfaction Questionnaire (MSQ).

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 being randomized to an evenamide dose, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline in PANSS total score at Day 43*) using a paired *t-test* for the mITT Population.

The baseline mean value of the PANSS total score did not differ between treatment groups. A steady improvement in the PANSS total score (lowering of score) was observed at all study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups (evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups), reflecting a continuation of improvement in symptoms of schizophrenia. At Day 43, a significant mean (SD) change from baseline of -9.0 (7.40) (95% CI: -11.13, 6.83; $p<0.001$), -10.6 (7.49) (95% CI: -12.63, -8.62; $p<0.001$) and -8.6 (6.35) (95% CI: -

10.43, -6.74; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. The results were supported by trends for the decreasing PANSS total score (improvement) observed in different models (*Primary estimand, LOCF and Multiple imputations*) of the Sensitivity Analysis on change from baseline at Day 43.

Mean change from baseline to Day 43 on the PANSS total score was compared between the evenamide dose groups using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. A statistically non-significant LS mean difference (SE) in PANSS total score between the combined evenamide (15 + 30 mg *bid*) versus evenamide low dose (7.5 mg *bid*) groups was observed [-0.7 (1.24) (95% CI: -3.16, 1.74; p=0.569)].

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 Day 43 was observed in all the 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 improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Syndrome sub-scale. By Day 43, the proportion of responders on the PANSS total score (patients who improved by at least 20% from baseline) increased to 9 (18.8%), 11 (18.6%) and 4 (8.2%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, compared to no responders at Day 8. The proportion of responders was higher in evenamide 7.5 mg and 15 mg *bid* treated groups compared to the 30 mg *bid* treated group. 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 Day 43, the proportion of responders on the PANSS Positive Syndrome total score (patients who improved by at least 4 points from baseline) was 23 (47.9%), 31 (52.5%) and 25 (51.0%) subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

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

A significant (*p<0.001*) improvement (lowering of scores) in the CGI-S was observed at all study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups, indicating 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 Day 43 within each dose group showed a significant reduction in the mean (SD) change from baseline of -0.6 (0.79) (95% CI: -0.87, -0.42; *p<0.001*), -0.8 (0.72) (95% CI: -1.01, -0.63; *p<0.001*) and -0.7 (0.62) (95% CI: -0.87, -0.51; *p<0.001*) in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups. The results were confirmed by the trends for decreasing CGI-S score (improvement) and significant (*p*<0.001) reductions observed in different models (*Primary estimand, LOCF and*

Multiple imputations) of the Sensitivity Analysis on change from baseline at Day 43.

A reduction in the mean CGI-C score was observed between Day 8 and Day 43, from 3.8 to 3.0 in evenamide 7.5 mg, from 3.7 to 2.9 in evenamide 15 mg, and from 3.8 to 3.1 evenamide 30 mg *bid* treated groups, indicating continuing improvement in overall severity of illness. A responder analysis was done considering change in subject's condition from baseline, as indicated by the CGI-C score (CGI-C score change ≤ 3 [indicating improvement]) and (CGI-C score change >3 [indicating no change or worsening]). An increase in the proportion of responders (CGI-C score change ≤ 3 [indicating improvement]) was observed at all the timepoints from Day 8 to Day 43 (from 22.44% to 75.00% in overall subjects) in all the three treatment groups, indicating that more subjects were experiencing meaningful benefit. The highest proportion of responders at Day 43 was seen in the evenamide 15 mg *bid* treated group (79.7%), compared to the 7.5 mg *bid* (70.8%) and 30 mg *bid* (73.5%) treated groups.

Strauss-Carpenter - Level of Functioning Scale (LOF)

A significant increase in the mean (SD) change from baseline in LOF Total Score at Day 43 of 0.9 (1.73) (95% CI: 0.37, 1.38; *p=0.001*), 1.3 (2.82) (95% CI: 0.53, 2.04; *p=0.001*) and 1.8 (3.35) (95% CI: 0.84, 2.79; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively. Similar trends were seen in the LOF subscales (Social Contacts, Work, Symptomatology, and Function) analysis indicating improvement in functionality of subjects after treatment with all the three doses of evenamide.

Patient's Medication Satisfaction Questionnaire (MSQ)

An improvement in the MSQ score was observed at Day 15 and Day 43 compared to baseline in all the three treatment groups, indicating patient's greater satisfaction with the current antipsychotic treatment compared to their previous treatment. At Day 43, a significant mean (SD) change from baseline in the MSQ scores of 0.9 (1.16) (95% CI: 0.54, 1.21; *p<0.001*), 0.9 (1.13) (95% CI: 0.57, 1.18; *p<0.001*) and 0.9 (0.88) (95% CI: 0.64, 1.15; *p<0.001*) was observed in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively.

Efficacy conclusion:

The efficacy of evenamide (evenamide 7.5 mg, 15 mg and 30 mg *bid*) 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, improvement in overall severity of illness assessed by the CGI-C, enhancement in functionality of patients assessed by the LOF, and an increase in patient's satisfaction with the current antipsychotic treatment compared to their previous treatment assessed by the MSQ scores. These beneficial effects, which increased over time across all the timepoints, were observed in patients with treatment-resistant schizophrenia 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. All currently available FGAs and SGAs, except clozapine, act through minor variations of monoaminergic modulation, therefore their therapeutic effects are similar. Overall, clinical data suggest that the currently available antipsychotic drugs targeting dopamine and serotonin receptors are inadequate for treating the unmet medical needs of schizophrenic patients, which include high frequency of relapse, fluctuating positive symptoms, negative symptoms, cognitive impairment, treatment resistance, and suicidality.

Evenamide (NW-3509) is an orally available new chemical entity that specifically targets 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.

Evenamide is intended to be administered as an adjunct to atypical antipsychotics in patients with schizophrenia who have not responded adequately to their current treatment. The safety and tolerability of evenamide has been evaluated in patients with schizophrenia who were partial responders to their current medication. However, evenamide has not been studied in the subpopulation of patients formally demonstrated to be treatment resistant. As there are pharmacodynamic differences in TRS patients compared with patients with schizophrenia who respond to antipsychotics, this pilot study was planned to determine the safety and tolerability of three different doses of evenamide added to a stable therapeutic dose of a single antipsychotic in this treatment-resistant population, and to provide preliminary evidence of efficacy in this group of patients with significant unmet need.

The current study was a prospective, randomized, rater-blinded, open-label, parallel-group, multi-center, 6-week study to determine the safety, tolerability, and preliminary efficacy of three fixed doses of evenamide (7.5, 15 and 30 mg *bid*) as add-on treatment in TRS patients on a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine). Overall, 161 subjects were randomized into the study, (50 subjects in evenamide 7.5 mg *bid*, 60 in evenamide 15 mg *bid* group and 51 in evenamide 30 mg *bid* treated group) of which 153 subjects (95.03%) (49 subjects in evenamide 7.5 mg *bid*, 56 in evenamide 15 mg *bid* group and 48 in evenamide 30 mg *bid* treated group) completed the study.

Subjects were predominantly male (69.38%), Asian (98.13%), single (50.00%), not employed (78.13%), living with family (100%), and had education of 9-16 years (69.38%). No demographic

or baseline characteristics differed notably between the treatment groups. The mean (SD) overall treatment compliance was 95.9% (9.97), with a median of 98.8 (range: 25 to 105), and uniform across the three treatment groups.

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

All the three evenamide (evenamide 7.5, 15 and 30 mg *bid*) treatment regimens were generally safe and well tolerated. The results of the analysis of safety in this trial were consistent with the established safety profile of evenamide. An overall low (9.4%) incidence of treatment-related TEAEs was reported. The proportion of subjects experiencing treatment-related TEAEs was found to be lowest in evenamide 15 mg *bid* treated group (6.7%) compared to evenamide 7.5 (10.0%) and 15 mg *bid* (12.0%) treated groups. None of the reported treatment-related TEAE were of severe intensity. The most commonly reported treatment-related TEAEs were asthenia and dizziness. None of the subjects in any of the 3 treatment groups reported a treatment-related SAE. At least one Serious TEAE (medication error) was reported by 7 (4.4%) subjects in the evenamide 30 mg *bid* treated group.

Laboratory tests, vital signs, physical and neurological examinations, eye examinations, and ECG evaluations did not show any pattern of clinically significant effects associated with any of the three doses of evenamide. No increases in extrapyramidal symptoms (ESRS-A), depressive symptoms (CDSS), and seizure-like symptoms (captured on the Seizure Checklist) were observed.

The secondary objectives of the study were to evaluate preliminary efficacy of the three fixed doses of evenamide, based on symptoms of schizophrenia, as assessed by the PANSS, CGI-S and CGI-C. Secondarily, the efficacy was determined by the effect of evenamide on daily functioning, based on changes on the LOF scale and patient's satisfaction with the current antipsychotic treatment compared to their previous treatment (MSQ).

Patients treated with evenamide (all three doses) showed improvement on the symptoms of schizophrenia assessed by the ratings on the PANSS Total score, PANSS subscales (Positive Syndrome, Negative Syndrome, and General Psychopathology symptoms). A steady improvement in PANSS scores (lowering of total scores and subscales scores) was observed at study visits (Days 8, 15, 29 and 43) compared to baseline, reflecting a decrease in symptoms of schizophrenia. The results were supported by the sensitivity analysis of change from baseline results at Day 43 using different models (*Primary estimand, LOCF and Multiple imputations*).

Mean change from baseline to Day 43 on the PANSS total score was compared between the evenamide dose groups using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. A statistically non-significant LS mean difference (SE) in PANSS total score between the

combined evenamide (15 + 30 mg *bid*) versus evenamide low dose (7.5 mg *bid*) groups was observed; therefore, no further between group testing was performed.

At Day 43, the proportion of responders (patients who improved by at least 20% on the PANSS total score from baseline) increased to 18.75%, 18.34%, 8.16% subjects in evenamide 7.5 mg, 15 mg and 30 mg *bid* treated groups, respectively, compared to no responders at Day 8. The proportion of responders was higher in the evenamide 7.5 mg and 15 mg *bid* treated groups compared to the 30 mg *bid* treated group. A similar trend was seen in responder analysis of PANSS Positive Syndrome sub-scale score, where approximately 50% of patients were considered responders (at least 4-point improvement from baseline) in each treatment group.

A significant improvement (lowering of scores) in the CGI-S was observed at study visits (Days 8, 15, 29 and 43) compared to baseline in all the three treatment groups, indicating improvement in overall severity of illness. The results were also confirmed by the decreasing CGI-S score trends (improvement) observed by the sensitivity analysis of change from baseline results at Day 43 by the sensitivity analysis of change from baseline results using different models (*Primary estimand, LOCF and Multiple imputations*).

A reduction in the mean CGI-C score was observed between Day 8 and Day 43, from 3.8 to 3.0 in evenamide 7.5 mg, from 3.7 to 2.9 in evenamide 15 mg, and from 3.8 to 3.1 in evenamide 30 mg *bid* treated groups, indicating continuing improvement in overall severity of illness. An increase in the proportion of responders (CGI-C score change ≤ 3 [indicating improvement]) was observed at all the timepoints from Day 8 to Day 43 (from 22.44% to 75.00% in overall subjects) in all the three treatment groups, indicating that more subjects were experiencing meaningful benefit. The highest proportion of responders was seen in the evenamide 15 mg *bid* treated group.

An increase in the LOF total score was observed at Day 43 compared to baseline in all the three treatment groups, indicating improvement in functionality of subjects after treatment. Similar trends were seen in the LOF subscales (Social Contacts, Work, Symptomatology, and Function) analysis indicating improvement in different aspects of function.

An improvement in the MSQ score was observed at Day 15 and Day 43 compared to baseline in all the three treatment groups, indicating patient's greater satisfaction with the current antipsychotic treatment compared to their previous treatment.

13.2 Overall Conclusions

In the current prospective, randomized, blinded-rater, open-label, parallel-group, multi-center, 6-week study, the safety and tolerability of fixed doses of evenamide of 7.5 mg *bid*, 15 mg *bid* and 30 mg *bid* as an add-on treatment in treatment-resistant schizophrenia patients on a stable therapeutic dose of an antipsychotic (typical or atypical, other than clozapine) was demonstrated by the various safety parameters (low incidence of treatment-related TEAEs; no trend of clinically

significant effects on laboratory tests, vital signs, physical and neurological examinations, eye examinations, and ECG evaluations; and no increase in extrapyramidal symptoms, depressive symptoms, and seizure-like symptoms on the Seizure Checklist).

The preliminary efficacy of fixed doses of evenamide of 7.5, 15 and 30 mg *bid* as an add-on treatment was demonstrated by improvement in symptoms of schizophrenia as assessed by the PANSS total score and subscales, decrease in overall disease severity as assessed by the CGI-S score, overall improvement in the severity of illness from baseline as assessed by the CGI-C, enhancement in patients' functionality as assessed by the LOF, and patient's having greater satisfaction with the current antipsychotic treatment compared to their previous treatment as assessed by the MSQ, in patients with treatment-resistant schizophrenia not responding adequately to their stable, therapeutically active dose of a single antipsychotic medication. These benefits were observed across all the timepoints and showed trends for greater improvement over time.

14 Tables, Figures, and Graphs Referred to but not included in the Text

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14.2 Efficacy Data Summary Figures and Tables

14.3 Safety Data Summary Figures and Tables

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

All Narratives presented in CSR main body in Section 11.6.2

15 Reference List

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16 Appendices

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16.3 Electronic Case Report Forms

16.3.1 Electronic Case Report Forms for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Events

16.4 Individual Subject Data Listings

Tables and Figures

Table 14.1.1.1
Summary of Screen Failures
All Subjects Screened

Category	Total (N=186) n(%)
Subjects Screened	186(100.0)
Screen Failures	25(13.44)
Primary Reason for Screen Failure	
Withdrawal of consent	9(4.84)
Did not meet entry criteria	7(3.76)
Others	5(2.69)
Lost to follow-up	4(2.15)
Pre-treatment Event/Adverse Event	0 (0.0)

Source: Listing 16.2.1.1
N - Total number of subjects in the Screened Subjects, n - number of subjects with available data.
Percentages are based on the total number of Subjects Screened.

Table 14.1.1.2
Subject Disposition
Randomized Population

Status	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=51) n(%)	Total (N=161) n(%)
Randomized Population [c]	50(100.0)	60(100.0)	51(100.0)	161(100.0)
Safety Population [a]	50(100.0)	60(100.0)	50(98.04)	160(99.38)
Modified Intent-to-Treat Population [b]	48(96.00)	59(98.33)	49(96.08)	156(96.89)
Completed Study	49(98.00)	56(93.33)	48(94.12)	153(95.03)
Discontinuation or Early Withdrawal	1(2.00)	4(6.67)	3(5.88)	8(4.97)
Primary Reason for Discontinuation or Early Withdrawal				
Withdrawal of consent	0 (0.0)	4(6.67)	3(5.88)	7(4.35)
Adverse Event	1(2.00)	0 (0.0)	0 (0.0)	1(0.62)
Major protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing 16.2.1.2
N - Total number of subjects in the Randomized Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Randomized Population.
Percentage for Rolled over/ Non-Rolled over subject is based on total number of subjects in each group (N) under number of subjects completed study.
[a] Safety Population: The safety Population consists of all subjects who took at least one dose of study medication.
[b] Modified Intent-to-Treat Population (mITT): A mITT population comprises all patients who received at least one dose of the study medication, and have both a baseline and at least one post-baseline PANSS efficacy assessment.
[c] Randomized population consists of all subjects who are randomized to any treatment, regardless of whether any dose is taken.

Table 14.1.1.2
Subject Disposition
Randomized Population

Status	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=51) n(%)	Total (N=161) n(%)
Lost to follow-up	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)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rolled over into Extension (or 015 Study)	45(66.18)	53(92.98)	46(164.3)	144(94.12)
Did not roll over into Extension	4(5.88)	3(5.26)	2(7.14)	9(5.88)
Reason for Non-Roll over				
Did Not Consent	4(5.88)	1(1.75)	2(7.14)	7(4.58)
Non-Compliance	0 (0.0)	2(3.51)	0 (0.0)	2(1.31)

Source: Listing 16.2.1.2
N - Total number of subjects in the Randomized Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Randomized Population.
Percentage for Rolled over/ Non-Rolled over subject is based on total number of subjects in each group (N) under number of subjects completed study.
[a] Safety Population: The safety Population consists of all subjects who took at least one dose of study medication.
[b] Modified Intent-to-Treat Population (mITT): A mITT population comprises all patients who received at least one dose of the study medication, and have both a baseline and at least one post-baseline PANSS efficacy assessment.
[c] Randomized population consists of all subjects who are randomized to any treatment, regardless of whether any dose is taken.

Table 14.1.2
Summary of Major and Critical Protocol Deviations
Safety Population

Category	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Subjects with Major Protocol Deviation	6(12.0)	3(5.0)	14(28.0)	23(14.4)
Subjects with Critical Protocol Deviation	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.2
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.

Table 14.1.3.1.1
Demographics and Baseline Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Age (years)	n	50	60	50	160
	Mean (SD)	37.7 (10.38)	37.2 (9.74)	38.3 (9.13)	37.7 (9.71)
	Median	37.0	35.0	38.0	37.0
	Min, Max	23,68	21,62	20,64	20,68
Weight (kg)	n	50	60	50	160
	Mean (SD)	66.6 (15.56)	66.2 (12.63)	69.9 (17.33)	67.5 (15.14)
	Median	66.6	64.8	65.8	65.8
	Min, Max	34,120	45,91	42,143	34,143
Height (cm)	n	50	60	50	160
	Mean (SD)	163.8 (9.85)	163.8 (7.87)	163.9 (7.44)	163.8 (8.37)
	Median	164.5	164.1	164.0	164.0
	Min, Max	137,183	145,183	149,182	137,183

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

Table 14.1.3.1.1
Demographics and Baseline Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
BMI (kg/m2)	n	50	60	50	160
	Mean (SD)	24.8 (5.28)	24.7 (4.60)	26.0 (5.65)	25.1 (5.16)
	Median	24.3	24.5	24.7	24.5
	Min, Max	15,37	17,35	16,44	15,44
Sex					
Male	n(%)	32(64.00)	42(70.00)	37(74.00)	111(69.38)
Female	n(%)	18(36.00)	18(30.00)	13(26.00)	49(30.63)
Childbearing Potential [a]					
Yes	n(%)	14(77.78)	11(61.11)	9(69.23)	34(69.39)
No	n(%)	4(22.22)	7(38.89)	4(30.77)	15(30.61)
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 Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.1
Demographics and Baseline Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Asian	n(%)	49(98.00)	60(100.0)	48(96.00)	157(98.13)
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 or Caucasian	n(%)	1(2.00)	0(0.0)	2(4.00)	3(1.88)
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 / Not Latino	n(%)	50(100.0)	60(100.0)	50(100.0)	160(100.0)
Education					
1-8 years	n(%)	11(22.00)	12(20.00)	10(20.00)	33(20.63)
9-16 years	n(%)	35(70.00)	42(70.00)	34(68.00)	111(69.38)
>16 years	n(%)	4(8.00)	6(10.00)	6(12.00)	16(10.00)

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

Table 14.1.3.1.1
Demographics and Baseline Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Marital Status					
Married	n(%)	18(36.00)	26(43.33)	21(42.00)	65(40.63)
Single	n(%)	29(58.00)	26(43.33)	25(50.00)	80(50.00)
Stable union	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Widow / Widower	n(%)	0(0.0)	2(3.33)	0(0.0)	2(1.25)
Divorced	n(%)	3(6.00)	6(10.00)	4(8.00)	13(8.13)
Employment					
Full-Time Employment	n(%)	4(8.00)	10(16.67)	3(6.00)	17(10.63)
Part-Time Employment	n(%)	5(10.00)	5(8.33)	8(16.00)	18(11.25)
Not employed	n(%)	41(82.00)	45(75.00)	39(78.00)	125(78.13)
Housing Status					
Living alone	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living with family	n(%)	50(100.0)	60(100.0)	50(100.0)	160(100.0)

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

Table 14.1.3.1.1
Demographics and Baseline Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
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 Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
[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=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total (N=156)
Age (years)	n	48	59	49	156
	Mean (SD)	37.9 (10.40)	37.2 (9.82)	38.3 (9.22)	37.8 (9.77)
	Median	37.0	35.0	38.0	37.0
	Min, Max	23,68	21,62	20,64	20,68
Weight (kg)	n	48	59	49	156
	Mean (SD)	67.2 (15.13)	66.5 (12.60)	69.4 (17.08)	67.6 (14.86)
	Median	66.6	65.3	65.3	65.8
	Min, Max	42,120	45,91	42,143	42,143
Height (cm)	n	48	59	49	156
	Mean (SD)	164.0 (9.91)	163.8 (7.94)	164.0 (7.47)	163.9 (8.40)
	Median	164.7	164.2	164.0	164.0
	Min, Max	137,183	145,183	149,182	137,183

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under mITT Population.
[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=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total (N=156)
BMI (kg/m2)	n	48	59	49	156
	Mean (SD)	25.0 (5.18)	24.8 (4.60)	25.7 (5.41)	25.1 (5.02)
	Median	24.3	24.8	24.6	24.5
	Min, Max	16,37	17,35	16,44	16,44
Sex					
Male	n(%)	32(66.67)	41(69.49)	36(73.47)	109(69.87)
Female	n(%)	16(33.33)	18(30.51)	13(26.53)	47(30.13)
Childbearing Potential [a]					
Yes	n(%)	12(75.00)	11(61.11)	9(69.23)	32(68.09)
No	n(%)	4(25.00)	7(38.89)	4(30.77)	15(31.91)
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.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under mITT Population.
[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=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total (N=156)
Asian	n(%)	47(97.92)	59(100.0)	47(95.92)	153(98.08)
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 or Caucasian	n(%)	1(2.08)	0(0.0)	2(4.08)	3(1.92)
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 / Not Latino	n(%)	48(100.0)	59(100.0)	49(100.0)	156(100.0)
Education					
1-8 years	n(%)	11(22.92)	12(20.34)	10(20.41)	33(21.15)
9-16 years	n(%)	35(72.92)	41(69.49)	33(67.35)	109(69.87)
>16 years	n(%)	2(4.17)	6(10.17)	6(12.24)	14(8.97)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under mITT Population.
[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=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total (N=156)
Marital Status					
Married	n(%)	18(37.50)	26(44.07)	21(42.86)	65(41.67)
Single	n(%)	28(58.33)	26(44.07)	24(48.98)	78(50.00)
Stable union	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Widow / Widower	n(%)	0(0.0)	2(3.39)	0(0.0)	2(1.28)
Divorced	n(%)	2(4.17)	5(8.47)	4(8.16)	11(7.05)
Employment					
Full-Time Employment	n(%)	4(8.33)	9(15.25)	3(6.12)	16(10.26)
Part-Time Employment	n(%)	5(10.42)	5(8.47)	8(16.33)	18(11.54)
Not employed	n(%)	39(81.25)	45(76.27)	38(77.55)	122(78.21)
Housing Status					
Living alone	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living with family	n(%)	48(100.0)	59(100.0)	49(100.0)	156(100.0)

Source: Listing 16.2.4.1
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under mITT Population.
[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=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total (N=156)
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.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under mITT Population.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.3
Demographics and Baseline Characteristics
Randomized Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=51)	Total (N=161)
Age (years)	n	50	60	51	161
	Mean (SD)	37.7 (10.38)	37.2 (9.74)	38.2 (9.08)	37.7 (9.69)
	Median	37.0	35.0	38.0	37.0
	Min, Max	23,68	21,62	20,64	20,68
Weight (kg)	n	50	60	51	161
	Mean (SD)	66.6 (15.56)	66.2 (12.63)	69.6 (17.28)	67.4 (15.12)
	Median	66.6	64.8	65.3	65.3
	Min, Max	34,120	45,91	42,143	34,143
Height (cm)	n	50	60	51	161
	Mean (SD)	163.8 (9.85)	163.8 (7.87)	163.9 (7.38)	163.8 (8.34)
	Median	164.5	164.1	164.0	164.0
	Min, Max	137,183	145,183	149,182	137,183

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

Table 14.1.3.1.3
Demographics and Baseline Characteristics
Randomized Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=51)	Total (N=161)
BMI (kg/m2)	n	50	60	51	161
	Mean (SD)	24.8 (5.28)	24.7 (4.60)	25.9 (5.67)	25.1 (5.16)
	Median	24.3	24.5	24.6	24.5
	Min, Max	15,37	17,35	16,44	15,44
Sex					
Male	n(%)	32(64.00)	42(70.00)	37(72.55)	111(68.94)
Female	n(%)	18(36.00)	18(30.00)	14(27.45)	50(31.06)
Childbearing Potential [a]					
Yes	n(%)	14(77.78)	11(61.11)	10(71.43)	35(70.00)
No	n(%)	4(22.22)	7(38.89)	4(28.57)	15(30.00)
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 Randomized Population, n - number of subjects with available data.
SD = Standard Deviation, Age = Age at Screening, Min = Minimum, Max = Maximum.
Percentages are based on the total number of subjects in each group (N) under Randomized Population.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.

Table 14.1.3.1.3
Demographics and Baseline Characteristics
Randomized Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=51)	Total (N=161)
Asian	n(%)	49(98.00)	60(100.0)	48(94.12)	157(97.52)
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 or Caucasian	n(%)	1(2.00)	0(0.0)	3(5.88)	4(2.48)
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 / Not Latino	n(%)	50(100.0)	60(100.0)	51(100.0)	161(100.0)
Education					
1-8 years	n(%)	11(22.00)	12(20.00)	10(19.61)	33(20.50)
9-16 years	n(%)	35(70.00)	42(70.00)	35(68.63)	112(69.57)
>16 years	n(%)	4(8.00)	6(10.00)	6(11.76)	16(9.94)

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

Table 14.1.3.1.3
Demographics and Baseline Characteristics
Randomized Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=51)	Total (N=161)
Marital Status					
Married	n(%)	18(36.00)	26(43.33)	21(41.18)	65(40.37)
Single	n(%)	29(58.00)	26(43.33)	26(50.98)	81(50.31)
Stable union	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Widow / Widower	n(%)	0(0.0)	2(3.33)	0(0.0)	2(1.24)
Divorced	n(%)	3(6.00)	6(10.00)	4(7.84)	13(8.07)
Employment					
Full-Time Employment	n(%)	4(8.00)	10(16.67)	3(5.88)	17(10.56)
Part-Time Employment	n(%)	5(10.00)	5(8.33)	8(15.69)	18(11.18)
Not employed	n(%)	41(82.00)	45(75.00)	40(78.43)	126(78.26)
Housing Status					
Living alone	n(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Living with family	n(%)	50(100.0)	60(100.0)	50(98.04)	160(99.38)

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

Table 14.1.3.1.3
Demographics and Baseline Characteristics
Randomized Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=51)	Total (N=161)
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)	1(1.96)	1(0.62)

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

Table 14.1.3.2
Disease Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Duration of Illness - Schizophrenia (Years)[a]	n	50	60	50	160
	Mean (SD)	7.1 (2.54)	6.3 (3.12)	7.1 (3.50)	6.8 (3.09)
	Median	7.2	6.2	7.3	6.6
	Min,Max	1,15	1,15	1,15	1,15
Duration of Current Episode of Schizophrenia (Months)[b]	n	50	60	50	160
	Mean (SD)	8.6 (5.46)	8.7 (5.27)	6.2 (3.23)	7.9 (4.90)
	Median	6.4	8.3	5.6	6.4
	Min,Max	3,25	2,23	2,15	2,25

Source: Listing 16.2.4.3.1, Listing 16.2.15.
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, mothers brother, father's sister's son, son, uncle, brother of father, daughter

Table 14.1.3.2
Disease Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Number of Psychiatric Hospitalization	n	50	60	50	160
	Mean (SD)	0.2 (0.48)	0.3 (0.72)	0.4 (0.88)	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 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, mothers brother, father's sister's son, son, uncle, brother of father, daughter

Table 14.1.3.2
Disease Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Family History of Schizophrenia					
None	n(%)	36(72.0)	46(76.7)	39(78.0)	121(75.6)
1st Degree Relatives [c]	n(%)	7(14.0)	8(13.3)	7(14.0)	22(13.8)
Father	n(%)	1(2.0)	3(5.0)	2(4.0)	6(3.8)
Mother	n(%)	2(4.0)	4(6.7)	1(2.0)	7(4.4)
Brother	n(%)	2(4.0)	1(1.7)	3(6.0)	6(3.8)
Sister	n(%)	2(4.0)	0(0.0)	1(2.0)	3(1.9)

Source: Listing 16.2.4.3.1, Listing 16.2.15.
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, mothers brother, father's sister's son, son, uncle, brother of father, daughter

Table 14.1.3.2
Disease Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
2nd Degree Relatives [d]	n(%)	4(8.0)	2(3.3)	0(0.0)	6(3.8)
Paternal Grandfather	n(%)	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Paternal Grandmother	n(%)	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Maternal Grandfather	n(%)	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Maternal Grandmother	n(%)	2(4.0)	1(1.7)	0(0.0)	3(1.9)
other	n(%)	5(10.0)	5(8.3)	5(10.0)	15(9.4)
Number of subjects with other psychiatric disorders	n(%)	3(6.0)	8(13.3)	13(26.0)	24(15.0)

Source: Listing 16.2.4.3.1, Listing 16.2.15.
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, mothers brother, father's sister's son, son, uncle, brother of father, daughter

Table 14.1.3.2
Disease Characteristics
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Calgary Depression Scale for Schizophrenia (CDSS)					
CDSS Total Score	n	50	60	50	160
	Mean (SD)	0.4 (0.97)	0.6 (1.29)	0.8 (1.65)	0.6 (1.33)
	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 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, mothers brother, father's sister's son, son, uncle, brother of father, daughter

Table 14.1.3.3.1
Medical History
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Number of Subjects with any Medical History	10(20.0)	14(23.3)	9(18.0)	33(20.6)
Blood and lymphatic system disorders	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Anaemia	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Endocrine disorders	0(0.0)	2(3.3)	3(6.0)	5(3.1)
Hypothyroidism	0(0.0)	2(3.3)	3(6.0)	5(3.1)
Eye disorders	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Cataract	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Pterygium	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Gastrointestinal disorders	1(2.0)	0(0.0)	1(2.0)	2(1.3)
Gastrooesophageal reflux disease	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Haemorrhoids	0(0.0)	0(0.0)	1(2.0)	1(0.6)
General disorders and administration site conditions	0(0.0)	1(1.7)	0(0.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Atrophy	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Infections and infestations	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Chikungunya virus infection	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Metabolism and nutrition disorders	5(10.0)	4(6.7)	2(4.0)	11(6.9)
Diabetes mellitus	5(10.0)	3(5.0)	2(4.0)	10(6.3)
Dyslipidaemia	1(2.0)	0(0.0)	1(2.0)	2(1.3)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Hyperlipidaemia	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Type 2 diabetes mellitus	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Adenoma benign	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Benign breast neoplasm	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Nervous system disorders	1(2.0)	1(1.7)	0(0.0)	2(1.3)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Akathisia	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Extrapyramidal disorder	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Reproductive system and breast disorders	0(0.0)	1(1.7)	1(2.0)	2(1.3)
Erectile dysfunction	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Sexual dysfunction	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Skin and subcutaneous tissue disorders	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Eczema	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Lichen planus	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Surgical and medical procedures	2(4.0)	4(6.7)	2(4.0)	8(5.0)
Arm amputation	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Female sterilisation	1(2.0)	0(0.0)	1(2.0)	2(1.3)
Otoplasty	0(0.0)	1(1.7)	0(0.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Salpingectomy	1(2.0)	3(5.0)	1(2.0)	5(3.1)
Vascular disorders	1(2.0)	1(1.7)	1(2.0)	3(1.9)
Hypertension	1(2.0)	1(1.7)	1(2.0)	3(1.9)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Number Of Subjects With Any Other Psychiatric History	3(6.0)	8(13.3)	13(26.0)	24(15.0)
Psychiatric Disorders	3(6.0)	8(13.3)	13(26.0)	24(15.0)
Acute Psychosis	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Anxiety	0(0.0)	0(0.0)	2(4.0)	2(1.3)
Brief Psychotic Disorder, With Postpartum Onset	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Depression	0(0.0)	1(1.7)	2(4.0)	3(1.9)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Insomnia	2(4.0)	3(5.0)	1(2.0)	6(3.8)
Mental Disorder	1(2.0)	2(3.3)	8(16.0)	11(6.9)
Nicotine Dependence	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Obsessive-Compulsive Disorder	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Sleep Disorder	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Prior Medication Any Prior Medication	32(64.0)	37(61.7)	32(64.0)	101(63.1)
Amino Acids, Incl. Combinations With Polypeptides	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Histidine;isoleucine;leucine;lysine;methionine;phenylalanine;threonine;tryptophan, L-;valine	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Anilides	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Paracetamol	0(0.0)	1 (1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Antidepressants In Combination With Psycholeptics	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Clonazepam;escitalopram	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Benzodiazepine Derivatives	18(36.0)	15 (25.0)	12 (24.0)	45(28.1)
Alprazolam	1(2.0)	0(0.0)	1 (2.0)	2(1.3)
Chlordiazepoxide	0(0.0)	0(0.0)	1 (2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Clonazepam	2(4.0)	1 (1.7)	4 (8.0)	7(4.4)
Diazepam	0(0.0)	1 (1.7)	1 (2.0)	2(1.3)
Lorazepam	13(26.0)	9 (15.0)	6 (12.0)	28(17.5)
Nitrazepam	2(4.0)	4 (6.7)	3 (6.0)	9(5.6)
Benzodiazepine Related Drugs	0(0.0)	1 (1.7)	1 (2.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Zolpidem	0(0.0)	1 (1.7)	1 (2.0)	2(1.3)
Beta Blocking Agents, Non-Selective	1(2.0)	1 (1.7)	1 (2.0)	3(1.9)
Propranolol	1(2.0)	1 (1.7)	1 (2.0)	3(1.9)
Biguanides	1(2.0)	1 (1.7)	0(0.0)	2(1.3)
Metformin	1(2.0)	1 (1.7)	0(0.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Centrally Acting Sympathomimetics	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Armodafinil	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Modafinil	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Combinations Of Vitamins	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Folic Acid;fursultiamine;mecobalamin;pyridoxine;tocopherol	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Contact Laxatives	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Sodium Picosulfate	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Corticosteroids, Potent (Group Iii)	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Mometasone	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Diazepines, Oxazepines, Thiazepines And Oxepines	1(2.0)	2 (3.3)	4 (8.0)	7(4.4)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Olanzapine	1(2.0)	1 (1.7)	2 (4.0)	4(2.5)
Quetiapine	0(0.0)	1 (1.7)	3 (6.0)	4(2.5)
Fat/Carbohydrates/Proteins/Minerals/Vitamins, Combinations	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Fat/Carbohydrates/Proteins/Minerals/Vitamins, Combinations	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Fatty Acid Derivatives	0(0.0)	2 (3.3)	0(0.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Valproate Semisodium	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Valproate Sodium	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Folic Acid And Derivatives	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Folic Acid	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Influenza Vaccines	0(0.0)	1 (1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Influenza Vaccine	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Iron Bivalent, Oral Preparations	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Ferrous Fumarate	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Iron In Other Combinations	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Folic Acid;iron;vitamin B12 Nos;zinc	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Multivitamins, Other Combinations	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Minerals Nos;vitamins Nos	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Multivitamins, Plain	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Vitamins Nos	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Non-Selective Monoamine Reuptake Inhibitors	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Doxepin	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Osmotically Acting Laxatives	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Lactulose	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Other Antiepileptics	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Lamotrigine	0(0.0)	0(0.0)	1 (2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Other Antihistamines For Systemic Use	1(2.0)	1 (1.7)	0(0.0)	2(1.3)
Azelastine Hydrochloride	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Ebastine	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Other Antipsychotics	1(2.0)	0(0.0)	3 (6.0)	4(2.5)
Aripiprazole	0(0.0)	0(0.0)	2 (4.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Valproate Semisodium	1(2.0)	0(0.0)	1 (2.0)	2(1.3)
Other Anxiolytics	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Escitalopram Oxalate	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Other Immunosuppressants	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Methotrexate	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Other Mineral Products	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Minerals Nos;vitamins Nos	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Phenothiazines With Aliphatic Side-Chain	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Chlorpromazine	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Phenothiazines With Piperazine Structure	0(0.0)	1 (1.7)	2 (4.0)	3(1.9)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Trifluoperazine	0(0.0)	1 (1.7)	2 (4.0)	3(1.9)
Propulsives	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Domperidone	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Proton Pump Inhibitors	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Domperidone;rabeprazole	0(0.0)	1 (1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Selective Serotonin Reuptake Inhibitors	1(2.0)	2 (3.3)	1 (2.0)	4(2.5)
Escitalopram Oxalate	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Fluoxetine	1(2.0)	1 (1.7)	1 (2.0)	3(1.9)
Sertraline	1(2.0)	0(0.0)	1 (2.0)	2(1.3)
Sulfonylureas	1(2.0)	1 (1.7)	0(0.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Gliclazide	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Glimepiride	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Tertiary Amines	22(44.0)	25 (41.7)	23 (46.0)	70(43.8)
Trihexyphenidyl	21(42.0)	25 (41.7)	23 (46.0)	69(43.1)
Trihexyphenidyl Hydrochloride	1(2.0)	0(0.0)	1 (2.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Vitamin B-Complex, Plain	1(2.0)	3 (5.0)	1 (2.0)	5(3.1)
Vitamin B Complex	1(2.0)	3 (5.0)	1 (2.0)	5(3.1)
Vitamin B12 (Cyanocobalamin And Analogues)	0(0.0)	1 (1.7)	1 (2.0)	2(1.3)
Benfotiamine;chromium;folic Acid;inositol;linolenic Acid;mecobalamin;pyridoxine	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Colecalciferol;levomefolic Acid;mecobalamin;pyridoxal	0(0.0)	1 (1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.1
Summary of Prior Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Vitamins, Other Combinations	1(2.0)	2 (3.3)	1 (2.0)	4(2.5)
Ascorbic Acid;vitamin B Nos	0(0.0)	1 (1.7)	0(0.0)	1(0.6)
Carbohydrates Nos;colecalciferol;copper;dexpanthenol;iodine;lysine Hydrochloride;nicotinamide;potassium Iodide;pyridoxine Hydrochloride;retinol;riboflavin;selenium;vitamin B1 Nos;vitamin B12 Nos;vitamin E Nos;zinc	1(2.0)	1 (1.7)	1 (2.0)	3(1.9)
Zinc	0(0.0)	0(0.0)	1 (2.0)	1(0.6)
Zinc Sulfate	0(0.0)	0(0.0)	1 (2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Concomitant Medication Any Concomitant Medication	41(82.0)	55(91.7)	42(84.0)	138(86.3)
Amino Acids, Incl. Combinations With Polypeptides	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Histidine;isoleucine;leucine;lysine;methionine;phenylalanine;threonine;tryptophan, L-;valine	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Angiotensin II Receptor Blockers (Arbs), Plain	0(0.0)	1(1.7)	1(2.0)	2(1.3)
Losartan	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Telmisartan	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Anilides	1(2.0)	1(1.7)	2(4.0)	4(2.5)
Caffeine;ephedrine;paracetamol	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Paracetamol	1(2.0)	1(1.7)	1(2.0)	3(1.9)
Artemisinin And Derivatives, Plain	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Artemether	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Benzodiazepine Derivatives	15(30.0)	17(28.3)	11(22.0)	43(26.9)
Alprazolam	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Benzodiazepine Derivatives	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Clobazam	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Clonazepam	2(4.0)	1(1.7)	4(8.0)	7(4.4)
Diazepam	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Lorazepam	12(24.0)	15(25.0)	6(12.0)	33(20.6)
Benzodiazepine Related Drugs	3(6.0)	2(3.3)	0(0.0)	5(3.1)
Zolpidem	3(6.0)	2(3.3)	0(0.0)	5(3.1)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Biguanides	5(10.0)	4(6.7)	3(6.0)	12(7.5)
Metformin	5(10.0)	4(6.7)	3(6.0)	12(7.5)
Contact Laxatives	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Sodium Picosulfate	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Diazepines, Oxazepines, Thiazepines And Oxepines	3(6.0)	3(5.0)	5(10.0)	11(6.9)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Quetiapine	3(6.0)	3(5.0)	5(10.0)	11(6.9)
Quetiapine Fumarate	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Fatty Acid Derivatives	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Valproate Sodium	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Glucocorticoids	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Betamethasone	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Heparins Or Heparinoids For Topical Use	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Benzyl Nicotinate;heparin	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Hmg Coa Reductase Inhibitors	2(4.0)	2(3.3)	1(2.0)	5(3.1)
Atorvastatin	2(4.0)	2(3.3)	1(2.0)	5(3.1)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Iron In Combination With Folic Acid	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Ferrous Ascorbate;folic Acid	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Leukotriene Receptor Antagonists	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Levocetirizine;montelukast	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Opium Alkaloids And Derivatives	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Cetirizine;dextromethorphan;menthol;phenylephrine	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Other Antiallergics	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Olopatadine	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Other Antidepressants	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Venlafaxine	0(0.0)	1(1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Other Antiinflammatory/Antirheumatic Agents In Combination With Other Drugs	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Diclofenac;paracetamol;serrapeptase	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Other Antimalarials	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Lumefantrine	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Other Antipsychotics	0(0.0)	1(1.7)	1(2.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Valproate Semisodium	0(0.0)	1(1.7)	1(2.0)	2(1.3)
Other Anxiolytics	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Sertraline	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Progestogens And Estrogens, Fixed Combinations	0(0.0)	2(3.3)	3(6.0)	5(3.1)
Desogestrel;ethinylestradiol	0(0.0)	1(1.7)	3(6.0)	4(2.5)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Ethinylestradiol;levonorgestrel	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Progestogens And Estrogens, Sequential Preparations	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Ethinylestradiol;levonorgestrel	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Proton Pump Inhibitors	3(6.0)	0(0.0)	0(0.0)	3(1.9)
Omeprazole	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Pantoprazole	2(4.0)	0(0.0)	0(0.0)	2(1.3)
Selective Serotonin Reuptake Inhibitors	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Sertraline	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Sulfonylureas	2(4.0)	2(3.3)	1(2.0)	5(3.1)
Gliclazide	1(2.0)	0(0.0)	1(2.0)	2(1.3)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Glimepiride	1(2.0)	2(3.3)	0(0.0)	3(1.9)
Tertiary Amines	33(66.0)	44(73.3)	31(62.0)	108(67.5)
Biperiden	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Trihexyphenidyl	32(64.0)	44(73.3)	30(60.0)	106(66.3)
Trihexyphenidyl Hydrochloride	0(0.0)	0(0.0)	1(2.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Third-Generation Cephalosporins	2(4.0)	0(0.0)	1(2.0)	3(1.9)
Cefixime	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Cefpodoxime Proxetil	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Ceftriaxone	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Thyroid Hormones	0(0.0)	2(3.3)	3(6.0)	5(3.1)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Levothyroxine Sodium	0(0.0)	2(3.3)	3(6.0)	5(3.1)
Vitamin B-Complex, Plain	0(0.0)	1(1.7)	1(2.0)	2(1.3)
Biotin;cyanocobalamin;folic Acid;nicotinamide;pantothenic Acid;pyridoxine;riboflavin;thiamine	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Vitamin B Complex	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Vitamins	0(0.0)	1(1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.1.2
Summary of Concomitant Medications
Safety Population

ATC4 and Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Vitamins Nos	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Vitamins, Other Combinations	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Ascorbic Acid;vitamin B Nos	0(0.0)	1(1.7)	0(0.0)	1(0.6)

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 ATC classification.

Table 14.1.4.2.1
Summary of Prior Antipsychotic Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Prior Antipsychotic Medication	50(100.0)	60(100.0)	50(100.0)	160(100.0)
Any Prior Antipsychotic Medication During Last 5 Years				
Amisulpride	8(16.0)	4(6.7)	10(20.0)	22(13.8)
Aripiprazole	10(20.0)	17(28.3)	17(34.0)	44(27.5)
Blonanserin	0(0.0)	1(1.7)	2(4.0)	3(1.9)
Cariprazine	0(0.0)	0(0.0)	2(4.0)	2(1.3)

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 Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Chlorpromazine	1(2.0)	2(3.3)	3(6.0)	6(3.8)
Fluoxetine;olanzapine	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Flupentixol	0(0.0)	1(1.7)	2(4.0)	3(1.9)
Fluphenazine	0(0.0)	3(5.0)	3(6.0)	6(3.8)
Fluphenazine Decanoate	1(2.0)	0(0.0)	1(2.0)	2(1.3)

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 Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Haloperidol	10(20.0)	9(15.0)	8(16.0)	27(16.9)
Haloperidol Decanoate	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Iloperidone	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Lurasidone	1(2.0)	0(0.0)	2(4.0)	3(1.9)
Lurasidone Hydrochloride	1(2.0)	0(0.0)	0(0.0)	1(0.6)

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 Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Memantine	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Olanzapine	39(78.0)	45(75.0)	33(66.0)	117(73.1)
Paliperidone	7(14.0)	3(5.0)	5(10.0)	15(9.4)
Quetiapine	16(32.0)	11(18.3)	10(20.0)	37(23.1)
Quetiapine Fumarate	1(2.0)	0(0.0)	1(2.0)	2(1.3)

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 Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Risperidone	40(80.0)	50(83.3)	45(90.0)	135(84.4)
Risperidone;trihexyphenidyl	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Sertraline	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Trifluoperazine	10(20.0)	12(20.0)	9(18.0)	31(19.4)
Trifluoperazine Hydrochloride	0(0.0)	1(1.7)	3(6.0)	4(2.5)

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 Medication
Safety Population

Preferred Drug Name	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)	Total (N=160) n (%)
Zuclopenthixol	0(0.0)	1(1.7)	1(2.0)	2(1.3)

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 14.1.4.2.2
Summary of Current Antipsychotic Medication
Safety Population

Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Current Antipsychotic Medication				
Aripiprazole	3(6.0)	4(6.7)	1(2.0)	8(5.0)
Olanzapine	13(26.0)	15(25.0)	14(28.0)	42(26.3)
Paliperidone	1(2.0)	0(0.0)	1(2.0)	2(1.3)
Quetiapine	2(4.0)	0(0.0)	0(0.0)	2(1.3)
Risperidone	26(52.0)	33(55.0)	29(58.0)	88(55.0)
Other	5(10.0)	8(13.3)	5(10.0)	18(11.3)

Source: Listing 16.2.4.4.3.2
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 Drug Name.

Table 14.1.4.2.2
Summary of Current Antipsychotic Medication
Safety Population

Drug Name	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Other Specify				
Amisulpride	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Blonanserin	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Haloperidol	2(4.0)	1(1.7)	2(4.0)	5(3.1)
Trifluoperazine	3(6.0)	6(10.0)	0(0.0)	9(5.6)
Trifluoperazine Hydrochloride	0(0.0)	0(0.0)	2(4.0)	2(1.3)

Source: Listing 16.2.4.4.3.2
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 Drug Name.

Table 14.1.4.3
Summary of Rescue Medication
Safety Population

Rescue Medication Name	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
No Subject meets these Criteria					

Source: Listing 16.2.4.4.3.3

Table 14.1.5
Summary of Global Assessment of Functioning (GAF)
Safety Population

Visit	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Screening	n	50	60	50	160
	Mean (SD)	41.6 (5.02)	42.1 (4.38)	42.9 (4.67)	42.2 (4.68)
	Median	41.0	41.0	43.0	41.5
	Min, Max	31, 50	30, 50	29, 50	29, 50
Baseline	n	50	60	50	160
	Mean (SD)	41.8 (5.02)	42.5 (4.54)	43.0 (4.49)	42.4 (4.67)
	Median	41.0	42.0	43.0	42.0
	Min, Max	31, 50	30, 50	30, 50	30, 50

Source: Listing 16.2.4.4.4
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.

Table 14.2.1.1
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score - Within Group Comparisons
(Primary Estimand) mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening	n	48		59		49	
	Mean (SD)	80.1 (5.30)		79.2 (5.09)		79.7 (5.30)	
	Median	80		80		79	
	Min, Max	71, 89		70, 89		71, 89	
Baseline	n	48		59		49	
	Mean (SD)	80.1 (5.19)		79.2 (5.17)		79.4 (4.77)	
	Median	82		80		79	
	Min, Max	72, 89		70, 89		71, 89	

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.
p-Value = Paired t-test.

Table 14.2.1.1
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score - Within Group Comparisons
(Primary Estimand) mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	n	48	48	59	59	47	47
	Mean (SD)	78.8 (5.49)	-1.3 (2.37)	77.2 (5.61)	-2.0 (2.94)	77.8 (5.09)	-1.3 (3.12)
	Median	78.5	-0.5	78	-1	76	0
	Min, Max	69, 91	-10, 2	65, 89	-16, 2	70, 94	-13, 5
Day 15	n	48	48	57	57	48	48
	Mean (SD)	76.0 (6.84)	-4.1 (3.63)	74.7 (6.54)	-4.5 (4.13)	75.8 (5.80)	-3.5 (4.17)
	Median	77	-4	74	-4	74.5	-2.5
	Min, Max	60, 89	-15, 0	60, 88	-17, 3	68, 91	-16, 2

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.
p-Value = Paired t-test.

Table 14.2.1.1
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score - Within Group Comparisons
(Primary Estimand) mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29	n	48	48	56	56	49	49
	Mean (SD)	73.3 (8.64)	-6.8 (5.80)	71.3 (7.37)	-8.0 (5.42)	74.1 (6.35)	-5.3 (5.16)
	Median	73	-5	72	-8.5	74	-4
	Min, Max	54, 88	-28, 2	55, 88	-22, 4	64, 90	-20, 3
Day 43	n	48	48	56	56	48	48
	Mean (SD)	71.1 (9.56)	-9.0 (7.40)	68.6 (8.07)	-10.6 (7.49)	70.6 (7.05)	-8.6 (6.35)
	Median	70.5	-8	68.5	-10	70.5	-8.5
	Min, Max	48, 91	-34, 3	49, 87	-28, 12	58, 85	-25, 1
	95% CI		(-11.13, -6.83)		(-12.63, -8.62)		(-10.43, -6.74)
	p-value		<.001		<.001		<.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.
p-Value = Paired t-test.

Table 14.2.1.1a
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Visit Between Dose Group Comparisons - MMRM
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		59		49	
	Mean(SD)	80.1 (5.19)		79.2 (5.17)		79.4 (4.77)	
	Median	82		80		79	
	Min, Max	72, 89		70, 89		71, 89	
Day 8	n	48	48	59	59	47	47
	Mean(SD)	78.8 (5.49)	-1.3 (2.37)	77.2 (5.61)	-2.0 (2.94)	77.8 (5.09)	-1.3 (3.12)
	Median	78.5	-0.5	78	-1	76	0
	Min, Max	69, 91	-10, 2	65, 89	-16, 2	70, 94	-13, 5

Source: Listing 16.2.6.1.2
MMRM = Mixed Model Repeated Measure, N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, Min = Minimum, Max = Maximum
[a] Results are for 15 mg bid + 30 mg bid combined. [b] If combined 15 mg bid + 30 mg bid result is significant then 30 mg will be compared with 7.5 mg bid.
A mixed model repeated measures (MMRM) linear regression model is fitted, with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline PANSS total score obtained at the scheduled visits Days 8, 15, 29 and 43(Endpoint) respectively. LS Mean Difference and p-value are corresponding to the difference between dose groups.

Table 14.2.1.1a
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Visit Between Dose Group Comparisons - MMRM
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	48	57	57	48	48
	Mean(SD)	76.0 (6.84)	-4.1 (3.63)	74.7 (6.54)	-4.5 (4.13)	75.8 (5.80)	-3.5 (4.17)
	Median	77	-4	74	-4	74.5	-2.5
	Min, Max	60, 89	-15, 0	60, 88	-17, 3	68, 91	-16, 2
Day 29	n	48	48	56	56	49	49
	Mean(SD)	73.3 (8.64)	-6.8 (5.80)	71.3 (7.37)	-8.0 (5.42)	74.1 (6.35)	-5.3 (5.16)
	Median	73	-5	72	-8.5	74	-4
	Min, Max	54, 88	-28, 2	55, 88	-22, 4	64, 90	-20, 3

Source: Listing 16.2.6.1.2
MMRM = Mixed Model Repeated Measure, N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, Min = Minimum, Max = Maximum
[a] Results are for 15 mg bid + 30 mg bid combined. [b] If combined 15 mg bid + 30 mg bid result is significant then 30 mg will be compared with 7.5 mg bid.
A mixed model repeated measures (MMRM) linear regression model is fitted, with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline PANSS total score obtained at the scheduled visits Days 8, 15, 29 and 43(Endpoint) respectively. LS Mean Difference and p-value are corresponding to the difference between dose groups.

Table 14.2.1.1a
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Visit Between Dose Group Comparisons - MMRM
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43	n	48	48	56	56	48	48
	Mean(SD)	71.1 (9.56)	-9.0 (7.40)	68.6 (8.07)	-10.6 (7.49)	70.6 (7.05)	-8.6 (6.35)
	Median	70.5	-8	68.5	-10	70.5	-8.5
	Min, Max	48, 91	-34, 3	49, 87	-28, 12	58, 85	-25, 1
	LS Mean (SE)		-8.9 (1.02)		-9.6 (0.69)		-8.5 (1.01)
	95% CI		(-10.96, -6.92)		(-11.01, -8.27)		(-10.46, -6.45)
	LS Mean Diff(SE)				-0.7(1.24)[a]		
	95% CI				(-3.16, 1.74)		
	p-value				0.569		

Source: Listing 16.2.6.1.2
MMRM = Mixed Model Repeated Measure, N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, SE = Standard Error, CI = Confidence Interval, Min = Minimum, Max = Maximum
[a] Results are for 15 mg bid + 30 mg bid combined. [b] If combined 15 mg bid + 30 mg bid result is significant then 30 mg will be compared with 7.5 mg bid.
A mixed model repeated measures (MMRM) linear regression model is fitted, with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline PANSS total score obtained at the scheduled visits Days 8, 15, 29 and 43(Endpoint) respectively. LS Mean Difference and p-value are corresponding to the difference between dose groups.

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\Table 14.2.1.1a.sas
Programmer:SK
Date of Extraction:05FEB2023

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		59		49	
	Mean (SD)	24.0 (3.61)		23.8 (3.35)		23.1 (2.90)	
	Median	24.5		24		23	
	Min, Max	17, 36		17, 30		17, 29	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	23.5 (3.56)	-0.5 (1.25)	23.1 (3.54)	-0.8 (1.21)	22.7 (3.06)	-0.5 (1.16)
	Median	24	0	24	0	22	0
	Min, Max	16, 32	-5, 2	14, 30	-4, 1	15, 29	-5, 1

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	48	57	57	48	48
	Mean (SD)	22.3 (4.07)	-1.8 (1.81)	21.8 (3.81)	-1.9 (2.23)	21.6 (3.33)	-1.5 (2.00)
	Median	22.5	-2	23	-1	21	-1
	Min, Max	11, 35	-9, 1	13, 30	-9, 2	13, 29	-7, 1
Day 29	n	48	48	56	56	49	49
	Mean (SD)	21.0 (4.61)	-3.0 (2.90)	20.3 (4.02)	-3.4 (2.80)	20.8 (3.53)	-2.3 (2.50)
	Median	21	-2.5	21	-3	21	-2
	Min, Max	11, 35	-15, 1	10, 31	-9, 3	14, 29	-7, 2

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Positive Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43	n	48	48	56	56	48	48
	Mean (SD)	20.1 (4.99)	-3.9 (3.52)	19.3 (4.30)	-4.5 (3.75)	19.6 (3.84)	-3.6 (2.77)
	Median	20	-3	19.5	-4	19	-4
	Min, Max	11, 35	-15, 3	10, 30	-13, 2	12, 28	-10, 1
	95% CI		(-4.94, -2.89)		(-5.49, -3.48)		(-4.41, -2.80)
	P-Value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		59		49	
	Mean (SD)	20.1 (3.27)		19.6 (3.72)		19.6 (3.05)	
	Median	20		20		20	
	Min, Max	12, 31		10, 29		12, 26	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	19.9 (3.12)	-0.3 (0.67)	19.3 (3.69)	-0.3 (0.94)	19.1 (2.99)	-0.3 (0.84)
	Median	20	0	20	0	19	0
	Min, Max	12, 29	-2, 1	10, 28	-6, 1	12, 26	-3, 1

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	48	57	57	48	48
	Mean (SD)	19.2 (2.94)	-1.0 (1.80)	19.0 (3.61)	-0.6 (1.55)	18.8 (2.98)	-0.8 (1.29)
	Median	19	0	20	0	19	0
	Min, Max	12, 26	-7, 1	10, 28	-6, 4	11, 24	-5, 1
Day 29	n	48	48	56	56	49	49
	Mean (SD)	18.7 (2.72)	-1.4 (2.51)	18.5 (3.43)	-1.4 (1.99)	18.3 (3.06)	-1.3 (1.55)
	Median	19	-1	19	-1	19	-1
	Min, Max	12, 25	-10, 2	11, 26	-7, 6	11, 24	-5, 1

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: Negative Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43	n	48	48	56	56	48	48
	Mean (SD)	18.3 (2.73)	-1.8 (2.71)	17.7 (3.79)	-2.1 (2.74)	17.7 (2.90)	-1.8 (2.18)
	Median	18	-1	18	-1.5	18	-1.5
	Min, Max	12, 25	-11, 3	10, 26	-10, 7	11, 23	-9, 1
	95% CI		(-2.62, -1.05)		(-2.86, -1.39)		(-2.47, -1.20)
	P-Value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: General Psychopathology Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		59		49	
	Mean (SD)	35.9 (3.93)		35.8 (3.48)		36.7 (3.77)	
	Median	36		35		37	
	Min, Max	28, 49		29, 46		30, 44	
Day 8	n	48	48	59	59	47	47
	Mean (SD)	35.3 (4.13)	-0.6 (1.05)	34.8 (3.43)	-0.9 (1.74)	36.0 (3.64)	-0.5 (1.88)
	Median	35.5	0	34	0	35	0
	Min, Max	28, 49	-5, 1	27, 44	-9, 2	30, 47	-8, 3

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: General Psychopathology Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	48	57	57	48	48
	Mean (SD)	34.5 (4.54)	-1.4 (1.67)	33.8 (3.74)	-1.9 (2.19)	35.4 (3.86)	-1.2 (1.98)
	Median	34	-1.5	33	-2	35	-1
	Min, Max	23, 49	-7, 2	26, 43	-10, 3	28, 46	-8, 2
Day 29	n	48	48	56	56	49	49
	Mean (SD)	33.5 (5.01)	-2.4 (2.13)	32.4 (3.68)	-3.2 (2.61)	34.9 (4.07)	-1.8 (2.32)
	Median	33	-2	33	-2.5	35	-2
	Min, Max	24, 48	-8, 2	24, 40	-12, 0	27, 46	-9, 2

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales – Within Group Comparisons
mITT Population

Scale: General Psychopathology Scale

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43	n	48	48	56	56	48	48
	Mean (SD)	32.7 (5.00)	-3.2 (3.05)	31.7 (3.50)	-4.0 (3.34)	33.4 (4.21)	-3.1 (2.94)
	Median	32	-2.5	31	-3	33	-3
	Min, Max	23, 46	-11, 4	25, 39	-14, 4	26, 43	-10, 2
	95% CI		(-4.12, -2.34)		(-4.91, -3.12)		(-4.00, -2.29)
	P-Value		<.001		<.001		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.3
Responder Analysis by Visit - Positive and Negative Syndrome Scale (PANSS)
mITT Population

Visit	PANSS	Improvement Category	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total [a] (N=156)
Day 8	Total Score	Change >=20%	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total Positive Score	>=4-Point Improvement	n (%)	2(4.17)	3(5.08)	1(2.04)	6(3.85)
Day 15	Total Score	Change >=20%	n (%)	0 (0.0)	1(1.69)	0 (0.0)	1(0.64)
	Total Positive Score	>=4-Point Improvement	n (%)	5(10.42)	13(22.03)	9(18.37)	27(17.31)
Day 29	Total Score	Change >=20%	n (%)	4(8.33)	4(6.78)	2(4.08)	10(6.41)
	Total Positive Score	>=4-Point Improvement	n (%)	19(39.58)	24(40.68)	16(32.65)	59(37.82)
Day 43	Total Score	Change >=20%	n (%)	9(18.75)	11(18.64)	4(8.16)	24(15.38)
	Total Positive Score	>=4-Point Improvement	n (%)	23(47.92)	31(52.54)	25(51.02)	79(50.64)

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat.
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.

Table 14.2.1.4
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Score at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Baseline	n	48	59	49
	Mean (SD)	80.1 (5.19)	79.2 (5.17)	79.4 (4.77)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 89
Day 43	n	48	59	49
	Mean (SD)	71.1 (9.56)	68.6 (7.92)	70.9 (7.29)
	Median	70.5	68	71
	Min, Max	48, 91	49, 87	58, 85

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. 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.

Table 14.2.1.4
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Score at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 43	Mean change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.33)	-8.5 (6.32)
	95% CI	(-11.13, -6.83)	(-12.52, -8.67)	(-10.27, -6.69)
	p-value	<.001	<.001	<.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. 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.

Table 14.2.1.5
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Day 43
Paired t-test Using LOCF Supportive Estimand
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Baseline	n	48	59	49
	Mean (SD)	80.1 (5.19)	79.2 (5.17)	79.4 (4.77)
	Median	82.0	80.0	79.0
	Min, Max	72, 89	70, 89	71, 89
Day 43	n	48	59	49
	Mean (SD)	71.1 (9.56)	69.0 (8.03)	71.0 (7.51)
	Median	70.5	70.0	71.0
	Min, Max	48, 91	49, 87	58, 90

Source: Listing 16.2.6.1.2
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. 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.

Table 14.2.1.5
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Day 43
Paired t-test Using LOCF Supportive Estimand
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 43	Mean change from Baseline (SD)	-9.0 (7.40)	-10.2 (7.49)	-8.4 (6.43)
	95% CI	(-11.13, -6.83)	(-12.19, -8.29)	(-10.23, -6.54)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.1.2
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. 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.

Table 14.2.1.6
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Day 43- Comparison of Different Models
mITT Population

Models	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Primary Estimand	Mean Change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.49)	-8.6 (6.35)
	95% CI	(-11.13, -6.83)	(-12.63, -8.62)	(-10.43, -6.74)
	p-value	<.001	<.001	<.001
LOCF@	Mean Change from Baseline (SD)	-9.0 (7.40)	-10.2 (7.49)	-8.4 (6.43)
	95% CI	(-11.13, -6.83)	(-12.19, -8.29)	(-10.23, -6.54)
	p-value	<.001	<.001	<.001
MI	Mean change from Baseline (SD)	-9.0 (7.40)	-10.6 (7.33)	-8.5 (6.32)
	95% CI	(-11.13, -6.83)	(-12.52, -8.67)	(-10.27, -6.69)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test.
LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, Min=Minimum, Max=Maximum, n - number of subjects in the specified category, The results obtained in each model are compared in this table.
@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF will be considered as supportive.

Table 14.2.2.1
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Within Group Comparisons
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening	n	48		59		49	
	Mean (SD)	4.5 (0.65)		4.5 (0.60)		4.4 (0.49)	
	Median	4		4		4	
	Min, Max	4, 6		4, 6		4, 5	
Baseline	n	48		59		49	
	Mean (SD)	4.6 (0.65)		4.5 (0.60)		4.4 (0.50)	
	Median	4		4		4	
	Min, Max	4, 6		4, 6		4, 5	

Source: Listing 16.2.6.2
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.

Table 14.2.2.1
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Within Group Comparisons
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	n	48	48	59	59	47	47
	Mean (SD)	4.5 (0.68)	-0.1 (0.35)	4.4 (0.59)	-0.1 (0.33)	4.3 (0.52)	-0.1 (0.31)
	Median	4	0	4	0	4	0
	Min, Max	3, 6	-2, 0	3, 6	-1, 0	3, 5	-1, 0
Day 15	n	48	48	57	57	48	48
	Mean (SD)	4.3 (0.74)	-0.3 (0.49)	4.2 (0.69)	-0.3 (0.57)	4.2 (0.48)	-0.3 (0.49)
	Median	4	0	4	0	4	0
	Min, Max	3, 6	-2, 0	2, 6	-3, 0	3, 5	-2, 0

Source: Listing 16.2.6.2
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.

Table 14.2.2.1
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – Within Group Comparisons
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29	n	48	48	56	56	49	49
	Mean (SD)	4.0 (0.81)	-0.5 (0.65)	3.9 (0.75)	-0.6 (0.62)	4.0 (0.54)	-0.4 (0.58)
	Median	4	0	4	-1	4	0
	Min, Max	2, 6	-3, 0	2, 6	-3, 0	3, 5	-2, 0
Day 43	n	48	48	56	56	48	48
	Mean (SD)	3.9 (0.87)	-0.6 (0.79)	3.7 (0.70)	-0.8 (0.72)	3.8 (0.64)	-0.7 (0.62)
	Median	4	-1	4	-1	4	-1
	Min, Max	2, 6	-3, 1	2, 6	-3, 0	3, 5	-2, 0
	95% CI		(-0.87, -0.42)		(-1.01, -0.63)		(-0.87, -0.51)
	P-Value		<.001		<.001		<.001

Source: Listing 16.2.6.2
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.

Table 14.2.2.2
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Baseline	n	48	59	49
	Mean (SD)	4.6 (0.65)	4.5 (0.60)	4.4 (0.50)
	Median	4.0	4.0	4.0
	Min, Max	4, 6	4, 6	4, 5
Day 43	n	48	59	49
	Mean (SD)	3.9 (0.87)	3.7 (0.69)	3.8 (0.64)
	Median	4.0	4.0	4.0
	Min, Max	2, 6	2, 6	3, 5

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min=Minimum, Max=Maximum.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. p-value = Paired t-test.

Table 14.2.2.2
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 43	Mean change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.70)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.00, -0.63)	(-0.86, -0.51)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min=Minimum, Max=Maximum.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. p-value = Paired t-test.

Table 14.2.2.3
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 – Paired t-test Using LOCF
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Baseline	n	48	59	49
	Mean (SD)	4.6 (0.65)	4.5 (0.60)	4.4 (0.50)
	Median	4.0	4.0	4.0
	Min, Max	4, 6	4, 6	4, 5
Day 43	n	48	59	49
	Mean (SD)	3.9 (0.87)	3.8 (0.70)	3.8 (0.65)
	Median	4.0	4.0	4.0
	Min, Max	2, 6	2, 6	3, 5

Source: Listing 16.2.6.2
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.
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.

Table 14.2.2.3
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 – Paired t-test Using LOCF
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 43	Mean change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.63)
	95% CI	(-0.87, -0.42)	(-0.97, -0.59)	(-0.85, -0.49)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2
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.
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.

Table 14.2.2.4
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43- Comparison of Different Models
mITT Population

Models	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Primary Estimand	Mean Change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.01, -0.63)	(-0.87, -0.51)
	p-value	<.001	<.001	<.001
LOCF@	Mean Change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.72)	-0.7 (0.63)
	95% CI	(-0.87, -0.42)	(-0.97, -0.59)	(-0.85, -0.49)
	p-value	<.001	<.001	<.001
MI	Mean Change from Baseline (SD)	-0.6 (0.79)	-0.8 (0.70)	-0.7 (0.62)
	95% CI	(-0.87, -0.42)	(-1.00, -0.63)	(-0.86, -0.51)
	p-value	<.001	<.001	<.001

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT Population, MI = Multiple Imputation, LOCF = Last observation-carried forward, CI = Confidence Interval, P-Value = Paired t-test, n=number of patient, Min=Minimum, Max=Maximum.
@ In case subject has not taken any rescue medication and not added any further efficacy data LOCF will be considered as supportive.

Table 14.2.3.1
Clinical Global Impression - Change from Baseline (CGI-C)
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 8	n	48	59	47
	Mean (SD)	3.8 (0.43)	3.7 (0.49)	3.8 (0.51)
	Median	4	4	4
	Min, max	2, 4	3, 5	2, 5
Day 15	n	48	57	48
	Mean (SD)	3.4 (0.50)	3.5 (0.60)	3.6 (0.57)
	Median	3	3	4
	Min, max	3, 4	2, 5	2, 5

Source: Listing 16.2.6.3
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

Table 14.2.3.1
Clinical Global Impression - Change from Baseline (CGI-C)
mITT Population

Visit	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)
Day 29	n	48	56	49
	Mean (SD)	3.2 (0.62)	3.1 (0.63)	3.5 (0.62)
	Median	3	3	4
	Min, max	2, 4	2, 4	2, 5
Day 43	n	48	56	48
	Mean (SD)	3.0 (0.80)	2.9 (0.72)	3.1 (0.65)
	Median	3	3	3
	Min, max	2, 5	2, 5	2, 4

Source: Listing 16.2.6.3
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

Table 14.2.3.2
Responder Analysis - Clinical Global Impression – Change from Baseline (CGI-C)
mITT Population

Visit	Category	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total [a] (N=156)
Day 8	CGI-C score <= 3	n (%)	7 (14.58)	18 (30.51)	10 (20.41)	35 (22.44)
	CGI-C score > 3	n (%)	41 (85.42)	41 (69.49)	37 (75.51)	119 (76.28)
Day 15	CGI-C score <= 3	n (%)	27 (56.25)	31 (52.54)	19 (38.78)	77 (49.36)
	CGI-C score > 3	n (%)	21 (43.75)	26 (44.07)	29 (59.18)	76 (48.72)
Day 29	CGI-C score <= 3	n (%)	33 (68.75)	41 (69.49)	23 (46.94)	97 (62.18)
	CGI-C score > 3	n (%)	15 (31.25)	15 (25.42)	26 (53.06)	56 (35.90)

Source: Listing 16.2.6.3
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat
Responder analysis is performed by summarizing the proportion of patients in each of the evenamide groups and Doses groups with different categories of improvement at each avisit on the CGI-C Score.
Responders: Patients with CGI-C Score of 1, 2 or 3.
[a] Total is the total number of subjects taking the active treatment evenamide included in each category.

Table 14.2.3.2
Responder Analysis - Clinical Global Impression – Change from Baseline (CGI-C)
mITT Population

Visit	Category	Statistic	Evenamide 7.5 mg BID (N=48)	Evenamide 15 mg BID (N=59)	Evenamide 30 mg BID (N=49)	Total [a] (N=156)
Day 43	CGI-C score <= 3	n (%)	34 (70.83)	47 (79.66)	36 (73.47)	117 (75.00)
	CGI-C score > 3	n (%)	14 (29.17)	9 (15.25)	12 (24.49)	35 (22.44)

Source: Listing 16.2.6.3
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat
Responder analysis is performed by summarizing the proportion of patients in each of the evenamide groups and Doses groups with different categories of improvement at each avisit on the CGI-C Score.
Responders: Patients with CGI-C Score of 1, 2 or 3.
[a] Total is the total number of subjects taking the active treatment evenamide included in each category.

Table 14.2.4
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43-Within Group Comparisons-mITT Population

			Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Social Contacts	Baseline	n	48		59		49	
		Mean (SD)	1.3 (0.83)		1.3 (0.94)		1.4 (1.03)	
		Median	1.5		1.5		2	
		Min, Max	0, 3		0, 4		0, 4	
	Day 43	n	48	48	56	56	48	48
		Mean (SD)	1.5 (0.81)	0.2 (0.51)	1.5 (0.99)	0.2 (0.51)	1.7 (1.20)	0.2 (0.65)
		Median	1.75	0	1.5	0	2	0
		Min, Max	0, 3	-0.5, 2.5	0, 4	-1, 1.5	0, 4	-2, 2

Source: Listing 16.2.6.4
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.

Table 14.2.4
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Within Group Comparisons-mITT Population

			Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Work	Baseline	n	48		59		49	
		Mean (SD)	1.3 (0.97)		1.2 (0.97)		1.1 (1.01)	
		Median	2		2		1	
		Min, Max	0, 3		0, 3		0, 3	
	Day 43	n	48	48	56	56	48	48
		Mean (SD)	1.3 (0.93)	0.0 (0.33)	1.3 (0.94)	0.2 (0.71)	1.3 (1.10)	0.2 (0.62)
		Median	2	0	2	0	2	0
		Min, Max	0, 3	-1, 1	0, 3	-2, 2	0, 4	-1, 2

Source: Listing 16.2.6.4
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.

Table 14.2.4
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43-Within Group Comparisons-mITT Population

			Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Symptomatology	Baseline	n	48		59		49	
		Mean (SD)	2.8 (0.32)		2.8 (0.38)		2.7 (0.60)	
		Median	3		3		3	
		Min, Max	2, 4		1, 4		0.5, 3.5	
	Day 43	n	48	48	56	56	48	48
		Mean (SD)	3.0 (0.40)	0.2 (0.33)	3.0 (0.48)	0.2 (0.53)	3.0 (0.57)	0.3 (0.51)
		Median	3	0	3	0	3	0
		Min, Max	2.5, 3.5	-1, 1	1, 3.5	-2, 2	0.5, 3.5	-1, 2.5

Source: Listing 16.2.6.4
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.

Table 14.2.4
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43-
Within Group Comparisons-mITT Population

			Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Function	Baseline	n	48		59		49	
		Mean (SD)	2.4 (0.50)		2.5 (0.42)		2.4 (0.52)	
		Median	2.7		2.7		2.7	
		Min, Max	0.7, 3.3		1.3, 4		0.7, 3.3	
	Day 43	n	48	48	56	56	48	48
		Mean (SD)	2.5 (0.48)	0.0 (0.10)	2.6 (0.33)	0.1 (0.29)	2.5 (0.58)	0.1 (0.34)
		Median	2.7	0	2.7	0	2.7	0
		Min, Max	0.7, 3.3	0, 0.7	1.3, 3.3	-0.7, 1.4	0.7, 4	-0.6, 1.3

Source: Listing 16.2.6.4
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.

Table 14.2.4
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43-Within Group Comparisons-mITT Population

			Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Total Score	Baseline	n	48		59		49	
		Mean (SD)	18.0 (4.11)		18.2 (3.87)		17.6 (4.27)	
		Median	19		19		19	
		Min, Max	6, 26		9, 30		3, 28	
	Day 43	n	48	48	56	56	48	48
		Mean (SD)	18.9 (3.75)	0.9 (1.73)	19.4 (3.44)	1.3 (2.82)	19.5 (5.26)	1.8 (3.35)
		Median	19.5	0	20	1	19.5	1
		Min, Max	9, 24	-4, 6	9, 26	-11, 8	3, 35	-1, 13
		95% CI		(0.37 ,1.38)		(0.53 ,2.04)		(0.84 ,2.79)
		p-value		0.001		0.001		<.001

Source: Listing 16.2.6.4
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.

Reference Datasets:ADSL,LOF
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Programmer:AG
Date of Extraction:05FEB2023 Final- 06FEB2023:16:12

Table 14.2.5
Change from Baseline in Medication Satisfaction Questionnaire (MSQ) – Within Group Comparisons
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		59		49	
	Mean (SD)	3.8 (0.73)		4.1 (0.76)		4.1 (0.83)	
	Median	4.0		4.0		4.0	
	Min, Max	3 ,6		2 ,6		2 ,6	
Day 15	n	48	48	57	57	49	49
	Mean (SD)	4.4 (0.79)	0.6 (0.79)	4.6 (0.76)	0.5 (0.91)	4.4 (0.82)	0.4 (0.84)
	Median	4.0	1.0	5.0	0.0	4.0	0.0
	Min, Max	3 ,7	-1 ,2	2 ,6	-2 ,3	3 ,7	-1 ,2

Source: Listing 16.2.6.5
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
P-Value = Paired t-test, Change from Baseline = Post Dose – Baseline.

Table 14.2.5
Change from Baseline in Medication Satisfaction Questionnaire (MSQ) – Within Group Comparisons
mITT Population

		Evenamide 7.5 mg BID (N=48)		Evenamide 15 mg BID (N=59)		Evenamide 30 mg BID (N=49)	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43	n	48	48	56	56	48	48
	Mean (SD)	4.6 (0.94)	0.9 (1.16)	5.0 (0.71)	0.9 (1.13)	4.9 (0.71)	0.9 (0.88)
	Median	5.0	1.0	5.0	1.0	5.0	1.0
	Min, Max	2 ,6	-4 ,3	3 ,6	-3 ,3	3 ,6	-1 ,3
	95% CI		(0.54 ,1.21)		(0.57 ,1.18)		(0.64 ,1.15)
	p-value		<.001		<.001		<.001

Source: Listing 16.2.6.5
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
P-Value = Paired t-test, Change from Baseline = Post Dose – Baseline.

Table 14.3.0.1
Study Drug Exposure
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)	Total (N=160)
Duration of Exposure (days) [a]	n	50	60	50	160
	Mean (SD)	43.2 (6.73)	41.4 (7.40)	43.0 (6.82)	42.5 (7.02)
	Median	43.0	43.0	43.0	43.0
	Min,Max	4,61	8,56	1,61	1,61
Overall Treatment Compliance (%) [b]	n	50	60	50	160
	Mean (SD)	97.0 (5.98)	95.9 (11.26)	94.7 (11.47)	95.9 (9.97)
	Median	98.8	98.8	98.8	98.8
	Min,Max	62,100	25,100	47,105	25,105

Source: Listing 16.2.5.2
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 [Number of capsules consumed / Number of capsules expected to be consumed]*100
Compliance was not calculated for those subjects for whom the returned kit information were not available.

Table 14.3.0.2
Summary of Dose Adjustments or Kit Replacement
Safety Population

Characteristics	Statistic	Evenamide 7.5 mg BID (N=50)	Evenamide 15 mg BID (N=60)	Evenamide 30 mg BID (N=50)
Number of Subjects with Dose Adjustments or Kit Replacement	n(%)	3(6.0)	4(6.7)	9(18.0)
Number of Subjects with Dose Adjustments	n(%)	1(2.0)	0(0.0)	0(0.0)
Number of Subjects with Kit Replacement	n(%)	2(4.0)	4(6.7)	9(18.0)
Reason for Adjustments				
Start of adverse event	n(%)	1(2.0)	0(0.0)	0(0.0)
End of adverse event	n(%)	0(0.0)	0(0.0)	0(0.0)
Other	n(%)	2(4.0)	4(6.7)	9(18.0)

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.

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
No. of Subjects with at least one TEAE	13 (26.0)	10 (16.7)	18 (36.0)	41 (25.6)
No. of Subjects with at least one Serious TEAE	0(0.0)	0(0.0)	7 (14.0)	7 (4.4)
No. of Subjects with at least one Treatment-related TEAE [a]	5 (10.0)	4 (6.7)	6 (12.0)	15 (9.4)
No. of Subjects with Any Serious and Treatment-related TEAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No. of Subjects with Any TEAE Leading to Study Drug Discontinuation	1 (2.0)	0(0.0)	1 (2.0)	2 (1.3)

Source: Listing 16.2.7.1 and Listing 16.2.7.2
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.
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.

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
No. of Subjects with Any TEAE Resulting in Death	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Any TEAE by Severity				
Mild	8 (16.0)	8 (13.3)	16 (32.0)	32 (20.0)
Moderate	5 (10.0)	2 (3.3)	2 (4.0)	9 (5.6)
Severe	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.7.1 and Listing 16.2.7.2
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.
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.

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Safety Population

Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Any Treatment-related TEAE by Severity				
Mild	4 (8.0)	3 (5.0)	4 (8.0)	11 (6.9)
Moderate	1 (2.0)	1 (1.7)	2 (4.0)	4 (2.5)
Severe	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Listing 16.2.7.1 and Listing 16.2.7.2
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.
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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Any TEAE	13(26.0)	10(16.7)	18(36.0)	41(25.6)
Eye disorders	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Oculogyric crisis	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Gastrointestinal disorders	5(10.0)	0(0.0)	0(0.0)	5(3.1)
Gastritis	2(4.0)	0(0.0)	0(0.0)	2(1.3)
Nausea	1(2.0)	0(0.0)	0(0.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Toothache	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Vomiting	1(2.0)	0(0.0)	0(0.0)	1(0.6)
General disorders and administration site conditions	4(8.0)	2(3.3)	4(8.0)	10(6.3)
Asthenia	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Fatigue	0(0.0)	0(0.0)	2(4.0)	2(1.3)
Feeling hot	0(0.0)	0(0.0)	1(2.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Peripheral swelling	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Pyrexia	2(4.0)	1(1.7)	1(2.0)	4(2.5)
Infections and infestations	0(0.0)	0(0.0)	4(8.0)	4(2.5)
COVID-19	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Coronavirus infection	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Nasopharyngitis	0(0.0)	0(0.0)	2(4.0)	2(1.3)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Injury, poisoning and procedural complications	0(0.0)	0(0.0)	7(14.0)	7(4.4)
Medication error	0(0.0)	0(0.0)	7(14.0)	7(4.4)
Investigations	1(2.0)	2(3.3)	3(6.0)	6(3.8)
Blood creatine phosphokinase increased	1(2.0)	0(0.0)	2(4.0)	3(1.9)
Blood glucose increased	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Blood lactate dehydrogenase increased	0(0.0)	0(0.0)	1(2.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Haemoglobin urine	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Platelet count increased	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Metabolism and nutrition disorders	3(6.0)	1(1.7)	0(0.0)	4(2.5)
Decreased appetite	2(4.0)	0(0.0)	0(0.0)	2(1.3)
Dyslipidaemia	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Nervous system disorders	5(10.0)	3(5.0)	2(4.0)	10(6.3)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Dizziness	1(2.0)	0(0.0)	2(4.0)	3(1.9)
Dizziness postural	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Extrapyramidal disorder	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Headache	2(4.0)	0(0.0)	0(0.0)	2(1.3)
Hypersomnia	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Somnolence	1(2.0)	0(0.0)	0(0.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Tremor	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Psychiatric disorders	0(0.0)	2(3.3)	1(2.0)	3(1.9)
Aggression	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Frustration tolerance decreased	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Insomnia	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Irritability	0(0.0)	1(1.7)	0(0.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.2
Summary of 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Personality change	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Sleep disorder	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Skin and subcutaneous tissue disorders	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Pruritus	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Vascular disorders	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Thrombophlebitis	0(0.0)	0(0.0)	1(2.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions 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.

Table 14.3.1.3
Summary of Treatment-Emergent Serious Adverse Events by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Any Serious TEAE	0 (0.00)	0 (0.00)	7 (14.00)	7 (4.38)
Injury, poisoning and procedural complications	0 (0.00)	0 (0.00)	7 (14.00)	7 (4.38)
Medication error	0 (0.00)	0 (0.00)	7 (14.00)	7 (4.38)

Source: Listing 16.2.7.2
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.
Subjects are counted only once per system organ class and per preferred term.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.4
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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Any Treatment-Related TEAE	5(10.0)	4(6.7)	6(12.0)	15(9.4)
Gastrointestinal disorders	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Gastritis	1(2.0)	0(0.0)	0(0.0)	1(0.6)
General disorders and administration site conditions	1(2.0)	1(1.7)	1(2.0)	3(1.9)
Asthenia	1(2.0)	1(1.7)	0(0.0)	2(1.3)
Feeling hot	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Investigations	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Blood creatine phosphokinase increased	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Blood lactate dehydrogenase increased	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Metabolism and nutrition disorders	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Decreased appetite	1(2.0)	0(0.0)	0(0.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication Treatment related TEAE's are the TEAE's which is possibly or probably related to study drug, or not reported Subjects are counted only once per system organ class and per preferred term.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.4
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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Nervous system disorders	2(4.0)	2(3.3)	2(4.0)	6(3.8)
Dizziness	0(0.0)	0(0.0)	2(4.0)	2(1.3)
Dizziness postural	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Hypersomnia	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Somnolence	1(2.0)	0(0.0)	0(0.0)	1(0.6)
Tremor	0(0.0)	1(1.7)	0(0.0)	1(0.6)
Psychiatric disorders	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Aggression	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Frustration tolerance decreased	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Insomnia	0(0.0)	0(0.0)	1(2.0)	1(0.6)
Personality change	0(0.0)	0(0.0)	1(2.0)	1(0.6)

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication Treatment related TEAE’s are the TEAE’s which is possibly or probably related to study drug, or not reported Subjects are counted only once per system organ class and per preferred term.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.5
Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation
Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)	Total (N=160) n(%)
Any TEAE Leading to Study Drug Discontinuation	1 (2.00)	0 (0.0)	1 (2.00)	2 (1.25)
Gastrointestinal disorders	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
Vomiting	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
General disorders and administration site conditions	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
Pyrexia	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
Nervous system disorders	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
Headache	1 (2.00)	0 (0.0)	0 (0.0)	1 (0.63)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.00)	1 (0.63)
Insomnia	0 (0.0)	0 (0.0)	1 (2.00)	1 (0.63)

Source: Listing 16.2.7.3
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 pre-existing conditions worsened in severity after the first administration of the study medication, Subjects are counted only once per SOC and per PT.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Any TEAE	Mild	8(16.0)	8(13.3)	16(32.0)
	Moderate	5(10.0)	2(3.3)	2(4.0)
	Severe	0	0	0
Eye disorders	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Oculogyric crisis	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0
Gastrointestinal disorders	Mild	3(6.0)	0	0
	Moderate	2(4.0)	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Gastritis	Mild	1(2.0)	0	0
	Moderate	1(2.0)	0	0
	Severe	0	0	0
Nausea	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Toothache	Mild	0	0	0
	Moderate	1(2.0)	0	0
	Severe	0	0	0
Vomiting	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
General disorders and administration site conditions	Mild	4(8.0)	1(1.7)	3(6.0)
	Moderate	0	1(1.7)	1(2.0)
	Severe	0	0	0
Asthenia	Mild	1(2.0)	0	0
	Moderate	0	1(1.7)	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Reference Datasets:ADSL,AE
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\Table 14.3.1.6.sas
Programmer:AK
Date of Extraction:05FEB2023 Final- 13FEB2023: 5:13 PM

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Fatigue	Mild	0	0	2(4.0)
	Moderate	0	0	0
	Severe	0	0	0
Feeling hot	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Peripheral swelling	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0
Pyrexia	Mild	2(4.0)	1(1.7)	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Infections and infestations	Mild	0	0	4(8.0)
	Moderate	0	0	0
	Severe	0	0	0
COVID-19	Mild	0	0	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Coronavirus infection	Mild	0	0	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0
Nasopharyngitis	Mild	0	0	2(4.0)
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Injury, poisoning and procedural complications	Mild	0	0	7(14.0)
	Moderate	0	0	0
	Severe	0	0	0
Medication error	Mild	0	0	7(14.0)
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Investigations	Mild	0	2(3.3)	2(4.0)
	Moderate	1(2.0)	0	1(2.0)
	Severe	0	0	0
Blood creatine phosphokinase increased	Mild	0	0	1(2.0)
	Moderate	1(2.0)	0	1(2.0)
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Blood glucose increased	Mild	0	0	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0
Blood lactate dehydrogenase increased	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Reference Datasets:ADSL,AE
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\Table 14.3.1.6.sas
Programmer:AK
Date of Extraction:05FEB2023 Final- 13FEB2023: 5:13 PM

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Haemoglobin urine	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0
Platelet count increased	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Metabolism and nutrition disorders	Mild	2(4.0)	0	0
	Moderate	1(2.0)	1(1.7)	0
	Severe	0	0	0
Decreased appetite	Mild	2(4.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyslipidaemia	Mild	0	0	0
	Moderate	1(2.0)	1(1.7)	0
	Severe	0	0	0
Nervous system disorders	Mild	4(8.0)	3(5.0)	2(4.0)
	Moderate	1(2.0)	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dizziness	Mild	1(2.0)	0	2(4.0)
	Moderate	0	0	0
	Severe	0	0	0
Dizziness postural	Mild	1(2.0)	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Extrapyramidal disorder	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0
Headache	Mild	1(2.0)	0	0
	Moderate	1(2.0)	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Hypersomnia	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0
Somnolence	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Tremor	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0
Aggression	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Psychiatric disorders	Mild	0	2(3.3)	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0
Frustration tolerance decreased	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Insomnia	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0
Irritability	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Personality change	Mild	0	0	0
	Moderate	0	0	1(2.0)
	Severe	0	0	0
Sleep disorder	Mild	0	1(1.7)	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Skin and subcutaneous tissue disorders	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0
Pruritus	Mild	1(2.0)	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.1.6
Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Vascular disorders	Mild	0	0	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0
Thrombophlebitis	Mild	0	0	1(2.0)
	Moderate	0	0	0
	Severe	0	0	0

Source: Listing 16.2.7.1
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 pre-existing conditions worsened in severity after the first administration of the study medication.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.
Adverse events are coded with MedDRA Version 23.0.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: BASOPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		60		48	
	Mean (SD)	0.05 (0.05)		0.04 (0.04)		0.04 (0.04)	
	Median	0.06		0.05		0.05	
	Min, Max	0, 0.21		0, 0.101		0, 0.136	
Day 1	n	42	41	58	58	45	45
	Mean (SD)	0.05 (0.04)	-0.00 (0.05)	0.04 (0.04)	-0.00 (0.05)	0.05 (0.04)	0.01 (0.04)
	Median	0.07	0.00	0.05	0.00	0.06	0.00
	Min, Max	0, 0.117	-0.14, 0.117	0, 0.111	-0.089, 0.098	0, 0.143	-0.069, 0.093
Day 8	n	44	44	55	55	47	47
	Mean (SD)	0.05 (0.04)	0.00 (0.06)	0.04 (0.03)	-0.00 (0.04)	0.04 (0.04)	-0.00 (0.05)
	Median	0.06	0.00	0.04	0.00	0.04	0.00
	Min, Max	0, 0.135	-0.155, 0.135	0, 0.096	-0.101, 0.095	0, 0.132	-0.136, 0.112

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: BASOPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	47	46	55	55	46	46
	Mean (SD)	0.05 (0.04)	0.00 (0.05)	0.04 (0.03)	0.00 (0.05)	0.04 (0.03)	-0.01 (0.05)
	Median	0.06	0.00	0.05	0.00	0.04	-0.01
	Min, Max	0, 0.139	-0.162, 0.139	0, 0.102	-0.101, 0.102	0, 0.129	-0.136, 0.129
Day 29	n	46	45	53	53	45	45
	Mean (SD)	0.05 (0.04)	-0.00 (0.06)	0.05 (0.04)	0.01 (0.04)	0.04 (0.03)	-0.00 (0.04)
	Median	0.06	0.00	0.06	0.00	0.05	0.00
	Min, Max	0, 0.128	-0.108, 0.123	0, 0.132	-0.089, 0.098	0, 0.1	-0.09, 0.092
Day 43	n	46	45	49	49	46	46
	Mean (SD)	0.05 (0.04)	0.00 (0.06)	0.04 (0.04)	0.00 (0.05)	0.04 (0.03)	0.00 (0.04)
	Median	0.06	0.00	0.05	0.00	0.05	-0.00
	Min, Max	0, 0.125	-0.137, 0.125	0, 0.101	-0.101, 0.101	0, 0.111	-0.088, 0.09

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: EOSINOPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		60		48	
	Mean (SD)	0.43 (0.58)		0.24 (0.24)		0.25 (0.23)	
	Median	0.26		0.16		0.15	
	Min, Max	0, 2.912		0, 1.056		0, 0.91	
Day 1	n	42	41	58	58	45	45
	Mean (SD)	0.38 (0.45)	-0.06 (0.34)	0.25 (0.26)	0.02 (0.20)	0.23 (0.22)	-0.01 (0.08)
	Median	0.24	-0.00	0.16	0.02	0.16	0.00
	Min, Max	0, 2.442	-1.622, 0.324	0, 1.332	-0.774, 0.744	0, 0.95	-0.208, 0.15
Day 8	n	44	44	55	55	47	47
	Mean (SD)	0.33 (0.42)	-0.11 (0.45)	0.23 (0.19)	-0.00 (0.16)	0.27 (0.31)	0.02 (0.18)
	Median	0.24	-0.04	0.16	-0.01	0.17	0.00
	Min, Max	0, 2.415	-2.612, 0.374	0, 0.768	-0.381, 0.736	0, 1.634	-0.356, 0.887

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: EOSINOPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	47	46	56	56	46	46
	Mean (SD)	0.39 (0.58)	-0.05 (0.48)	0.25 (0.22)	0.01 (0.15)	0.27 (0.27)	0.02 (0.19)
	Median	0.25	0.00	0.21	0.00	0.21	0.02
	Min, Max	0, 3.737	-2.562, 1.064	0, 1.056	-0.413, 0.744	0, 1.37	-0.88, 0.57
Day 29	n	46	45	53	53	46	46
	Mean (SD)	0.31 (0.32)	-0.13 (0.42)	0.24 (0.20)	0.00 (0.16)	0.24 (0.23)	0.00 (0.16)
	Median	0.20	-0.04	0.20	0.02	0.19	0.00
	Min, Max	0, 1.508	-2.012, 0.297	0, 0.888	-0.616, 0.513	0, 1.245	-0.6, 0.601
Day 43	n	46	45	49	49	46	46
	Mean (SD)	0.32 (0.37)	-0.12 (0.37)	0.25 (0.22)	0.01 (0.18)	0.26 (0.33)	0.02 (0.27)
	Median	0.16	-0.05	0.22	0.01	0.16	0.00
	Min, Max	0, 1.776	-1.881, 0.424	0, 1.064	-0.792, 0.382	0, 1.998	-0.57, 1.354

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: LYMPHOCYTES (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		60		48	
	Mean (SD)	1.86 (0.62)		1.88 (0.60)		2.04 (0.86)	
	Median	1.77		1.86		1.93	
	Min, Max	0.7, 3.567		0.697, 3.3		0.476, 4.62	
Day 1	n	42	41	58	58	45	45
	Mean (SD)	1.89 (0.58)	-0.01 (0.46)	1.78 (0.64)	-0.09 (0.35)	1.97 (0.83)	-0.09 (0.44)
	Median	1.74	0.07	1.70	-0.08	1.86	-0.02
	Min, Max	0.858, 3.317	-1.394, 1.377	0.525, 3.56	-1.068, 0.592	0.64, 4.89	-1.37, 0.698
Day 8	n	44	44	55	55	47	47
	Mean (SD)	1.81 (0.75)	-0.05 (0.57)	1.80 (0.79)	-0.07 (0.47)	1.93 (0.81)	-0.08 (0.39)
	Median	1.62	-0.07	1.63	-0.12	1.73	-0.02
	Min, Max	0.094, 3.51	-1.908, 1.494	0.45, 4.72	-1.201, 1.7	0.858, 5.26	-1.32, 0.64

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: LYMPHOCYTES (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	47	46	56	56	46	46
	Mean (SD)	1.84 (0.71)	-0.02 (0.64)	1.80 (0.61)	-0.07 (0.40)	1.88 (0.69)	-0.14 (0.44)
	Median	1.74	0.02	1.66	-0.06	1.82	-0.08
	Min, Max	0.559, 3.565	-1.952, 1.486	0.637, 3.3	-1.064, 1.042	0.855, 4.59	-1.305, 0.647
Day 29	n	46	45	53	53	46	46
	Mean (SD)	1.83 (0.74)	-0.05 (0.46)	1.85 (0.76)	-0.05 (0.56)	1.95 (0.82)	-0.05 (0.42)
	Median	1.62	-0.07	1.72	-0.06	1.90	-0.01
	Min, Max	0.7, 4.096	-1.271, 1.082	0.282, 4.52	-1.608, 1.5	0.91, 5.37	-1.295, 0.752
Day 43	n	46	45	49	49	46	46
	Mean (SD)	1.92 (0.77)	0.03 (0.47)	1.85 (0.75)	-0.03 (0.45)	1.96 (0.86)	-0.04 (0.49)
	Median	1.84	0.05	1.49	0.04	1.84	-0.00
	Min, Max	0.69, 4	-1.553, 1.287	0.812, 3.71	-1.28, 1.111	0.924, 5.17	-1.31, 1.439

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: MONOCYTES (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		60		48	
	Mean (SD)	0.38 (0.17)		0.38 (0.18)		0.37 (0.20)	
	Median	0.36		0.40		0.33	
	Min, Max	0.07, 0.861		0, 0.84		0, 0.897	
Day 1	n	42	41	58	58	45	45
	Mean (SD)	0.37 (0.18)	-0.02 (0.14)	0.38 (0.16)	-0.01 (0.18)	0.39 (0.23)	0.01 (0.15)
	Median	0.35	0.00	0.36	0.01	0.36	0.00
	Min, Max	0.08, 0.936	-0.339, 0.251	0.12, 0.888	-0.424, 0.74	0.047, 1.342	-0.365, 0.532
Day 8	n	44	44	55	55	47	47
	Mean (SD)	0.35 (0.19)	-0.03 (0.17)	0.33 (0.16)	-0.03 (0.17)	0.37 (0.18)	0.01 (0.13)
	Median	0.32	-0.02	0.34	-0.02	0.37	0.01
	Min, Max	0.057, 0.872	-0.422, 0.523	0.072, 0.73	-0.41, 0.364	0.051, 0.92	-0.321, 0.281

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: MONOCYTES (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	47	46	56	56	46	46
	Mean (SD)	0.34 (0.15)	-0.03 (0.17)	0.35 (0.15)	-0.03 (0.16)	0.37 (0.19)	0.01 (0.15)
	Median	0.34	0.00	0.35	-0.03	0.35	0.01
	Min, Max	0.057, 0.721	-0.363, 0.328	0.068, 0.816	-0.394, 0.356	0.072, 1.02	-0.305, 0.424
Day 29	n	46	45	53	53	46	46
	Mean (SD)	0.34 (0.17)	-0.04 (0.14)	0.36 (0.17)	-0.02 (0.16)	0.36 (0.17)	0.00 (0.14)
	Median	0.32	-0.04	0.34	-0.03	0.32	0.01
	Min, Max	0.092, 0.847	-0.368, 0.289	0.102, 0.726	-0.316, 0.308	0.135, 0.81	-0.385, 0.337
Day 43	n	46	45	49	49	46	46
	Mean (SD)	0.33 (0.17)	-0.04 (0.20)	0.37 (0.15)	-0.01 (0.15)	0.39 (0.21)	0.03 (0.14)
	Median	0.32	-0.02	0.35	0.00	0.35	0.02
	Min, Max	0.102, 0.794	-0.5, 0.724	0.104, 0.708	-0.385, 0.325	0.085, 0.891	-0.562, 0.461

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: NEUTROPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	48		60		48	
	Mean (SD)	5.12 (1.44)		5.03 (1.73)		4.47 (1.40)	
	Median	5.01		5.00		4.28	
	Min, Max	2.454, 8.176		1.947, 9.605		1.887, 7.742	
Day 1	n	42	41	58	58	45	45
	Mean (SD)	5.56 (1.61)	0.40 (1.49)	5.09 (1.78)	0.07 (1.54)	4.96 (1.79)	0.49 (1.23)
	Median	5.61	0.37	5.04	0.07	4.80	0.22
	Min, Max	2.4, 9.216	-4.72, 3.7	1.71, 10.92	-4.361, 3.865	1.87, 11.297	-1.909, 4.69
Day 8	n	44	44	55	55	47	47
	Mean (SD)	4.90 (1.62)	-0.22 (1.49)	4.50 (1.69)	-0.36 (1.83)	4.19 (1.60)	-0.22 (1.35)
	Median	4.92	-0.07	4.28	-0.54	3.93	-0.22
	Min, Max	1.638, 9.118	-5.275, 2.655	1.632, 10.24	-4.145, 5.726	1.976, 10.541	-2.581, 4.364

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: NEUTROPHILS (ABS) (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	47	46	56	56	46	46
	Mean (SD)	4.70 (1.63)	-0.47 (1.54)	4.53 (1.53)	-0.54 (1.51)	4.40 (1.80)	-0.02 (1.52)
	Median	4.56	-0.20	4.22	-0.67	3.91	0.05
	Min, Max	2.013, 9.035	-3.801, 4.228	1.711, 7.956	-4.28, 2.438	1.961, 10.062	-2.865, 5.42
Day 29	n	46	45	53	53	46	46
	Mean (SD)	4.89 (1.52)	-0.32 (1.39)	4.62 (1.94)	-0.34 (1.85)	4.34 (1.39)	-0.11 (1.23)
	Median	4.42	-0.19	4.19	-0.50	4.12	-0.16
	Min, Max	2.28, 7.552	-4.676, 3.384	2.067, 13.677	-3.765, 7.017	1.924, 8.774	-2.204, 4.627
Day 43	n	46	45	49	49	46	46
	Mean (SD)	4.98 (1.32)	-0.25 (1.25)	4.43 (1.69)	-0.66 (1.47)	4.32 (1.29)	-0.13 (1.24)
	Median	4.90	-0.13	4.18	-0.61	4.22	-0.18
	Min, Max	2.501, 8.556	-4.408, 2.292	1.593, 8.968	-5.187, 1.999	2.035, 7.17	-2.485, 4.76

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: BASOPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	0.61 (0.53)		0.58 (0.48)		0.63 (0.49)	
	Median	1.00		1.00		0.95	
	Min, Max	0, 2		0, 1		0, 2	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	0.60 (0.49)	-0.04 (0.57)	0.57 (0.48)	-0.01 (0.68)	0.67 (0.44)	0.06 (0.61)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 1	-1, 1	0, 1	-1, 1	0, 1.2	-1, 1
Day 8	n	45	45	55	55	49	49
	Mean (SD)	0.66 (0.46)	0.06 (0.66)	0.60 (0.48)	-0.00 (0.61)	0.61 (0.53)	-0.02 (0.70)
	Median	1.00	0.00	1.00	0.00	0.70	0.00
	Min, Max	0, 1	-1, 1	0, 1	-1, 1	0, 2	-2, 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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: BASOPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	55	55	48	48
	Mean (SD)	0.65 (0.47)	0.07 (0.51)	0.65 (0.46)	0.09 (0.68)	0.60 (0.48)	-0.02 (0.67)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 1	-1, 1	0, 1	-1, 1	0, 1.6	-2, 1
Day 29	n	47	46	53	53	47	47
	Mean (SD)	0.59 (0.53)	-0.02 (0.68)	0.74 (0.46)	0.19 (0.59)	0.64 (0.47)	0.02 (0.59)
	Median	1.00	0.00	1.00	0.00	1.00	0.00
	Min, Max	0, 2	-1, 1	0, 2	-1, 1	0, 1.4	-1, 1.1
Day 43	n	47	46	49	49	47	47
	Mean (SD)	0.64 (0.47)	0.03 (0.67)	0.61 (0.47)	0.04 (0.68)	0.64 (0.45)	0.00 (0.61)
	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

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: EOSINOPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	5.03 (6.03)		3.20 (2.81)		3.57 (3.35)	
	Median	3.00		2.50		2.25	
	Min, Max	0, 33		0, 14		0, 15	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	4.41 (4.68)	-0.63 (3.55)	3.45 (3.18)	0.35 (2.73)	3.23 (3.18)	-0.27 (1.14)
	Median	3.00	0.00	2.35	0.00	2.00	0.00
	Min, Max	0, 22	-11, 9	0, 12	-8, 12	0, 15	-4, 2
Day 8	n	45	45	55	55	49	49
	Mean (SD)	3.99 (3.99)	-1.07 (4.17)	3.31 (2.50)	0.18 (2.58)	3.99 (4.04)	0.37 (2.15)
	Median	3.00	0.00	2.00	0.00	3.00	0.00
	Min, Max	0, 23	-21, 5	0, 13	-8, 13	0, 19.3	-6, 10

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: EOSINOPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	4.73 (5.71)	-0.33 (3.72)	3.65 (3.04)	0.53 (2.35)	4.01 (3.94)	0.42 (2.34)
	Median	3.00	0.00	3.00	0.00	3.00	0.00
	Min, Max	0, 37	-19, 7	0, 14	-5, 12	0, 19.8	-10.1, 6.8
Day 29	n	47	46	53	53	48	48
	Mean (SD)	4.10 (4.71)	-0.89 (3.63)	3.51 (2.78)	0.34 (2.36)	3.46 (3.07)	0.03 (2.16)
	Median	3.00	0.00	3.00	0.20	2.75	0.00
	Min, Max	0, 29	-16, 5	0, 15	-6, 11	0, 15	-6.4, 8
Day 43	n	47	46	49	49	47	47
	Mean (SD)	3.84 (4.32)	-1.11 (3.21)	3.67 (2.90)	0.42 (2.41)	3.57 (3.52)	0.03 (3.08)
	Median	2.00	0.00	3.00	0.20	2.00	0.00
	Min, Max	0, 24	-13, 5	0, 14	-8, 5	0, 18	-10.4, 11

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: LYMPHOCYTES (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	24.19 (6.38)		25.72 (8.13)		28.60 (9.59)	
	Median	25.00		26.00		28.45	
	Min, Max	10, 37.4		11, 52		7, 49	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	23.55 (6.91)	-0.94 (5.54)	24.27 (8.42)	-1.44 (6.40)	26.47 (8.96)	-2.21 (6.71)
	Median	22.00	-2.00	23.50	-0.50	26.00	0.00
	Min, Max	11, 42	-12, 13	7, 51	-19, 12	10, 47.6	-21, 8
Day 8	n	45	45	55	55	49	49
	Mean (SD)	24.81 (8.00)	0.54 (7.83)	26.52 (9.45)	0.36 (7.18)	28.97 (8.13)	0.42 (6.44)
	Median	25.00	0.00	25.00	2.00	29.00	1.00
	Min, Max	1, 44	-21, 31	10, 58	-21, 12	11, 44.9	-19, 14

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: LYMPHOCYTES (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	25.66 (7.64)	1.65 (7.68)	26.47 (8.14)	0.95 (6.62)	28.10 (8.88)	-0.51 (7.81)
	Median	26.00	2.00	26.00	1.35	29.00	-0.50
	Min, Max	12, 41.5	-18, 20	13, 46	-14, 20	8, 45.1	-20, 15
Day 29	n	47	46	53	53	48	48
	Mean (SD)	24.93 (7.26)	0.79 (6.41)	26.63 (9.01)	0.53 (7.88)	28.44 (8.13)	0.10 (7.45)
	Median	25.00	2.00	27.00	2.00	29.50	1.15
	Min, Max	10, 45.6	-13, 18	2, 56.6	-27, 13	14, 47	-25, 15.7
Day 43	n	47	46	49	49	47	47
	Mean (SD)	25.23 (6.96)	1.07 (5.46)	27.33 (10.07)	1.73 (6.46)	28.52 (8.72)	0.24 (7.66)
	Median	26.00	1.00	27.00	2.00	28.00	0.00
	Min, Max	10, 41.7	-14, 15	11, 59.9	-14, 16.2	11.6, 48.2	-27.2, 18.3

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: MONOCYTES (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	4.90 (1.97)		5.18 (2.31)		5.19 (2.48)	
	Median	5.00		5.00		5.00	
	Min, Max	1, 9		0, 11		0, 13	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	4.41 (1.78)	-0.53 (1.66)	5.19 (2.05)	-0.11 (2.21)	5.03 (2.09)	-0.30 (1.76)
	Median	5.00	0.00	4.80	0.00	5.00	0.00
	Min, Max	1, 9	-4, 2	1, 10	-8, 6	1, 11	-6, 4
Day 8	n	45	45	55	55	49	49
	Mean (SD)	4.72 (2.15)	-0.16 (2.13)	4.99 (2.33)	-0.10 (2.21)	5.58 (2.35)	0.40 (1.99)
	Median	4.90	0.00	5.00	0.00	5.30	0.00
	Min, Max	1, 10	-5, 6	1, 11	-7, 4	1, 11	-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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: MONOCYTES (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	4.83 (2.01)	0.01 (2.00)	5.23 (2.23)	0.10 (1.92)	5.48 (2.26)	0.21 (1.97)
	Median	5.00	0.00	5.00	0.00	5.00	0.00
	Min, Max	1, 10	-4, 5	1, 12	-4, 6	1, 10	-5, 6
Day 29	n	47	46	53	53	48	48
	Mean (SD)	4.61 (2.00)	-0.21 (1.92)	5.19 (2.29)	-0.08 (1.94)	5.35 (2.14)	0.24 (1.91)
	Median	5.00	-0.10	5.00	0.00	5.00	0.00
	Min, Max	2, 11	-4, 6	1, 11	-4, 4	2, 10	-5, 5
Day 43	n	47	46	49	49	47	47
	Mean (SD)	4.40 (2.11)	-0.34 (2.90)	5.54 (2.18)	0.43 (1.97)	5.51 (2.40)	0.41 (1.86)
	Median	4.00	-0.30	5.30	0.20	5.00	0.40
	Min, Max	2, 13	-7, 12	2, 12	-5, 5	1, 11	-8, 3.3

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: NEUTROPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	65.27 (7.60)		65.31 (9.76)		62.00 (11.54)	
	Median	66.00		64.00		61.00	
	Min, Max	45, 80		35, 85		39.2, 86	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	67.03 (8.39)	2.14 (7.68)	66.51 (10.55)	1.21 (8.51)	64.59 (10.31)	2.71 (7.71)
	Median	67.50	2.00	68.00	1.00	65.80	1.30
	Min, Max	48, 82	-20, 18.1	36, 91	-22, 22	40.5, 79	-11, 23
Day 8	n	45	45	55	55	49	49
	Mean (SD)	65.82 (9.03)	0.62 (8.52)	64.59 (11.16)	-0.44 (9.47)	60.84 (10.91)	-1.18 (7.54)
	Median	66.00	1.00	66.00	-1.00	62.00	-2.10
	Min, Max	51, 97	-29, 24	35, 86	-18, 27	36.4, 85	-18, 16

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: NEUTROPHILS (%)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	64.13 (9.12)	-1.41 (8.63)	64.01 (9.53)	-1.66 (7.78)	61.81 (11.06)	-0.11 (9.51)
	Median	66.00	-1.00	65.00	-3.00	61.00	-1.00
	Min, Max	45, 81	-25, 21	45, 81	-19, 16	38.2, 88	-18, 26
Day 29	n	47	46	53	53	48	48
	Mean (SD)	65.77 (8.85)	0.32 (7.77)	63.93 (10.71)	-0.98 (9.47)	62.13 (10.00)	-0.37 (8.52)
	Median	67.00	1.00	62.00	-2.00	61.00	-1.70
	Min, Max	46, 87	-19, 18	35.6, 97	-17, 32	42.9, 82	-16, 26
Day 43	n	47	46	49	49	47	47
	Mean (SD)	65.89 (8.48)	0.36 (6.92)	62.85 (11.86)	-2.63 (7.81)	61.76 (10.77)	-0.68 (9.61)
	Median	65.00	0.00	62.00	-3.00	62.00	-1.00
	Min, Max	49, 86	-15, 21	28, 83	-22, 14	39, 84	-20, 38.7

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: HB (g/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	130.84 (15.82)		131.87 (17.77)		135.70 (17.43)	
	Median	132.00		135.00		136.00	
	Min, Max	88, 161		81, 157		85, 174	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	130.31 (15.75)	-1.61 (6.14)	130.45 (17.11)	-1.38 (4.98)	135.70 (17.34)	-0.55 (5.98)
	Median	132.50	-1.00	133.50	-1.00	137.00	0.00
	Min, Max	88, 163	-22, 11	80, 156	-15, 15	88, 174	-16, 16
Day 8	n	45	45	55	55	49	49
	Mean (SD)	130.62 (15.75)	-1.13 (7.47)	131.16 (15.49)	-1.87 (7.06)	134.98 (16.74)	-0.84 (7.31)
	Median	131.00	-1.00	131.00	-1.00	135.00	0.00
	Min, Max	96, 165	-23, 14	94, 164	-17, 11	92, 172	-24, 16

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: HB (g/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	129.63 (15.11)	-2.04 (8.00)	130.84 (17.31)	-0.95 (5.87)	134.88 (15.63)	-0.73 (8.56)
	Median	131.00	-2.00	133.50	-1.00	137.00	-0.50
	Min, Max	92, 163	-15, 33	76, 161	-13, 12	97, 166	-22, 17
Day 29	n	47	46	53	53	48	48
	Mean (SD)	130.09 (15.88)	-1.87 (7.10)	130.74 (16.25)	-1.13 (6.73)	135.52 (14.95)	-0.35 (10.32)
	Median	127.00	-1.50	132.00	-1.00	137.00	0.00
	Min, Max	94, 176	-17, 12	72, 154	-17, 17	106, 175	-30, 31
Day 43	n	47	46	49	49	47	47
	Mean (SD)	129.60 (15.53)	-1.67 (6.80)	130.06 (17.20)	-1.18 (7.01)	133.28 (14.48)	-2.26 (10.07)
	Median	128.00	-2.00	131.00	1.00	135.00	-1.00
	Min, Max	93, 158	-21, 12	79, 157	-19, 13	105, 164	-33, 26

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: HCT (Proportion of 1.0)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	0.42 (0.05)		0.42 (0.05)		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	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	0.42 (0.05)	-0.00 (0.02)	0.42 (0.05)	-0.01 (0.02)	0.42 (0.05)	-0.00 (0.02)
	Median	0.42	-0.00	0.42	-0.00	0.42	-0.00
	Min, Max	0.319, 0.543	-0.076, 0.043	0.278, 0.504	-0.065, 0.051	0.309, 0.552	-0.051, 0.059
Day 8	n	45	45	55	55	49	49
	Mean (SD)	0.43 (0.04)	-0.00 (0.03)	0.42 (0.05)	-0.01 (0.03)	0.42 (0.05)	-0.00 (0.02)
	Median	0.42	-0.00	0.42	-0.00	0.42	0.00
	Min, Max	0.349, 0.526	-0.055, 0.076	0.306, 0.533	-0.074, 0.037	0.296, 0.562	-0.054, 0.041

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: HCT (Proportion of 1.0)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	0.42 (0.05)	-0.01 (0.02)	0.42 (0.05)	-0.00 (0.02)	0.42 (0.05)	-0.00 (0.03)
	Median	0.42	-0.01	0.42	-0.00	0.42	-0.01
	Min, Max	0.331, 0.52	-0.056, 0.063	0.282, 0.529	-0.07, 0.043	0.317, 0.529	-0.06, 0.079
Day 29	n	47	46	53	53	48	48
	Mean (SD)	0.42 (0.05)	-0.00 (0.03)	0.42 (0.05)	0.00 (0.03)	0.42 (0.05)	-0.00 (0.04)
	Median	0.42	-0.01	0.42	-0.00	0.42	-0.01
	Min, Max	0.324, 0.531	-0.059, 0.067	0.264, 0.546	-0.06, 0.059	0.327, 0.556	-0.094, 0.104
Day 43	n	47	46	49	49	47	47
	Mean (SD)	0.42 (0.04)	-0.00 (0.02)	0.42 (0.05)	-0.01 (0.02)	0.41 (0.04)	-0.01 (0.03)
	Median	0.42	-0.01	0.42	-0.00	0.42	-0.01
	Min, Max	0.349, 0.492	-0.053, 0.05	0.277, 0.515	-0.064, 0.043	0.318, 0.518	-0.082, 0.068

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: PLATELETS (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		59		50	
	Mean (SD)	281.98 (73.71)		278.93 (92.01)		263.58 (75.21)	
	Median	283.00		277.00		264.50	
	Min, Max	144, 450		144, 652		151, 543	
Day 1	n	42	41	58	57	47	47
	Mean (SD)	281.64 (80.60)	0.85 (48.33)	282.57 (88.83)	5.44 (37.00)	263.83 (72.12)	2.62 (34.26)
	Median	283.00	-1.00	267.50	6.00	260.00	4.00
	Min, Max	162, 535	-100, 155	150, 652	-90, 140	144, 505	-101, 79
Day 8	n	45	45	55	55	49	49
	Mean (SD)	271.67 (94.21)	-6.33 (56.43)	267.29 (77.39)	-1.73 (83.87)	257.57 (60.62)	-0.31 (40.51)
	Median	265.00	-8.00	267.00	2.00	258.00	-3.00
	Min, Max	153, 688	-143, 238	118, 499	-534, 121	150, 421	-105, 127

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: PLATELETS (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	55	48	48
	Mean (SD)	268.88 (75.93)	-12.45 (45.45)	280.11 (89.97)	1.64 (42.76)	257.31 (60.88)	-1.10 (43.88)
	Median	265.00	-18.00	271.00	0.00	256.00	-2.50
	Min, Max	150, 530	-175, 96	133, 636	-87, 165	135, 385	-123, 103
Day 29	n	47	46	52	52	48	48
	Mean (SD)	276.89 (69.17)	-6.46 (44.27)	278.29 (81.78)	2.83 (47.27)	260.17 (80.93)	3.27 (62.55)
	Median	278.00	-6.50	274.00	-1.00	259.00	-1.50
	Min, Max	150, 401	-113, 120	146, 546	-125, 166	28.1, 432	-292.9, 184
Day 43	n	47	46	49	49	47	47
	Mean (SD)	273.60 (80.62)	-6.87 (57.17)	284.04 (81.05)	-4.16 (47.17)	250.79 (66.81)	-5.38 (38.64)
	Median	262.00	-11.00	285.00	-5.00	240.00	-2.00
	Min, Max	158, 487	-158, 183	150, 536	-116, 113	147, 390	-153, 75

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: RED BLOOD CELLS (10^12/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	4.70 (0.50)		4.72 (0.55)		4.79 (0.47)	
	Median	4.70		4.80		4.75	
	Min, Max	3.58, 6.25		3.66, 5.73		3.65, 5.64	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	4.70 (0.54)	-0.03 (0.19)	4.68 (0.51)	-0.04 (0.19)	4.79 (0.47)	-0.02 (0.22)
	Median	4.69	0.01	4.69	-0.03	4.80	0.01
	Min, Max	3.52, 6.12	-0.41, 0.43	3.6, 5.75	-0.54, 0.6	3.86, 5.85	-0.55, 0.65
Day 8	n	45	45	55	55	49	49
	Mean (SD)	4.74 (0.46)	0.00 (0.31)	4.67 (0.49)	-0.07 (0.27)	4.76 (0.48)	-0.02 (0.26)
	Median	4.63	-0.01	4.70	-0.06	4.74	0.02
	Min, Max	3.82, 5.91	-0.53, 1.42	3.49, 5.62	-0.69, 0.46	3.6, 5.74	-0.79, 0.6

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: RED BLOOD CELLS (10^12/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	4.65 (0.53)	-0.08 (0.29)	4.68 (0.52)	-0.04 (0.21)	4.73 (0.46)	-0.05 (0.31)
	Median	4.55	-0.05	4.65	-0.05	4.72	-0.07
	Min, Max	3.68, 5.94	-0.7, 0.86	3.62, 5.61	-0.44, 0.51	3.79, 5.64	-0.86, 0.68
Day 29	n	47	46	54	54	48	48
	Mean (SD)	4.71 (0.55)	-0.04 (0.28)	4.73 (0.54)	0.00 (0.31)	4.77 (0.50)	-0.02 (0.35)
	Median	4.58	-0.06	4.82	-0.03	4.68	-0.01
	Min, Max	3.41, 6.2	-0.61, 0.56	3.56, 5.72	-0.59, 1.48	3.79, 6.36	-0.87, 1.29
Day 43	n	47	46	49	49	47	47
	Mean (SD)	4.67 (0.55)	-0.04 (0.27)	4.69 (0.50)	-0.02 (0.24)	4.67 (0.48)	-0.10 (0.33)
	Median	4.56	-0.06	4.70	0.00	4.71	-0.12
	Min, Max	3.71, 6.18	-0.62, 0.53	3.83, 5.55	-0.59, 0.64	3.74, 5.67	-1.12, 0.52

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: WHITE BLOOD COUNT (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	49		60		50	
	Mean (SD)	7.79 (2.00)		7.58 (1.89)		7.21 (1.71)	
	Median	7.40		7.65		7.15	
	Min, Max	4.3, 12.6		3.3, 11.6		3.7, 11.8	
Day 1	n	42	41	58	58	47	47
	Mean (SD)	8.25 (2.06)	0.32 (1.68)	7.54 (1.90)	-0.02 (1.57)	7.70 (2.22)	0.47 (1.25)
	Median	8.37	0.30	7.30	-0.08	7.30	0.20
	Min, Max	4.2, 12.8	-4.5, 3.4	3, 12	-3.7, 3.7	3.4, 14.3	-2.2, 4.86
Day 8	n	45	45	55	55	49	49
	Mean (SD)	7.40 (2.19)	-0.39 (1.74)	6.90 (1.97)	-0.47 (1.93)	6.87 (1.92)	-0.26 (1.39)
	Median	7.10	-0.10	6.70	-0.70	6.80	-0.13
	Min, Max	2.1, 13.5	-5.2, 2.4	2.63, 12.8	-4.1, 5.4	3.8, 12.7	-2.9, 4

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.

Table 14.3.2.1
Summary of Change from Baseline in Laboratory Data: Hematology
Safety Population

Test: WHITE BLOOD COUNT (10^9/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	48	47	56	56	48	48
	Mean (SD)	7.31 (2.23)	-0.53 (2.01)	6.98 (1.79)	-0.61 (1.56)	7.12 (2.18)	-0.03 (1.70)
	Median	6.90	-0.20	6.90	-0.57	6.91	0.00
	Min, Max	3.3, 13.9	-6.2, 4.4	2.9, 10.6	-4.2, 3.6	3.7, 14.04	-3.2, 5.39
Day 29	n	47	46	54	54	48	48
	Mean (SD)	7.38 (2.07)	-0.51 (1.56)	7.17 (2.07)	-0.38 (1.78)	7.00 (1.77)	-0.14 (1.11)
	Median	7.00	-0.50	6.99	-0.55	6.98	-0.15
	Min, Max	4.6, 12.8	-5.5, 3.52	3.7, 14.1	-3.6, 5.1	3.7, 11.43	-2.63, 3.5
Day 43	n	47	46	49	49	47	47
	Mean (SD)	7.55 (2.06)	-0.36 (1.55)	6.94 (1.91)	-0.69 (1.56)	7.00 (1.77)	-0.12 (1.26)
	Median	7.30	-0.25	6.50	-0.80	7.10	-0.20
	Min, Max	4.1, 13.8	-5, 3	2.9, 11.8	-5.1, 2.3	3.7, 11.1	-2.8, 3.14

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	45.11 (3.16)		45.34 (3.19)		45.38 (3.97)	
	Median	44.85		45.70		45.55	
	Min, Max	38.8, 51.2		38.6, 51.2		35, 53.1	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	45.07 (3.19)	-0.12 (2.54)	45.01 (3.25)	-0.42 (2.74)	45.27 (4.02)	-0.31 (3.45)
	Median	45.20	-0.30	45.40	-0.40	45.20	-0.60
	Min, Max	38, 52.6	-5.9, 7.1	37.4, 50.5	-6.2, 6.8	34, 59.4	-6.9, 13.8
Day 8	n	49	49	59	59	49	49
	Mean (SD)	45.37 (3.00)	0.22 (2.90)	44.64 (3.16)	-0.61 (2.88)	44.96 (3.78)	-0.35 (3.65)
	Median	45.40	0.00	44.50	-0.20	44.90	-0.80
	Min, Max	38.7, 50.8	-4.1, 10.9	36.7, 52.5	-7.9, 6.3	33, 55.2	-8.1, 13.8

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	44.76 (3.15)	-0.38 (3.09)	45.19 (3.35)	0.03 (2.43)	45.02 (3.36)	-0.34 (3.62)
	Median	45.10	-0.30	45.40	0.10	45.45	-1.00
	Min, Max	38.4, 50.6	-7.9, 10.1	32.5, 51.6	-7.9, 5.6	33, 52.2	-6.2, 13.6
Day 29	n	49	49	55	55	48	48
	Mean (SD)	44.99 (3.21)	-0.16 (3.04)	45.31 (2.95)	0.18 (2.24)	45.33 (3.60)	-0.01 (4.07)
	Median	44.70	0.10	45.80	0.00	45.70	0.00
	Min, Max	38.1, 52.9	-9, 6.2	39.8, 51.7	-4.3, 5.7	34, 52.9	-9.5, 14.2
Day 43	n	48	48	56	56	48	48
	Mean (SD)	45.10 (3.36)	-0.05 (2.97)	45.59 (2.71)	0.53 (2.64)	45.44 (2.64)	-0.09 (3.97)
	Median	45.10	0.00	45.75	0.35	45.65	-0.25
	Min, Max	35.7, 53.7	-8.6, 6.4	40.1, 51.5	-5.5, 6.8	40.1, 51.8	-7.6, 16.3

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: ALP (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	83.00 (26.86)		89.00 (26.12)		80.44 (23.12)	
	Median	79.50		84.50		80.00	
	Min, Max	37, 160		43, 190		48, 183	
Day 1	n	48	48	58	58	48	48
	Mean (SD)	81.21 (27.75)	-1.83 (14.26)	87.38 (25.69)	-1.81 (17.90)	79.31 (20.93)	-1.79 (18.50)
	Median	74.50	-2.50	83.50	-1.50	77.50	-0.50
	Min, Max	38, 161	-27, 56	49, 179	-90, 52	44, 162	-112, 23
Day 8	n	49	49	59	59	49	49
	Mean (SD)	81.59 (26.46)	-2.35 (19.72)	87.46 (23.08)	-1.86 (16.13)	76.45 (19.78)	-3.53 (19.54)
	Median	79.00	-3.00	87.00	1.00	76.00	-1.00
	Min, Max	38, 150	-52, 86	49, 159	-90, 35	40, 141	-113, 43

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: ALP (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	48
	Mean (SD)	82.43 (28.37)	-1.51 (18.13)	87.05 (25.48)	-2.73 (23.68)	79.42 (21.54)	-0.69 (20.70)
	Median	77.00	-3.00	80.00	-1.00	78.50	0.00
	Min, Max	38, 187	-55, 73	47, 172	-121, 50	44, 148	-110, 58
Day 29	n	49	49	55	55	48	48
	Mean (SD)	83.33 (29.62)	-0.61 (20.05)	89.18 (24.24)	-0.04 (21.48)	77.85 (21.06)	-2.48 (20.75)
	Median	79.00	-1.00	85.00	3.00	75.00	0.00
	Min, Max	36, 168	-54, 66	41, 152	-122, 36	37, 140	-122, 34
Day 43	n	47	47	56	56	48	48
	Mean (SD)	81.94 (28.92)	-2.74 (23.17)	91.27 (25.85)	2.30 (23.35)	77.42 (20.50)	-2.77 (20.72)
	Median	76.00	-2.00	85.00	2.50	78.00	-2.50
	Min, Max	11, 167	-73, 77	55, 169	-122, 51	33, 132	-111, 58

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: ALT (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	24.00 (17.51)		26.62 (25.00)		25.50 (18.72)	
	Median	19.00		19.00		18.00	
	Min, Max	8, 87		7, 175		7, 77	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	22.53 (13.74)	-1.37 (11.95)	30.54 (46.46)	3.90 (38.93)	26.08 (18.19)	0.08 (14.14)
	Median	19.00	0.00	18.00	-1.00	19.50	-0.50
	Min, Max	8, 78	-67, 25	6, 310	-31, 286	6, 86	-38, 64
Day 8	n	49	49	59	59	49	49
	Mean (SD)	24.10 (15.82)	-0.23 (13.81)	25.42 (22.02)	-1.44 (14.28)	26.65 (21.43)	1.06 (17.66)
	Median	20.00	-1.00	17.00	-2.00	19.00	0.00
	Min, Max	7, 75	-66, 41	7, 145	-45, 50	8, 110	-49, 87

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: ALT (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	23.18 (15.61)	-1.14 (12.59)	26.18 (22.20)	-1.18 (13.96)	28.08 (19.62)	2.13 (13.56)
	Median	18.00	-1.00	18.00	0.00	21.50	2.00
	Min, Max	8, 84	-60, 30	7, 151	-46, 41	9, 93	-52, 43
Day 29	n	49	49	55	55	48	48
	Mean (SD)	22.90 (15.20)	-1.43 (14.07)	24.53 (19.29)	-0.38 (17.42)	26.85 (17.75)	1.06 (12.22)
	Median	17.00	0.00	18.00	-1.00	22.00	1.50
	Min, Max	8, 94	-71, 22	7, 99	-50, 80	8, 92	-40, 27
Day 43	n	48	48	56	56	48	48
	Mean (SD)	22.23 (12.94)	-2.31 (14.99)	24.25 (16.04)	-0.46 (13.27)	26.58 (17.00)	2.06 (12.06)
	Median	19.50	-1.00	17.00	0.00	21.50	1.50
	Min, Max	7, 66	-74, 25	8, 76	-48, 33	9, 82	-44, 29

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: AST (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	21.44 (8.29)		24.45 (11.60)		22.24 (9.09)	
	Median	19.50		22.00		20.00	
	Min, Max	8.1, 48		11, 75		9, 50	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	21.06 (6.08)	-0.37 (7.09)	29.39 (48.82)	4.95 (49.37)	22.44 (9.04)	0.00 (8.04)
	Median	20.00	0.00	19.00	-1.00	18.00	0.00
	Min, Max	11, 37	-32, 14.9	8, 384	-23, 370	9, 50	-23, 34
Day 8	n	49	49	59	59	49	49
	Mean (SD)	21.90 (8.71)	0.32 (9.50)	23.10 (10.50)	-1.52 (10.23)	22.65 (9.46)	0.51 (8.80)
	Median	19.00	0.00	20.00	-1.00	20.00	0.00
	Min, Max	10, 53	-30, 35	11, 54	-28, 31	12, 48	-27, 24

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: AST (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	22.00 (7.78)	0.43 (9.11)	22.75 (11.55)	-2.21 (8.27)	23.00 (8.10)	0.63 (7.87)
	Median	19.00	0.00	21.00	-1.00	21.50	0.50
	Min, Max	13, 49	-30, 31	5, 75	-28, 16	10, 44	-29, 18
Day 29	n	49	49	55	55	48	48
	Mean (SD)	22.16 (8.68)	0.59 (9.86)	22.35 (11.04)	-1.89 (10.34)	22.15 (7.30)	-0.08 (7.58)
	Median	20.00	0.00	21.00	-1.00	19.50	0.00
	Min, Max	11, 51	-31, 27	6, 64	-24, 37	12, 42	-25, 17
Day 43	n	48	48	56	56	48	48
	Mean (SD)	21.50 (8.19)	-0.15 (10.49)	22.45 (11.17)	-1.63 (9.10)	23.10 (8.42)	1.27 (7.36)
	Median	19.50	-1.50	19.50	-1.00	21.50	1.00
	Min, Max	11, 57	-33, 28	11, 78	-24, 27	11, 52	-26, 16

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	23.78 (3.86)		23.55 (3.04)		23.16 (2.91)	
	Median	23.50		24.00		23.00	
	Min, Max	15, 31		10, 30		16, 30	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	24.18 (3.52)	0.51 (4.49)	24.03 (3.37)	0.51 (4.07)	24.04 (3.18)	0.90 (4.13)
	Median	24.00	1.00	24.00	1.00	24.00	1.00
	Min, Max	15, 32	-12, 8	16, 34	-10, 10	18, 31	-11, 13
Day 8	n	49	49	59	59	49	49
	Mean (SD)	24.10 (3.69)	0.24 (4.59)	23.80 (3.56)	0.29 (4.32)	23.27 (2.94)	0.00 (3.20)
	Median	24.00	1.00	24.00	1.00	23.00	-1.00
	Min, Max	11, 31	-10, 12	15, 31	-9, 10	19, 30	-6, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	23.69 (3.50)	-0.16 (4.80)	22.63 (2.96)	-0.82 (3.94)	23.08 (4.57)	-0.23 (5.29)
	Median	24.00	0.00	23.00	0.00	23.00	0.00
	Min, Max	17, 32	-12, 12	15, 28	-9, 13	1, 29	-26, 8
Day 29	n	48	48	55	55	48	48
	Mean (SD)	24.23 (3.24)	0.48 (4.92)	22.85 (3.74)	-0.65 (4.68)	23.56 (3.34)	0.29 (3.67)
	Median	24.00	1.00	23.00	-1.00	23.50	1.00
	Min, Max	19, 32	-12, 13	12, 31	-12, 16	12, 29	-11, 7
Day 43	n	48	48	56	56	48	48
	Mean (SD)	22.65 (3.56)	-1.25 (4.16)	22.75 (2.89)	-0.73 (3.67)	23.54 (2.91)	0.35 (3.55)
	Median	22.50	-1.00	22.00	-1.00	23.50	1.00
	Min, Max	14, 32	-9, 9	18, 29	-7, 14	16, 29	-14, 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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL BILIRUBIN (µmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	7.68 (4.43)		7.39 (5.69)		8.42 (5.53)	
	Median	6.84		6.07		7.01	
	Min, Max	1.71, 22.401		0.15, 37.107		2.565, 24.453	
Day 1	n	49	49	59	59	49	49
	Mean (SD)	6.84 (3.65)	-0.78 (2.56)	6.69 (4.30)	-0.75 (3.34)	8.45 (5.96)	-0.08 (4.21)
	Median	6.33	-0.68	5.30	-0.34	6.33	-0.51
	Min, Max	1.71, 16.245	-7.182, 4.788	1.71, 20.007	-17.1, 7.011	2.565, 22.059	-7.182, 19.494
Day 8	n	49	49	59	59	49	49
	Mean (SD)	8.00 (3.88)	0.34 (3.53)	6.97 (4.60)	-0.41 (3.29)	9.29 (6.87)	0.84 (4.13)
	Median	7.52	-0.17	5.30	-0.17	6.84	0.00
	Min, Max	2.565, 21.717	-10.431, 9.576	1.71, 21.204	-15.903, 8.721	2.565, 38.817	-5.13, 16.929

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL BILIRUBIN (µmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	7.13 (3.69)	-0.53 (2.67)	7.36 (5.30)	-0.06 (3.45)	8.30 (5.32)	-0.23 (4.09)
	Median	5.81	-1.03	5.30	0.00	6.84	-0.51
	Min, Max	1.71, 17.442	-5.985, 6.84	2.565, 26.163	-10.944, 11.97	2.907, 25.821	-6.498, 23.256
Day 29	n	49	49	55	55	48	48
	Mean (SD)	7.96 (4.98)	0.30 (3.06)	6.61 (4.15)	-0.82 (3.57)	9.37 (7.18)	0.85 (6.08)
	Median	6.50	0.00	5.30	-0.34	7.27	0.00
	Min, Max	1.71, 23.085	-6.498, 10.089	1.71, 18.639	-19.836, 5.13	2.565, 42.066	-4.617, 39.501
Day 43	n	48	48	56	56	48	48
	Mean (SD)	7.06 (3.72)	-0.65 (2.56)	7.08 (4.80)	-0.31 (3.73)	8.82 (5.92)	0.52 (4.29)
	Median	6.41	-0.68	5.64	-0.26	6.84	0.00
	Min, Max	2.565, 18.297	-6.156, 3.762	1.71, 23.94	-16.929, 8.55	2.565, 26.676	-8.892, 24.111

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	2.28 (0.14)		2.30 (0.12)		2.33 (0.13)	
	Median	2.28		2.30		2.33	
	Min, Max	1.75, 2.525		2.075, 2.725		1.95, 2.525	
Day 1	n	48	48	58	58	48	48
	Mean (SD)	2.29 (0.13)	0.02 (0.12)	2.30 (0.14)	0.00 (0.10)	2.32 (0.11)	-0.02 (0.13)
	Median	2.30	0.02	2.30	0.00	2.33	-0.02
	Min, Max	1.975, 2.55	-0.225, 0.275	1.75, 2.675	-0.35, 0.275	2.05, 2.525	-0.275, 0.525
Day 8	n	49	49	59	59	49	49
	Mean (SD)	2.31 (0.12)	0.04 (0.13)	2.30 (0.12)	0.01 (0.11)	2.31 (0.11)	-0.01 (0.14)
	Median	2.33	0.02	2.30	0.00	2.30	-0.02
	Min, Max	1.95, 2.55	-0.275, 0.4	2.05, 2.575	-0.2, 0.275	2.075, 2.575	-0.25, 0.525

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	48
	Mean (SD)	2.27 (0.15)	-0.00 (0.12)	2.28 (0.14)	-0.01 (0.13)	2.31 (0.11)	-0.02 (0.14)
	Median	2.30	0.00	2.30	0.02	2.30	-0.03
	Min, Max	1.775, 2.5	-0.35, 0.3	1.7, 2.575	-0.6, 0.225	2.05, 2.55	-0.275, 0.55
Day 29	n	49	49	55	55	48	48
	Mean (SD)	2.30 (0.13)	0.02 (0.15)	2.30 (0.11)	0.01 (0.09)	2.30 (0.11)	-0.02 (0.12)
	Median	2.30	0.02	2.30	-0.02	2.31	-0.02
	Min, Max	1.975, 2.625	-0.25, 0.325	2.125, 2.7	-0.175, 0.2	1.85, 2.525	-0.275, 0.4
Day 43	n	46	46	56	56	48	48
	Mean (SD)	2.28 (0.18)	0.01 (0.16)	2.32 (0.11)	0.03 (0.10)	2.30 (0.10)	-0.02 (0.13)
	Median	2.30	0.01	2.30	0.02	2.31	-0.04
	Min, Max	1.475, 2.75	-0.775, 0.3	2.075, 2.6	-0.175, 0.35	2.075, 2.525	-0.275, 0.475

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL CHOLESTEROL (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	4.49 (0.91)		4.50 (0.96)		4.58 (0.90)	
	Median	4.48		4.48		4.56	
	Min, Max	2.745, 7.382		2.461, 6.993		3.004, 7.459	
Day 1	n	49	49	58	58	49	48
	Mean (SD)	4.58 (1.03)	0.10 (0.45)	4.48 (1.17)	-0.02 (0.57)	4.56 (0.97)	-0.06 (0.51)
	Median	4.38	0.10	4.34	-0.05	4.46	-0.05
	Min, Max	2.927, 8.184	-0.984, 1.606	1.658, 8.107	-0.803, 2.487	2.849, 7.252	-1.554, 1.425
Day 8	n	49	49	58	58	49	48
	Mean (SD)	4.47 (0.95)	-0.00 (0.58)	4.40 (1.08)	-0.07 (0.55)	4.44 (0.88)	-0.16 (0.70)
	Median	4.43	0.10	4.31	-0.12	4.61	-0.16
	Min, Max	2.953, 7.226	-1.476, 1.062	2.279, 7.744	-1.243, 1.269	2.771, 6.915	-3.263, 1.761

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL CHOLESTEROL (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	47
	Mean (SD)	4.43 (0.93)	-0.05 (0.61)	4.45 (1.05)	-0.03 (0.61)	4.47 (0.90)	-0.15 (0.73)
	Median	4.48	0.00	4.40	-0.12	4.44	-0.18
	Min, Max	2.771, 6.838	-2.331, 1.01	2.279, 8.21	-1.709, 1.58	2.901, 6.76	-3.47, 1.606
Day 29	n	49	49	54	54	48	47
	Mean (SD)	4.47 (0.99)	-0.00 (0.75)	4.42 (1.08)	-0.07 (0.63)	4.62 (1.01)	0.02 (0.75)
	Median	4.38	0.03	4.22	-0.09	4.58	0.08
	Min, Max	2.59, 7.356	-2.28, 2.046	2.383, 8.91	-2.59, 1.917	2.668, 6.889	-3.289, 1.295
Day 43	n	48	48	55	55	48	47
	Mean (SD)	4.51 (0.91)	0.01 (0.71)	4.45 (1.17)	-0.01 (0.78)	4.57 (0.95)	-0.01 (0.62)
	Median	4.35	0.00	4.14	-0.02	4.60	0.05
	Min, Max	2.616, 7.045	-2.383, 2.02	2.486, 8.754	-2.331, 2.202	2.875, 6.449	-2.771, 1.191

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	103.44 (2.42)		103.87 (3.29)		103.52 (3.28)	
	Median	103.00		104.00		104.00	
	Min, Max	98, 111		96, 112		95, 110	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	103.18 (3.00)	-0.22 (3.31)	103.86 (3.01)	0.03 (3.64)	102.77 (2.87)	-0.83 (2.42)
	Median	103.00	0.00	104.00	0.00	103.00	-1.00
	Min, Max	94, 109	-10, 7	97, 111	-7, 9	95, 107	-7, 5
Day 8	n	49	49	59	59	49	49
	Mean (SD)	103.12 (2.92)	-0.37 (2.77)	104.05 (2.55)	0.14 (3.50)	102.80 (3.19)	-0.90 (2.58)
	Median	103.00	-1.00	104.00	0.00	103.00	-1.00
	Min, Max	95, 109	-7, 5	98, 110	-7, 9	96, 111	-7, 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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023 Final- 07JUN2023:18:05

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	103.94 (3.17)	0.45 (3.22)	103.60 (2.74)	-0.26 (3.25)	102.96 (3.23)	-0.69 (2.81)
	Median	103.00	1.00	104.00	0.00	103.00	-1.00
	Min, Max	95, 111	-7, 9	97, 110	-8, 8	95, 112	-7, 4
Day 29	n	49	49	55	55	48	48
	Mean (SD)	103.45 (2.89)	-0.04 (2.85)	103.76 (2.50)	-0.09 (3.56)	103.00 (2.80)	-0.75 (2.58)
	Median	103.00	0.00	104.00	0.00	103.00	-0.50
	Min, Max	98, 111	-7, 6	98, 109	-7, 11	97, 108	-7, 5
Day 43	n	48	48	56	56	48	48
	Mean (SD)	103.54 (2.63)	0.02 (3.11)	103.70 (2.61)	-0.18 (3.25)	102.06 (3.26)	-1.56 (2.63)
	Median	103.50	0.00	104.00	0.00	102.00	-1.00
	Min, Max	96, 110	-7, 10	96, 110	-7, 9	94, 109	-7, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	136.48 (113.7)		170.10 (195.9)		175.16 (154.5)	
	Median	105.00		114.00		143.00	
	Min, Max	1.17, 776		40, 1246		43, 1054	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	131.24 (63.58)	-8.00 (103.7)	144.29 (117.9)	-7.37 (134.3)	167.52 (134.0)	-2.60 (98.32)
	Median	112.00	-3.00	109.00	3.00	115.50	-7.00
	Min, Max	38, 308	-591, 148	35, 750	-859, 338	38, 665	-389, 324
Day 8	n	49	49	59	59	49	49
	Mean (SD)	131.47 (77.31)	-5.35 (120.3)	160.10 (137.8)	6.59 (140.6)	138.39 (86.67)	-18.84 (60.66)
	Median	100.00	-7.00	108.00	-1.00	118.00	-8.00
	Min, Max	41, 432	-591, 289.83	46, 762	-849, 358	29, 407	-222, 143

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
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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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	148.82 (133.5)	12.00 (152.1)	148.39 (123.9)	-7.44 (131.7)	153.35 (152.4)	-4.79 (112.5)
	Median	119.00	1.00	109.00	-2.00	116.00	-7.50
	Min, Max	35, 879	-532, 695	43, 652	-838, 365	31, 1011	-180, 665
Day 29	n	49	49	55	55	48	48
	Mean (SD)	128.24 (64.57)	-8.57 (110.6)	149.24 (115.8)	-4.51 (138.4)	150.29 (105.4)	-8.25 (64.66)
	Median	121.00	8.00	108.00	-5.00	119.50	-10.50
	Min, Max	21, 284	-613, 186.83	36, 515	-809, 308	33, 503	-155, 234
Day 43	n	48	48	56	56	48	48
	Mean (SD)	132.98 (75.99)	-4.52 (115.1)	153.09 (114.8)	1.23 (140.0)	172.31 (130.2)	14.85 (81.48)
	Median	116.00	-3.50	118.00	0.50	123.50	2.00
	Min, Max	37, 398	-584, 230	31, 661	-814, 347	59, 557	-163, 244

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	75.02 (33.15)		75.91 (32.12)		77.18 (15.19)	
	Median	72.05		69.39		77.79	
	Min, Max	45.084, 269.62		38.896, 292.604		42.432, 114.92	
Day 1	n	48	48	58	57	48	46
	Mean (SD)	69.23 (14.13)	-5.76 (29.53)	72.66 (26.90)	-3.61 (36.21)	75.53 (15.52)	-1.88 (13.16)
	Median	68.07	-2.65	69.84	-0.88	72.93	-2.65
	Min, Max	42.432, 103.428	-193.596, 26.52	42.432, 244.868	-217.464, 145.86	50.388, 111.384	-30.056, 53.924
Day 8	n	49	49	58	57	49	47
	Mean (SD)	72.52 (19.66)	-3.05 (33.90)	70.25 (13.86)	-6.16 (31.26)	76.02 (16.16)	-0.94 (12.84)
	Median	70.72	0.88	69.39	-2.65	76.02	-1.77
	Min, Max	48.62, 162.656	-204.204, 87.51	44.2, 113.152	-224.536, 24.752	47.736, 116.688	-30.056, 51.272

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
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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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	55	48	46
	Mean (SD)	71.50 (14.93)	-4.08 (28.15)	78.49 (59.50)	2.19 (68.20)	77.83 (17.70)	0.15 (14.00)
	Median	70.72	0.88	68.07	-0.88	78.23	-2.65
	Min, Max	43.316, 101.66	-182.988, 21.216	44.2, 502.112	-222.768, 442	45.084, 116.688	-21.216, 45.968
Day 29	n	49	49	54	53	48	46
	Mean (SD)	73.30 (23.16)	-2.27 (32.37)	71.01 (14.95)	-5.55 (31.91)	77.18 (17.17)	-0.17 (13.85)
	Median	71.60	-0.88	70.28	-1.77	80.00	0.88
	Min, Max	43.316, 196.248	-191.828, 91.052	39.78, 121.992	-221, 16.796	43.316, 133.484	-33.592, 48.62
Day 43	n	48	48	55	54	48	46
	Mean (SD)	73.91 (22.96)	-1.51 (35.83)	76.75 (48.51)	0.57 (58.45)	75.82 (17.79)	-1.36 (12.65)
	Median	70.72	0.88	68.95	0.00	76.47	-3.98
	Min, Max	46.852, 191.828	-204.204, 114.036	34.476, 411.06	-216.58, 358.904	41.548, 121.108	-21.216, 44.2

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
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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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	6.01 (1.69)		5.59 (1.38)		5.61 (1.11)	
	Median	5.44		5.22		5.33	
	Min, Max	3.885, 11.267		3.33, 12.21		4.107, 10.601	
Day 1	n	49	49	58	58	48	47
	Mean (SD)	6.40 (2.68)	0.40 (1.86)	6.57 (2.73)	0.97 (2.14)	5.86 (1.37)	0.20 (1.55)
	Median	5.33	0.00	5.83	0.50	5.47	-0.11
	Min, Max	4.052, 16.317	-2.775, 7.7705	3.275, 18.87	-1.943, 12.765	4.163, 10.934	-3.386, 5.828
Day 8	n	48	48	58	58	46	45
	Mean (SD)	6.16 (2.39)	0.18 (1.55)	5.82 (2.00)	0.20 (1.29)	5.61 (0.95)	0.03 (1.06)
	Median	5.41	0.06	5.16	0.06	5.44	0.00
	Min, Max	3.441, 14.541	-3.719, 6.826	3.83, 17.039	-2.608, 4.829	4.052, 7.715	-2.886, 2.553

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	55	55	48	47
	Mean (SD)	5.89 (1.99)	-0.09 (1.38)	5.96 (2.43)	0.32 (1.51)	5.64 (1.24)	0.09 (1.08)
	Median	5.38	-0.06	5.22	0.06	5.30	0.00
	Min, Max	3.386, 12.876	-3.83, 4.606	3.941, 18.204	-1.72, 6.493	4.0515, 9.879	-1.998, 4.606
Day 29	n	49	49	55	55	45	44
	Mean (SD)	5.98 (2.04)	0.00 (1.35)	6.06 (2.63)	0.44 (1.58)	5.36 (0.82)	-0.25 (1.16)
	Median	5.27	-0.06	5.27	0.17	5.22	0.03
	Min, Max	3.83, 14.319	-3.33, 3.552	3.83, 21.59	-1.443, 9.38	3.552, 7.493	-4.607, 1.998
Day 43	n	47	47	54	54	46	46
	Mean (SD)	5.63 (1.58)	-0.36 (1.47)	5.81 (2.43)	0.21 (1.43)	5.48 (0.89)	-0.08 (1.35)
	Median	5.33	-0.39	5.05	-0.06	5.41	0.06
	Min, Max	3.386, 11.822	-5.606, 6.105	3.941, 18.704	-1.943, 6.494	4.107, 8.381	-4.496, 4.274

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: GGT (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	27.76 (25.23)		30.70 (38.60)		24.02 (12.74)	
	Median	17.50		20.00		21.50	
	Min, Max	7, 118		8, 266		9, 79	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	24.84 (19.15)	-2.96 (11.42)	28.03 (26.37)	-2.81 (25.76)	23.58 (11.04)	-0.75 (7.98)
	Median	18.00	0.00	20.00	0.00	21.00	-1.00
	Min, Max	7, 106	-46, 22	5, 166	-172, 72	8, 52	-37, 26
Day 8	n	49	49	59	59	49	49
	Mean (SD)	24.98 (18.56)	-3.20 (13.00)	27.08 (22.55)	-3.88 (28.53)	22.86 (10.32)	-0.82 (8.69)
	Median	20.00	-1.00	18.00	-1.00	20.00	0.00
	Min, Max	5, 98	-54, 20	6, 139	-197, 45	9, 57	-44, 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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: GGT (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	24.67 (18.96)	-3.51 (13.12)	27.42 (21.24)	-3.86 (30.60)	24.29 (12.78)	0.40 (10.21)
	Median	19.00	-1.00	21.00	0.00	21.50	0.00
	Min, Max	8, 106	-59, 14	6, 118	-211, 34	8, 69	-39, 37
Day 29	n	49	49	55	55	48	48
	Mean (SD)	24.94 (17.99)	-3.24 (16.19)	26.95 (20.82)	-3.15 (35.03)	24.21 (9.54)	0.23 (9.77)
	Median	20.00	0.00	19.00	0.00	23.00	1.00
	Min, Max	8, 101	-77, 39	6, 111	-233, 69	7, 53	-47, 20
Day 43	n	48	48	56	56	48	48
	Mean (SD)	24.67 (18.55)	-3.73 (19.52)	26.23 (19.39)	-3.93 (34.64)	23.73 (9.65)	0.10 (9.44)
	Median	17.50	-0.50	19.00	0.00	20.00	1.00
	Min, Max	7, 89	-80, 61	7, 96	-240, 40	9, 45	-40, 18

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: HIGH-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	1.10 (0.36)		1.11 (0.30)		1.07 (0.53)	
	Median	1.08		1.06		1.04	
	Min, Max	0.363, 2.538		0.518, 2.072		0.389, 4.0663	
Day 1	n	49	49	58	58	48	47
	Mean (SD)	1.05 (0.35)	-0.05 (0.22)	1.07 (0.30)	-0.04 (0.17)	0.98 (0.27)	-0.10 (0.47)
	Median	1.01	-0.05	1.05	-0.05	0.95	0.00
	Min, Max	0.285, 2.538	-0.803, 0.44	0.544, 2.124	-0.388, 0.803	0.466, 1.658	-3.0562, 0.336
Day 8	n	49	49	58	58	49	48
	Mean (SD)	1.05 (0.31)	-0.03 (0.19)	1.02 (0.28)	-0.09 (0.19)	1.07 (0.71)	0.00 (0.26)
	Median	1.01	-0.03	0.97	-0.05	1.01	0.00
	Min, Max	0.44, 1.684	-0.622, 0.518	0.155, 1.709	-0.907, 0.259	0.492, 5.5685	-0.389, 1.5022

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023 Final- 07JUN2023:18:05

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: HIGH-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	47
	Mean (SD)	1.03 (0.29)	-0.04 (0.27)	1.05 (0.32)	-0.05 (0.27)	0.99 (0.27)	-0.08 (0.47)
	Median	1.01	-0.08	1.00	-0.04	0.96	-0.03
	Min, Max	0.44, 1.606	-0.959, 0.777	0.518, 1.994	-0.88, 1.062	0.44, 1.735	-2.9267, 0.802
Day 29	n	49	49	54	54	48	47
	Mean (SD)	1.03 (0.26)	-0.04 (0.28)	1.07 (0.29)	-0.04 (0.21)	1.00 (0.28)	-0.06 (0.46)
	Median	0.98	-0.05	1.02	-0.05	0.98	0.03
	Min, Max	0.57, 1.5799	-0.674, 0.674	0.492, 1.968	-0.622, 0.622	0.492, 2.02	-2.9267, 0.362
Day 43	n	48	48	55	55	48	47
	Mean (SD)	1.01 (0.27)	-0.07 (0.25)	1.04 (0.29)	-0.07 (0.21)	1.00 (0.28)	-0.01 (0.16)
	Median	0.96	-0.05	1.01	-0.05	0.96	0.00
	Min, Max	0.44, 1.606	-0.647, 0.595	0.544, 1.787	-0.518, 0.285	0.492, 1.684	-0.362, 0.362

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	4.33 (0.37)		4.36 (0.45)		4.33 (0.40)	
	Median	4.30		4.40		4.30	
	Min, Max	3.8, 5.2		3.1, 5.8		3.4, 5.4	
Day 1	n	49	49	59	59	48	48
	Mean (SD)	4.26 (0.37)	-0.08 (0.44)	4.22 (0.40)	-0.13 (0.45)	4.31 (0.44)	-0.05 (0.57)
	Median	4.20	-0.10	4.20	-0.10	4.30	-0.05
	Min, Max	3.6, 5.1	-1.1, 1	3.4, 5.6	-1.4, 1	3.5, 5.8	-1, 1.5
Day 8	n	49	49	59	59	49	49
	Mean (SD)	4.28 (0.45)	-0.05 (0.38)	4.26 (0.42)	-0.10 (0.44)	4.26 (0.38)	-0.06 (0.50)
	Median	4.30	0.00	4.30	0.00	4.30	-0.10
	Min, Max	3.5, 5.4	-0.9, 0.8	3.4, 5.4	-1.8, 0.6	3.5, 5.1	-1.1, 1.2

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023 Final- 07JUN2023:18:05

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	4.26 (0.35)	-0.07 (0.37)	4.32 (0.46)	-0.04 (0.50)	4.28 (0.28)	-0.05 (0.39)
	Median	4.30	-0.10	4.30	0.00	4.30	-0.10
	Min, Max	3.5, 5.2	-1, 0.9	3.6, 6.8	-1.4, 1.7	3.7, 5.1	-0.9, 0.8
Day 29	n	49	49	55	55	48	48
	Mean (SD)	4.31 (0.48)	-0.02 (0.50)	4.19 (0.33)	-0.17 (0.46)	4.36 (0.34)	0.02 (0.41)
	Median	4.20	0.00	4.20	-0.20	4.30	-0.05
	Min, Max	3.5, 6.2	-1, 2	3.4, 4.9	-1.3, 0.7	3.7, 5.2	-1.1, 0.8
Day 43	n	47	47	56	56	47	47
	Mean (SD)	4.27 (0.35)	-0.07 (0.38)	4.29 (0.37)	-0.08 (0.48)	4.25 (0.28)	-0.07 (0.36)
	Median	4.30	0.00	4.30	-0.05	4.20	-0.10
	Min, Max	3.5, 5.2	-1, 0.8	3.1, 5.3	-1.3, 1.1	3.7, 4.9	-0.9, 1.1

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LDH (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	185.84 (44.45)		183.33 (47.74)		188.38 (42.01)	
	Median	179.00		177.00		183.00	
	Min, Max	116, 392		30, 365		124, 318	
Day 1	n	48	48	59	58	48	47
	Mean (SD)	187.40 (48.74)	1.48 (38.92)	178.69 (57.09)	-1.59 (68.25)	191.85 (51.38)	4.28 (33.20)
	Median	180.00	-1.00	168.00	-5.50	182.00	-2.00
	Min, Max	104, 368	-72, 215	122, 549	-202, 389	116, 361	-61, 140
Day 8	n	49	49	59	58	49	48
	Mean (SD)	181.12 (35.38)	-5.10 (29.32)	183.61 (46.21)	0.64 (54.23)	190.41 (54.42)	2.00 (45.64)
	Median	177.00	-3.00	167.00	-2.50	185.00	-6.00
	Min, Max	119, 269	-123, 54	132, 376	-205, 157	107, 373	-76, 164

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
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Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LDH (U/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	56	48	47
	Mean (SD)	181.86 (39.98)	-4.37 (41.01)	180.23 (32.82)	-3.88 (47.05)	189.25 (43.33)	-0.81 (22.80)
	Median	174.00	-3.00	175.00	0.00	184.50	-4.00
	Min, Max	88, 329	-138, 176	130, 308	-188, 160	128, 294	-43, 59
Day 29	n	49	49	55	54	48	47
	Mean (SD)	197.96 (112.7)	11.73 (92.45)	180.18 (34.36)	-2.24 (45.90)	186.96 (46.55)	-2.64 (25.87)
	Median	178.00	-8.00	173.00	-1.50	178.50	-2.00
	Min, Max	102, 787	-62, 465	127, 275	-180, 128	101, 295	-59, 94
Day 43	n	48	48	56	55	48	47
	Mean (SD)	187.42 (40.70)	1.23 (39.95)	186.61 (36.08)	4.11 (48.37)	190.19 (48.72)	1.81 (35.46)
	Median	175.50	2.00	178.00	11.00	185.00	0.00
	Min, Max	125, 304	-156, 151	128, 274	-188, 129	114, 338	-73, 159

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
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Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LOW-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	2.66 (0.82)		2.62 (0.84)		2.79 (0.79)	
	Median	2.42		2.67		2.71	
	Min, Max	1.212, 5.486		1.036, 5.004		1.02, 5.335	
Day 1	n	49	49	58	58	48	47
	Mean (SD)	2.61 (0.96)	-0.04 (0.49)	2.51 (0.93)	-0.11 (0.56)	2.67 (0.81)	-0.12 (0.46)
	Median	2.38	0.05	2.33	-0.11	2.59	-0.11
	Min, Max	0.596, 6.361	-2.196, 1.119	0.414, 5.755	-1.373, 2.398	1.145, 4.61	-1.295, 0.984
Day 8	n	49	49	58	58	49	48
	Mean (SD)	2.61 (0.74)	-0.06 (0.48)	2.59 (0.89)	-0.01 (0.55)	2.68 (0.77)	-0.13 (0.58)
	Median	2.62	-0.08	2.44	0.01	2.67	-0.07
	Min, Max	1.471, 4.558	-1.357, 0.782	1.233, 5.071	-1.052, 1.554	1.15, 4.33	-2.693, 1.175

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: LOW-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	47
	Mean (SD)	2.57 (0.75)	-0.09 (0.49)	2.57 (0.90)	-0.04 (0.71)	2.68 (0.78)	-0.15 (0.65)
	Median	2.54	-0.06	2.48	-0.02	2.70	-0.13
	Min, Max	1.295, 4.828	-2.072, 0.917	0.865, 4.895	-2.875, 1.461	1.14, 4.771	-2.849, 1.616
Day 29	n	49	49	54	54	48	47
	Mean (SD)	2.62 (0.84)	-0.05 (0.63)	2.50 (0.84)	-0.11 (0.52)	2.85 (0.95)	0.02 (0.68)
	Median	2.46	0.05	2.36	-0.10	2.77	0.06
	Min, Max	0.673, 5.537	-2.124, 1.171	0.725, 4.776	-2.378, 1.223	0.974, 5.47	-2.564, 1.968
Day 43	n	48	48	55	55	48	47
	Mean (SD)	2.71 (0.78)	0.03 (0.63)	2.60 (0.90)	0.00 (0.71)	2.79 (0.86)	0.01 (0.59)
	Median	2.44	0.04	2.39	-0.03	2.84	0.03
	Min, Max	1.145, 4.817	-2.227, 1.497	1.129, 6.475	-1.86, 1.471	1.145, 4.724	-2.356, 1.222

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	140.10 (2.89)		139.75 (3.11)		139.86 (2.70)	
	Median	140.00		140.00		140.00	
	Min, Max	134, 150		128, 146		132, 144	
Day 1	n	48	48	58	58	49	49
	Mean (SD)	139.63 (2.69)	-0.42 (3.39)	139.88 (3.04)	0.17 (4.24)	139.10 (2.94)	-0.90 (3.39)
	Median	140.00	0.00	140.00	0.50	139.00	-1.00
	Min, Max	129, 145	-11, 8	131, 147	-14, 11	130, 145	-11, 7
Day 8	n	49	49	59	59	49	49
	Mean (SD)	139.20 (3.09)	-1.00 (3.04)	139.56 (2.55)	-0.17 (3.41)	138.98 (2.52)	-1.04 (2.61)
	Median	140.00	-1.00	140.00	-1.00	139.00	-1.00
	Min, Max	130, 146	-10, 5	132, 148	-7, 9	134, 145	-8, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	48
	Mean (SD)	140.06 (3.00)	-0.14 (3.15)	139.39 (2.86)	-0.21 (3.16)	139.33 (2.76)	-0.65 (3.21)
	Median	140.00	0.00	139.00	0.00	139.00	0.00
	Min, Max	132, 148	-9, 6	131, 148	-6, 9	131, 148	-8, 4
Day 29	n	49	49	55	55	48	48
	Mean (SD)	139.10 (2.27)	-1.10 (2.94)	139.51 (2.52)	-0.15 (3.45)	139.38 (2.27)	-0.69 (2.67)
	Median	139.00	-1.00	140.00	0.00	140.00	-1.00
	Min, Max	134, 143	-9, 4	133, 145	-8, 7	132, 144	-6, 7
Day 43	n	47	47	56	56	48	48
	Mean (SD)	139.45 (2.29)	-0.77 (3.31)	139.48 (2.50)	-0.18 (2.95)	138.40 (2.43)	-1.65 (2.85)
	Median	140.00	-1.00	139.00	-0.50	139.00	-1.00
	Min, Max	134, 148	-10, 9	132, 145	-6, 6	132, 144	-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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL PROTEIN (g/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		50	
	Mean (SD)	73.82 (3.80)		74.11 (5.05)		72.45 (5.08)	
	Median	73.75		73.70		72.15	
	Min, Max	67.2, 81.8		60.2, 89.9		59, 81.9	
Day 1	n	49	49	59	59	49	49
	Mean (SD)	73.12 (4.83)	-0.82 (4.49)	72.64 (4.88)	-1.50 (4.64)	71.99 (5.40)	-0.43 (4.77)
	Median	73.40	-0.40	72.20	-1.20	73.10	-1.00
	Min, Max	63.3, 82.8	-14.2, 7	62.2, 85.5	-11.9, 11.9	60.5, 81.7	-10.9, 19.1
Day 8	n	49	49	59	59	49	49
	Mean (SD)	73.21 (4.04)	-0.70 (4.59)	73.00 (4.29)	-1.04 (4.55)	71.44 (5.13)	-1.00 (5.12)
	Median	73.00	-0.10	72.70	-1.40	71.00	-1.80
	Min, Max	64.8, 85.5	-10.3, 10.4	65.5, 86.2	-9.9, 17.5	60.1, 80.9	-11.1, 16.7

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: TOTAL PROTEIN (g/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	48
	Mean (SD)	71.92 (4.06)	-1.98 (4.60)	73.31 (5.01)	-0.79 (4.33)	72.13 (4.34)	-0.45 (4.64)
	Median	71.70	-1.60	72.40	-1.20	72.75	-1.00
	Min, Max	63.2, 80.6	-13.2, 7.6	62.1, 86.3	-11.2, 18.2	58.9, 83.6	-9.2, 15.1
Day 29	n	49	49	55	55	48	48
	Mean (SD)	72.90 (4.74)	-1.00 (4.54)	73.04 (4.86)	-0.90 (4.14)	72.50 (4.91)	0.09 (4.31)
	Median	72.00	-0.40	72.90	-1.50	72.00	-0.20
	Min, Max	65.7, 82.9	-13.8, 9.2	65.2, 88.6	-7.8, 13.8	60, 81.6	-10.1, 13.3
Day 43	n	48	48	56	56	48	48
	Mean (SD)	72.38 (4.32)	-1.60 (4.34)	73.22 (4.22)	-0.75 (5.07)	72.00 (4.88)	-0.49 (5.65)
	Median	72.25	-0.85	72.45	-1.00	72.15	-0.90
	Min, Max	63.8, 85.1	-9.7, 8.7	65.2, 84.2	-11.9, 19.6	63.1, 84.1	-11.9, 20.6

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	1.70 (1.40)		1.70 (1.07)		1.78 (1.15)	
	Median	1.25		1.35		1.35	
	Min, Max	0.384, 8.961		0.554, 6.023		0.486, 6.102	
Day 1	n	49	49	58	58	49	48
	Mean (SD)	2.02 (1.20)	0.31 (0.95)	2.00 (1.75)	0.30 (1.15)	2.07 (1.28)	0.29 (0.89)
	Median	1.82	0.20	1.46	0.14	1.58	0.09
	Min, Max	0.644, 6.509	-2.452, 3.401	0.633, 11.537	-2.61, 6.836	0.407, 4.995	-1.729, 2.8137
Day 8	n	49	49	58	58	49	48
	Mean (SD)	1.89 (1.20)	0.17 (0.73)	1.74 (1.21)	0.05 (0.77)	1.71 (0.91)	-0.01 (0.73)
	Median	1.46	0.15	1.42	-0.01	1.46	0.02
	Min, Max	0.429, 6.678	-2.283, 1.605	0.667, 7.413	-1.955, 2.712	0.475, 4.204	-2.068, 1.616

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	56	56	48	47
	Mean (SD)	1.85 (1.25)	0.13 (0.94)	1.83 (1.56)	0.13 (1.08)	1.84 (1.12)	0.09 (0.56)
	Median	1.61	-0.02	1.38	0.05	1.52	0.01
	Min, Max	0.35, 7.526	-2.181, 2.994	0.599, 11.085	-1.898, 6.384	0.565, 5.322	-1.548, 1.424
Day 29	n	49	49	54	54	48	47
	Mean (SD)	1.73 (1.05)	0.01 (0.83)	1.88 (1.48)	0.18 (0.82)	1.81 (1.15)	0.06 (0.80)
	Median	1.46	0.09	1.40	-0.05	1.44	-0.01
	Min, Max	0.52, 5.729	-3.232, 2.237	0.633, 9.424	-2.023, 3.401	0.542, 5.435	-1.808, 2.768
Day 43	n	48	48	55	55	48	47
	Mean (SD)	1.81 (1.02)	0.09 (0.91)	1.68 (1.12)	-0.00 (0.86)	1.77 (0.93)	0.00 (0.71)
	Median	1.57	0.10	1.42	0.00	1.55	0.16
	Min, Max	0.565, 5.887	-3.074, 2.486	0.588, 7.808	-2.734, 3.107	0.463, 4.102	-2.486, 1.526

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: BUN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	50		60		49	
	Mean (SD)	2.99 (1.57)		2.83 (1.06)		2.77 (1.38)	
	Median	2.59		2.70		2.57	
	Min, Max	1.035, 11.424		1.178, 7.104		0.893, 11.067	
Day 1	n	49	49	59	59	48	47
	Mean (SD)	2.78 (0.91)	-0.04 (0.93)	2.74 (0.84)	-0.09 (0.94)	3.07 (2.14)	0.10 (0.68)
	Median	2.86	0.14	2.61	-0.07	2.50	0.00
	Min, Max	1.142, 4.641	-3.927, 1.714	1.071, 4.82	-4.676, 1.607	1.535, 13.566	-1.714, 1.785
Day 8	n	49	49	58	58	49	48
	Mean (SD)	3.10 (1.96)	0.11 (1.09)	2.73 (0.89)	-0.12 (0.85)	3.05 (2.23)	0.04 (0.71)
	Median	2.79	0.11	2.75	0.00	2.54	0.09
	Min, Max	1.499, 14.994	-3.427, 3.57	1.285, 6.105	-4.248, 1.464	1.035, 13.209	-1.357, 1.785

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.

Reference Datasets:ADSL, ADLB
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\14.3.2.2.sas
Programmer:PJ
Date of Extraction:5Feb2023

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: BUN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	49	49	57	57	48	47
	Mean (SD)	2.87 (2.02)	-0.12 (1.20)	2.84 (1.45)	-0.04 (1.40)	3.15 (2.16)	0.13 (0.83)
	Median	2.57	-0.07	2.71	0.00	2.64	0.14
	Min, Max	0.785, 15.351	-4.177, 3.927	0.714, 11.603	-4.355, 8.14	1.499, 13.209	-1.571, 2.856
Day 29	n	49	49	55	55	48	47
	Mean (SD)	3.03 (2.04)	0.04 (1.17)	2.67 (0.89)	-0.23 (0.87)	3.10 (1.98)	0.13 (0.71)
	Median	2.61	0.00	2.75	-0.04	2.79	0.04
	Min, Max	0.785, 15.708	-3.856, 4.284	0.785, 5.034	-4.212, 1.499	1.25, 12.495	-1.642, 1.499
Day 43	n	48	48	56	56	48	48
	Mean (SD)	2.98 (2.10)	-0.04 (1.30)	2.84 (1.06)	-0.05 (1.01)	2.89 (1.95)	0.09 (0.99)
	Median	2.82	-0.18	2.71	0.07	2.50	-0.02
	Min, Max	1.107, 16.065	-3.82, 4.641	0.821, 6.997	-4.498, 4.177	1.642, 14.994	-1.714, 3.927

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: VERY LOW-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline	n	45		57		44	
	Mean (SD)	0.64 (0.30)		0.68 (0.29)		0.72 (0.37)	
	Median	0.57		0.61		0.60	
	Min, Max	0.176, 1.481		0.254, 1.487		0.223, 1.549	
Day 1	n	45	43	54	54	38	37
	Mean (SD)	0.80 (0.35)	0.15 (0.29)	0.75 (0.33)	0.08 (0.26)	0.70 (0.33)	0.04 (0.29)
	Median	0.71	0.09	0.66	0.06	0.66	0.03
	Min, Max	0.295, 1.538	-0.564, 0.963	0.29, 1.44	-0.632, 0.803	0.186, 1.466	-0.792, 0.912
Day 8	n	43	41	54	54	44	43
	Mean (SD)	0.73 (0.33)	0.12 (0.26)	0.68 (0.29)	0.02 (0.29)	0.72 (0.35)	0.01 (0.30)
	Median	0.65	0.07	0.60	-0.02	0.62	0.01
	Min, Max	0.197, 1.518	-0.497, 0.736	0.306, 1.425	-0.694, 1.005	0.218, 1.549	-0.948, 0.741

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.

Table 14.3.2.2
Summary of Change from Baseline in Laboratory Data: Chemistry
Safety Population

Test: VERY LOW-DENSITY LIPOPROTEIN (mmol/L)

		Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	n	44	42	52	52	43	42
	Mean (SD)	0.74 (0.35)	0.08 (0.29)	0.68 (0.29)	0.02 (0.27)	0.75 (0.38)	0.04 (0.25)
	Median	0.65	0.05	0.57	0.01	0.63	0.00
	Min, Max	0.161, 1.544	-0.616, 0.741	0.275, 1.497	-0.611, 0.715	0.259, 1.549	-0.71, 0.653
Day 29	n	45	43	49	49	39	38
	Mean (SD)	0.71 (0.33)	0.07 (0.28)	0.68 (0.28)	0.02 (0.27)	0.63 (0.24)	-0.03 (0.27)
	Median	0.64	0.05	0.59	-0.04	0.62	-0.01
	Min, Max	0.238, 1.544	-0.564, 1.026	0.29, 1.43	-0.928, 0.674	0.249, 1.212	-0.829, 0.518
Day 43	n	44	42	51	51	43	42
	Mean (SD)	0.76 (0.34)	0.11 (0.26)	0.66 (0.24)	0.01 (0.27)	0.72 (0.32)	0.01 (0.25)
	Median	0.71	0.05	0.63	0.00	0.66	0.06
	Min, Max	0.259, 1.549	-0.43, 0.819	0.269, 1.217	-0.643, 0.725	0.212, 1.492	-0.756, 0.466

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.

Table 14.3.2.3
Laboratory Hematology: Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline
Safety Population

Test Unit	Notable Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
EOSINOPHILS (ABS) (10^9/L)	>= 1.5	2 (4.0)	0 (0.0)	2 (4.0)
HB (g/L)	<= 0.85 x LLN	7 (14.0)	10 (16.7)	6 (12.0)
HCT (Proportion of 1.0)	<= 0.85 x LLN	2 (4.0)	5 (8.3)	4 (8.0)
PLATELETS (10^9/L)	<= 100	0 (0.0)	0 (0.0)	1 (2.0)
	>=600	1 (2.0)	1 (1.7)	0 (0.0)
WHITE BLOOD COUNT (10^9/L)	<= 3.0	1 (2.0)	3 (5.0)	0 (0.0)

Source: Listing 16.2.8.1, Clinical notable values source = Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023.
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: 32/14, Evenamide 15 mg BID: 36/10 and Evenamide 30 mg BID: 37/9) whenever the criterion is specific for Male/Female.

Table 14.3.2.4
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline
Safety Population

Test Unit	Notable Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
BICARBONATE (mmol/L)	<= 18	12(24.0)	16(26.7)	10(20.0)
	>=33	0(0.0)	1(1.7)	0(0.0)
CALCIUM (mmol/L)	<= 1.9	3(6.0)	2(3.3)	1(2.0)
	>= 2.7	1(2.0)	1(1.7)	0(0.0)
CREATINE KINASE (U/L)	>=400	2(4.0)	9(15.0)	7(14.0)
CREATININE (µmol/L)	>= 177	2(4.0)	3(5.0)	0(0.0)

Source: Listing 16.2.8.2, Clinical notable values source = Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023.
Glucose = Fasting Glucose or Random Glucose.
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: 32/14, Evenamide 15 mg BID: 36/10 and Evenamide 30 mg BID: 37/9) whenever the criterion is specific for Male/Female.

Table 14.3.2.4
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline
Safety Population

Test Unit	Notable Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
GLUCOSE (mmol/L)	>= 11.1	7(14.0)	5(8.3)	0(0.0)
HIGH-DENSITY LIPOPROTEIN (mmol/L)	<=0.8	19(38.0)	19(31.7)	21(42.0)
	>=2.3	1(2.0)	0(0.0)	1(2.0)
LDH (U/L)	>= 500	2(4.0)	1(1.7)	0(0.0)
LOW-DENSITY LIPOPROTEIN (mmol/L)	>= 4.1	4(8.0)	6(10.0)	7(14.0)
POTASSIUM (mmoI/L)	>= 6.0	1(2.0)	1(1.7)	0(0.0)

Source: Listing 16.2.8.2, Clinical notable values source = Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023.
Glucose = Fasting Glucose or Random Glucose.
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: 32/14, Evenamide 15 mg BID: 36/10 and Evenamide 30 mg BID: 37/9) whenever the criterion is specific for Male/Female.

Table 14.3.2.4
Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline
Safety Population

Test Unit	Notable Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
TOTAL BILIRUBIN (µmol/L)	>= 34	0(0.0)	0(0.0)	2(4.0)
TOTAL CHOLESTEROL (mmol/L)	>= 7.25	1(2.0)	3(5.0)	1(2.0)
TRIGLYCERIDES (mmol/L)	>= 4.5	2(4.0)	5(8.3)	4(8.0)

Source: Listing 16.2.8.2, Clinical notable values source = Lab Data SI Unit Conversion and Normalization, V1.0, 24JAN2023.
Glucose = Fasting Glucose or Random Glucose.
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: 32/14, Evenamide 15 mg BID: 36/10 and Evenamide 30 mg BID: 37/9) whenever the criterion is specific for Male/Female.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	24.8 (5.39)		24.6 (4.45)		26.0 (5.65)	
		Median	24.3		24.5		24.7	
		Min, Max	15, 37		17, 35		16, 44	
Baseline		n	50		60		50	
		Mean (SD)	24.8 (5.28)		24.7 (4.61)		26.0 (5.65)	
		Median	24.3		24.5		24.7	
		Min, Max	15, 37		17, 35		16, 44	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	24.8 (5.27)	0.0 (0.06)	24.7 (4.61)	0.0 (0.09)	26.0 (5.66)	-0.0 (0.06)
		Median	24.4	0.0	24.5	0.0	24.7	0.0
		Min, Max	15, 37	-0, 0	17, 35	-0, 0	16, 44	-0, 0
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	24.8 (5.28)	0.0 (0.05)	24.7 (4.62)	0.0 (0.07)	25.7 (5.41)	0.0 (0.06)
		Median	24.4	0.0	24.5	0.0	24.6	0.0
		Min, Max	15, 37	-0, 0	17, 35	-0, 0	16, 44	-0, 0

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	25.0 (5.16)	-0.0 (0.22)	24.8 (4.61)	0.0 (0.18)	25.8 (5.42)	0.0 (0.19)
		Median	24.5	0.0	24.8	0.0	24.6	0.0
		Min, Max	16, 37	-0, 1	17, 35	-0, 1	16, 44	-0, 1
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	25.0 (5.15)	0.0 (0.22)	24.8 (4.62)	0.0 (0.20)	25.9 (5.57)	-0.0 (0.45)
		Median	24.5	0.0	24.8	0.0	24.6	0.0
		Min, Max	16, 37	-0, 1	17, 35	-0, 1	16, 44	-3, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	25.0 (5.15)	0.0 (0.23)	24.9 (4.60)	0.0 (0.19)	25.9 (5.57)	-0.0 (0.45)
		Median	24.5	0.0	24.8	0.0	24.6	0.0
		Min, Max	16, 37	-0, 1	17, 35	-0, 1	16, 44	-3, 1
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	25.0 (5.11)	0.0 (0.28)	25.0 (4.58)	0.0 (0.24)	25.7 (5.51)	0.0 (0.54)
		Median	24.5	0.0	24.9	0.0	24.6	0.0
		Min, Max	16, 37	-1, 1	17, 35	-1, 1	16, 44	-3, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	25.1 (5.09)	0.0 (0.27)	24.9 (4.52)	0.1 (0.26)	25.9 (5.56)	-0.0 (0.52)
		Median	24.5	0.0	24.7	0.0	24.8	0.0
		Min, Max	16, 37	-1, 1	17, 35	-0, 1	16, 44	-3, 1
Day 29		n	49	49	56	56	49	49
		Mean (SD)	25.0 (5.11)	0.0 (0.32)	25.1 (4.68)	0.1 (0.33)	25.8 (5.48)	0.0 (0.55)
		Median	24.5	0.0	25.3	0.0	24.7	0.0
		Min, Max	16, 37	-1, 1	17, 36	-1, 1	16, 44	-3, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	25.1 (5.10)	0.1 (0.37)	25.1 (4.70)	0.1 (0.38)	25.5 (4.73)	0.1 (0.32)
		Median	24.5	0.0	25.3	0.1	24.6	0.1
		Min, Max	16, 37	-1, 1	17, 35	-1, 1	16, 38	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	18.5 (1.67)		18.3 (2.12)		18.4 (3.30)	
		Median	18.0		18.0		19.0	
		Min, Max	13, 22		12, 24		12, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	18.3 (1.45)		18.0 (2.17)		18.7 (3.58)	
		Median	18.0		18.0		19.0	
		Min, Max	15, 21		11, 21		10, 30	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	18.3 (1.72)	0.0 (0.88)	18.2 (2.17)	0.2 (0.99)	18.7 (3.35)	0.1 (1.30)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	13, 22	-2, 2	10, 22	-3, 3	10, 29	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	18.5 (1.89)	0.2 (0.93)	18.0 (2.29)	0.0 (1.04)	18.8 (3.72)	0.1 (1.09)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	14, 22	-2, 2	10, 22	-2, 4	10, 28	-2, 2
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	18.3 (1.69)	0.0 (0.97)	17.9 (2.32)	-0.1 (1.40)	18.4 (2.96)	-0.3 (2.13)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	13, 22	-2, 2	12, 24	-3, 6	11, 23	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	18.3 (1.72)	0.0 (1.05)	18.0 (2.40)	-0.0 (1.27)	18.1 (2.95)	-0.5 (1.99)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	14, 22	-3, 2	10, 24	-2, 6	10, 24	-7, 4
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	18.3 (1.80)	0.0 (0.87)	18.1 (2.35)	0.1 (1.13)	18.2 (3.13)	-0.3 (2.05)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	13, 22	-2, 2	10, 22	-2, 4	10, 24	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	18.4 (2.08)	0.2 (1.11)	18.2 (2.64)	0.2 (1.53)	18.6 (3.10)	-0.1 (2.11)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	13, 24	-2, 3	10, 28	-3, 8	10, 24	-9, 6
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	18.3 (1.90)	0.0 (0.95)	18.1 (2.36)	0.2 (1.11)	18.5 (2.89)	-0.1 (1.75)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	14, 24	-2, 3	11, 22	-2, 4	12, 24	-7, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	18.5 (1.65)	0.2 (1.09)	18.2 (2.19)	0.2 (1.06)	18.7 (3.10)	0.0 (2.09)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	15, 22	-3, 3	12, 22	-2, 4	10, 24	-7, 5
Day 43		n	49	49	56	56	48	48
		Mean (SD)	18.3 (1.99)	0.1 (1.33)	18.4 (2.27)	0.4 (1.15)	19.3 (2.95)	0.5 (2.16)
		Median	18.0	0.0	18.0	0.0	19.0	0.0
		Min, Max	13, 22	-4, 4	12, 22	-2, 4	12, 27	-4, 7

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	78.3 (8.67)		78.8 (10.10)		78.5 (10.46)	
		Median	78.0		80.0		77.0	
		Min, Max	60, 96		53, 98		62, 98	
Baseline		n	50		60		50	
		Mean (SD)	76.8 (8.26)		76.6 (8.36)		79.9 (9.99)	
		Median	79.0		78.0		78.0	
		Min, Max	52, 97		57, 93		61, 99	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	77.3 (7.92)	0.5 (4.58)	76.0 (7.91)	-0.6 (5.11)	80.5 (9.52)	0.6 (7.58)
		Median	78.0	0.0	78.0	0.0	81.0	0.5
		Min, Max	59, 94	-13, 13	60, 90	-19, 10	59, 99	-16, 20
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	78.4 (7.79)	1.6 (4.85)	77.5 (8.55)	0.9 (5.84)	80.0 (9.88)	0.4 (7.60)
		Median	79.0	1.5	78.0	0.5	80.0	0.0
		Min, Max	56, 96	-11, 12	58, 99	-15, 20	61, 106	-20, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	76.0 (8.38)	-0.7 (6.41)	76.7 (8.78)	0.2 (6.88)	78.2 (9.51)	-1.5 (8.47)
		Median	77.0	-1.0	78.0	0.0	78.0	-1.0
		Min, Max	55, 92	-16, 15	54, 96	-19, 15	60, 98	-22, 16
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	77.7 (7.25)	1.1 (7.97)	77.6 (8.52)	1.0 (7.12)	80.6 (11.11)	0.8 (9.50)
		Median	80.0	1.0	78.0	0.0	82.0	0.0
		Min, Max	60, 88	-24, 20	52, 98	-15, 25	60, 100	-20, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	75.8 (7.24)	-0.9 (8.12)	76.9 (8.32)	0.5 (7.16)	79.7 (9.56)	-0.1 (9.80)
		Median	76.0	-1.0	77.0	1.0	82.0	-1.0
		Min, Max	54, 90	-26, 19	56, 94	-15, 23	60, 96	-21, 20
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	76.3 (8.83)	-0.4 (8.31)	75.7 (8.61)	-1.0 (7.06)	78.0 (9.89)	-1.6 (8.14)
		Median	78.0	0.0	76.0	-1.0	78.0	-2.0
		Min, Max	54, 92	-19, 18	54, 92	-19, 14	56, 98	-25, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	76.2 (7.73)	-0.4 (8.60)	77.4 (8.67)	0.4 (6.65)	80.6 (10.01)	0.8 (9.31)
		Median	78.0	0.0	78.0	0.0	80.0	-1.0
		Min, Max	56, 92	-25, 16	52, 92	-20, 16	60, 100	-14, 26
Day 29		n	49	49	56	56	49	49
		Mean (SD)	75.0 (8.43)	-1.6 (8.31)	77.6 (8.99)	0.9 (7.40)	79.7 (8.71)	0.1 (8.91)
		Median	74.0	-1.0	78.5	1.0	80.0	1.0
		Min, Max	56, 93	-22, 17	58, 97	-17, 22	60, 99	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	75.3 (8.46)	-1.3 (7.11)	77.1 (8.62)	0.4 (7.25)	78.5 (9.44)	-0.9 (8.67)
		Median	76.0	-1.0	78.0	0.5	77.0	-1.0
		Min, Max	57, 92	-14, 13	60, 96	-14, 19	60, 99	-25, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	82.9 (9.49)		83.0 (9.39)		83.5 (9.20)	
		Median	83.5		84.0		82.0	
		Min, Max	63, 102		56, 100		66, 100	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	80.8 (8.85)		81.1 (8.85)		83.9 (9.82)	
		Median	81.0		81.5		85.0	
		Min, Max	57, 96		59, 98		59, 97	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	82.1 (9.28)	1.3 (5.41)	80.4 (9.47)	-0.7 (5.42)	84.3 (10.42)	0.4 (5.43)
		Median	83.0	1.0	83.5	-1.0	85.5	0.0
		Min, Max	63, 98	-7, 23	58, 100	-15, 25	61, 104	-9, 20

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	82.2 (8.87)	1.5 (4.36)	81.5 (9.40)	0.4 (6.06)	84.3 (10.77)	0.7 (5.59)
		Median	82.5	2.0	82.0	1.0	82.0	0.0
		Min, Max	62, 98	-9, 15	56, 108	-17, 20	61, 122	-8, 25
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	80.2 (9.91)	-0.3 (6.71)	81.5 (10.02)	0.4 (7.03)	82.8 (9.81)	-0.9 (8.34)
		Median	84.0	0.0	82.0	1.0	82.0	0.0
		Min, Max	56, 100	-23, 13	50, 102	-17, 15	61, 99	-24, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	81.1 (9.47)	0.6 (8.00)	81.8 (9.40)	0.7 (6.62)	85.3 (11.61)	1.4 (8.99)
		Median	82.0	0.0	82.0	1.0	86.0	1.0
		Min, Max	62, 109	-25, 19	58, 100	-15, 18	59, 112	-22, 24
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	80.6 (9.64)	0.1 (7.41)	81.2 (9.42)	0.2 (6.61)	83.6 (9.60)	-0.3 (7.69)
		Median	82.0	0.0	82.0	1.0	87.0	-1.0
		Min, Max	56, 100	-27, 17	52, 98	-16, 13	58, 98	-20, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	80.1 (10.82)	-0.4 (7.78)	81.0 (9.81)	-0.3 (7.00)	83.2 (9.99)	-0.5 (7.93)
		Median	82.0	0.0	83.0	0.0	84.0	1.0
		Min, Max	57, 100	-21, 17	50, 99	-22, 13	56, 100	-21, 20
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	80.3 (9.04)	-0.2 (7.62)	81.2 (9.14)	-0.3 (7.14)	84.3 (10.63)	0.4 (9.19)
		Median	81.0	0.0	82.0	0.0	86.0	-1.0
		Min, Max	56, 93	-23, 17	58, 99	-20, 13	57, 103	-20, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	78.7 (9.85)	-1.8 (8.10)	81.3 (9.75)	-0.0 (7.31)	83.3 (8.74)	-0.3 (9.13)
		Median	78.0	-1.0	82.0	0.0	84.0	1.0
		Min, Max	56, 105	-21, 15	54, 98	-15, 29	64, 100	-29, 13
Day 43		n	49	49	56	56	48	48
		Mean (SD)	80.4 (9.45)	-0.1 (6.08)	81.6 (8.49)	0.3 (6.85)	83.1 (9.10)	-0.5 (7.88)
		Median	80.0	1.0	83.0	-0.5	82.0	0.0
		Min, Max	58, 95	-11, 13	56, 98	-13, 19	62, 101	-19, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	81.3 (9.41)		81.3 (9.57)		82.4 (9.14)	
		Median	80.0		82.0		82.0	
		Min, Max	61, 100		54, 100		65, 100	
Baseline		n	50		60		50	
		Mean (SD)	79.3 (8.87)		79.7 (8.41)		82.9 (9.76)	
		Median	81.0		81.0		81.5	
		Min, Max	57, 97		58, 99		60, 99	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	80.9 (9.11)	1.6 (5.23)	79.2 (8.35)	-0.5 (4.94)	84.2 (10.58)	1.2 (5.88)
		Median	82.0	0.0	80.5	0.5	84.0	0.0
		Min, Max	59, 96	-7, 19	59, 94	-13, 10	59, 108	-11, 15
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	80.2 (9.33)	0.9 (4.65)	80.6 (8.81)	1.0 (6.08)	83.7 (11.29)	1.0 (6.33)
		Median	80.0	1.0	82.0	1.0	82.0	-1.0
		Min, Max	58, 98	-8, 19	60, 99	-15, 20	60, 119	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	78.5 (9.50)	-0.5 (6.29)	80.3 (9.53)	0.8 (6.85)	82.5 (9.67)	-0.2 (7.39)
		Median	80.0	0.0	82.0	1.0	84.0	1.0
		Min, Max	55, 102	-19, 14	52, 98	-15, 17	58, 100	-24, 11
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	79.9 (9.47)	0.9 (8.22)	80.7 (9.50)	1.1 (7.15)	83.4 (11.22)	0.5 (8.03)
		Median	82.0	0.0	82.0	2.0	82.0	1.0
		Min, Max	57, 106	-23, 26	52, 98	-15, 16	61, 108	-24, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	79.4 (9.04)	0.4 (7.61)	79.8 (9.06)	0.5 (6.45)	81.9 (9.67)	-1.0 (7.50)
		Median	80.0	1.0	82.0	1.5	83.0	-2.0
		Min, Max	58, 102	-25, 17	54, 98	-15, 13	60, 96	-24, 15
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	79.1 (10.07)	0.1 (8.11)	79.7 (8.88)	-0.1 (6.83)	81.9 (10.34)	-0.8 (7.78)
		Median	80.0	1.0	80.0	1.0	81.0	0.0
		Min, Max	56, 97	-21, 16	54, 94	-25, 15	60, 99	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	78.7 (8.47)	-0.3 (8.18)	80.0 (8.99)	0.2 (7.39)	83.2 (10.70)	0.3 (7.90)
		Median	82.0	1.0	82.0	1.0	84.0	-1.0
		Min, Max	57, 95	-21, 18	52, 94	-21, 13	59, 100	-17, 16
Day 29		n	49	49	56	56	49	49
		Mean (SD)	78.3 (9.37)	-0.7 (8.07)	80.7 (8.56)	1.0 (7.59)	81.6 (9.32)	-1.0 (9.54)
		Median	78.0	0.0	82.0	1.0	83.0	1.0
		Min, Max	57, 104	-23, 16	58, 95	-17, 26	62, 97	-31, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	78.0 (9.35)	-1.0 (7.18)	80.7 (8.04)	0.9 (7.02)	82.3 (8.88)	-0.4 (8.50)
		Median	80.0	-1.0	82.0	1.0	81.0	0.5
		Min, Max	58, 97	-19, 14	58, 98	-15, 21	65, 100	-19, 25

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	119.6 (7.42)		119.8 (7.21)		120.5 (7.38)	
		Median	120.0		120.0		120.0	
		Min, Max	101, 135		100, 139		106, 138	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	119.0 (6.17)		119.5 (7.57)		120.2 (5.98)	
		Median	120.0		119.5		120.5	
		Min, Max	101, 130		93, 141		105, 135	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	119.3 (6.85)	0.3 (3.24)	119.3 (7.38)	-0.2 (4.87)	121.3 (5.93)	1.0 (3.00)
		Median	120.0	1.0	119.0	0.0	120.0	0.0
		Min, Max	99, 132	-8, 10	100, 140	-12, 14	104, 138	-4, 7

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	119.0 (6.13)	0.0 (4.64)	119.3 (6.55)	-0.2 (5.40)	120.4 (6.32)	0.1 (4.35)
		Median	120.0	1.0	120.0	0.5	120.0	0.0
		Min, Max	102, 130	-12, 10	102, 132	-30, 12	102, 140	-8, 17
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	118.1 (7.30)	-0.8 (5.02)	119.1 (7.86)	-0.2 (4.56)	121.7 (6.52)	1.4 (5.44)
		Median	118.0	-1.0	120.0	0.0	121.0	1.0
		Min, Max	91, 135	-12, 9	90, 135	-13, 11	105, 138	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	119.8 (8.14)	0.9 (5.50)	118.1 (7.81)	-1.3 (5.80)	120.0 (6.27)	-0.3 (4.92)
		Median	120.0	1.0	118.0	-1.0	120.0	0.0
		Min, Max	88, 135	-13, 18	99, 132	-18, 14	100, 132	-13, 7
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	118.9 (8.79)	0.0 (5.53)	118.3 (6.38)	-1.2 (5.22)	120.7 (6.25)	0.4 (4.94)
		Median	120.0	0.0	118.0	-1.0	120.0	0.0
		Min, Max	80, 132	-21, 12	100, 130	-16, 12	103, 135	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	118.6 (7.20)	-0.3 (4.68)	119.2 (8.60)	-0.1 (6.02)	119.9 (6.98)	-0.4 (5.04)
		Median	120.0	0.0	120.0	0.0	120.0	-1.0
		Min, Max	102, 135	-12, 9	93, 138	-19, 14	104, 134	-10, 11
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	118.9 (7.19)	0.0 (4.26)	119.4 (6.40)	-0.4 (4.78)	119.6 (6.86)	-0.7 (4.74)
		Median	120.0	0.0	120.0	0.0	120.0	0.0
		Min, Max	104, 132	-14, 10	102, 132	-17, 10	102, 132	-11, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	118.7 (6.76)	-0.2 (6.04)	119.3 (6.64)	0.1 (6.75)	120.0 (6.26)	-0.2 (5.15)
		Median	120.0	0.0	120.0	0.0	120.0	0.0
		Min, Max	102, 135	-14, 15	102, 132	-16, 28	103, 130	-13, 13
Day 43		n	49	49	56	56	48	48
		Mean (SD)	118.6 (6.30)	-0.3 (4.35)	118.8 (7.89)	-0.4 (6.72)	120.8 (6.98)	0.4 (5.59)
		Median	120.0	0.0	120.0	0.0	120.0	0.0
		Min, Max	98, 130	-13, 10	98, 140	-19, 16	100, 136	-13, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	120.2 (6.97)		119.3 (8.15)		119.0 (7.39)	
		Median	120.0		120.0		118.0	
		Min, Max	102, 142		99, 138		105, 140	
Baseline		n	50		60		50	
		Mean (SD)	118.7 (5.06)		118.8 (7.17)		119.4 (6.10)	
		Median	119.0		119.0		119.0	
		Min, Max	104, 129		91, 135		102, 132	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	119.3 (6.37)	0.7 (4.53)	119.0 (7.88)	0.2 (3.93)	119.7 (6.14)	0.3 (3.29)
		Median	120.0	1.0	120.0	0.0	118.5	0.0
		Min, Max	96, 136	-8, 19	94, 138	-9, 12	104, 132	-9, 7
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	118.1 (6.00)	-0.6 (4.91)	119.0 (7.51)	0.2 (5.46)	119.4 (7.53)	-0.0 (4.61)
		Median	118.0	0.5	118.0	1.0	120.0	0.0
		Min, Max	97, 130	-13, 15	100, 136	-26, 11	100, 135	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	118.2 (7.15)	-0.3 (4.65)	118.1 (8.59)	-0.5 (5.14)	120.2 (6.50)	0.8 (6.09)
		Median	120.0	-1.0	118.0	0.0	120.0	0.0
		Min, Max	84, 136	-20, 10	90, 143	-17, 11	102, 135	-15, 24
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	119.4 (8.34)	0.9 (5.85)	118.0 (7.40)	-0.6 (4.05)	118.6 (6.66)	-0.7 (6.10)
		Median	120.0	1.0	118.0	-1.0	119.0	0.0
		Min, Max	84, 135	-20, 14	92, 136	-9, 16	102, 131	-15, 20

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	119.2 (7.45)	0.7 (5.50)	117.7 (7.54)	-1.0 (4.09)	119.4 (6.47)	0.0 (5.84)
		Median	120.0	1.0	118.0	-1.0	118.0	0.0
		Min, Max	88, 130	-16, 15	94, 134	-11, 8	102, 130	-17, 17
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	118.3 (6.79)	-0.2 (4.99)	117.5 (7.07)	-0.9 (5.31)	118.9 (7.49)	-0.6 (5.86)
		Median	118.0	1.0	118.0	0.0	118.0	-1.0
		Min, Max	94, 130	-18, 12	91, 130	-20, 10	100, 130	-20, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	117.8 (6.84)	-0.7 (4.14)	118.0 (6.36)	-0.9 (3.82)	118.6 (7.55)	-0.8 (5.72)
		Median	118.0	0.0	118.0	-1.0	120.0	0.0
		Min, Max	98, 136	-17, 7	100, 134	-9, 7	102, 134	-18, 12
Day 29		n	49	49	56	56	49	49
		Mean (SD)	118.8 (6.55)	0.3 (4.29)	119.5 (6.52)	1.1 (6.53)	118.8 (7.67)	-0.7 (7.27)
		Median	118.0	0.0	120.0	0.0	120.0	0.0
		Min, Max	100, 138	-11, 9	105, 138	-11, 25	100, 139	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	118.7 (6.63)	0.2 (5.14)	118.5 (8.30)	0.1 (6.36)	120.2 (6.96)	0.8 (5.85)
		Median	118.0	-1.0	118.0	0.0	120.0	0.0
		Min, Max	99, 131	-8, 18	93, 142	-14, 24	102, 133	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	118.0 (7.79)		117.7 (8.70)		118.1 (7.44)	
		Median	118.0		120.0		119.0	
		Min, Max	102, 144		93, 142		105, 136	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	116.4 (5.85)		117.3 (7.35)		117.0 (6.46)	
		Median	118.0		118.5		118.0	
		Min, Max	101, 130		92, 135		100, 129	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	117.1 (6.58)	0.7 (3.16)	117.6 (7.50)	0.3 (3.73)	117.5 (5.77)	0.5 (4.21)
		Median	118.0	0.0	118.0	0.0	118.0	0.0
		Min, Max	96, 130	-6, 9	100, 138	-9, 13	102, 129	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	117.3 (6.38)	0.8 (4.57)	117.1 (6.67)	-0.2 (4.17)	118.2 (7.68)	1.2 (5.11)
		Median	118.0	0.0	118.0	1.0	118.0	1.0
		Min, Max	100, 130	-9, 18	100, 132	-19, 10	100, 140	-8, 18
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	116.1 (7.35)	-0.2 (5.46)	116.8 (8.45)	-0.2 (5.62)	118.4 (6.99)	1.5 (5.26)
		Median	118.0	0.0	118.0	1.0	118.0	1.0
		Min, Max	88, 130	-13, 20	90, 138	-15, 16	100, 135	-8, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	116.9 (8.28)	0.6 (5.73)	116.2 (6.29)	-0.8 (5.50)	117.2 (6.91)	0.3 (5.71)
		Median	118.0	0.0	116.0	0.0	118.0	0.0
		Min, Max	86, 134	-15, 19	100, 130	-29, 12	100, 134	-10, 21
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	116.9 (7.73)	0.6 (5.52)	116.9 (6.77)	-0.1 (4.12)	117.8 (6.71)	0.9 (5.60)
		Median	118.0	0.0	117.0	1.0	118.0	1.0
		Min, Max	86, 130	-15, 19	97, 132	-13, 11	100, 132	-12, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	116.3 (6.95)	0.0 (4.22)	115.9 (6.42)	-1.1 (4.99)	116.0 (6.88)	-1.0 (6.14)
		Median	120.0	0.0	118.0	0.0	116.0	-1.0
		Min, Max	98, 130	-13, 10	91, 128	-20, 9	100, 129	-19, 11
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	116.8 (6.64)	0.5 (3.37)	117.2 (5.52)	-0.2 (4.46)	116.7 (6.65)	-0.1 (6.03)
		Median	118.0	0.0	118.0	1.0	118.0	0.0
		Min, Max	98, 136	-6, 12	102, 130	-15, 13	104, 131	-15, 20

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	116.1 (6.63)	-0.2 (4.61)	116.9 (6.28)	0.0 (4.82)	117.9 (7.29)	1.0 (7.06)
		Median	116.0	0.0	120.0	1.0	118.0	1.0
		Min, Max	100, 129	-10, 16	100, 130	-12, 11	101, 140	-15, 20
Day 43		n	49	49	56	56	48	48
		Mean (SD)	117.1 (6.42)	0.8 (5.08)	116.4 (7.70)	-0.5 (5.72)	118.9 (7.69)	1.8 (6.14)
		Median	118.0	0.0	117.0	-1.0	120.0	1.0
		Min, Max	98, 128	-8, 18	97, 142	-14, 21	100, 136	-13, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	79.0 (5.04)		79.1 (4.65)		80.0 (6.45)	
		Median	80.0		80.0		80.0	
		Min, Max	67, 91		70, 90		70, 103	
Baseline		n	50		60		50	
		Mean (SD)	77.9 (3.85)		79.0 (4.90)		79.7 (5.27)	
		Median	79.0		79.0		80.0	
		Min, Max	67, 84		65, 93		65, 93	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	78.7 (4.99)	0.7 (3.13)	78.9 (5.02)	-0.1 (4.48)	80.3 (5.38)	0.7 (3.80)
		Median	80.0	1.0	80.0	0.5	80.0	1.0
		Min, Max	63, 88	-7, 8	65, 94	-12, 15	69, 93	-7, 10
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	78.3 (5.41)	0.3 (3.23)	78.6 (4.70)	-0.4 (4.35)	80.2 (4.92)	0.5 (3.13)
		Median	80.0	0.0	80.0	0.0	80.0	0.0
		Min, Max	64, 90	-7, 11	60, 88	-18, 8	66, 94	-7, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	78.4 (4.39)	0.6 (3.51)	78.2 (5.79)	-0.7 (4.67)	80.6 (4.57)	0.9 (3.72)
		Median	80.0	0.0	80.0	-1.0	82.0	0.0
		Min, Max	66, 90	-8, 10	60, 94	-12, 20	68, 89	-7, 11
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	78.5 (5.26)	0.7 (4.01)	77.5 (5.05)	-1.4 (5.22)	79.0 (5.19)	-0.6 (3.32)
		Median	80.0	1.0	80.0	0.0	80.0	0.0
		Min, Max	57, 90	-10, 12	64, 88	-17, 13	62, 90	-10, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	78.0 (4.91)	0.1 (3.44)	76.9 (4.86)	-1.9 (4.72)	79.6 (5.19)	0.1 (3.71)
		Median	80.0	0.0	78.0	-1.0	80.0	0.0
		Min, Max	68, 90	-9, 10	60, 88	-17, 7	66, 89	-9, 10
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	77.6 (5.34)	-0.2 (3.70)	78.4 (5.46)	-0.6 (4.51)	80.2 (5.67)	0.5 (4.42)
		Median	80.0	0.0	80.0	0.0	80.0	0.0
		Min, Max	60, 90	-10, 10	60, 91	-13, 15	68, 98	-11, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	78.2 (4.32)	0.4 (3.17)	78.5 (4.72)	-0.7 (4.37)	78.3 (6.90)	-1.2 (4.49)
		Median	80.0	0.0	80.0	-1.0	80.0	0.0
		Min, Max	70, 90	-7, 10	62, 86	-9, 15	55, 98	-20, 11
Day 29		n	49	49	56	56	49	49
		Mean (SD)	79.1 (4.69)	1.3 (4.80)	79.8 (5.73)	0.8 (7.11)	78.6 (5.12)	-1.1 (4.48)
		Median	80.0	1.0	80.0	0.5	80.0	-1.0
		Min, Max	70, 90	-11, 17	60, 100	-17, 35	60, 93	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	78.5 (5.17)	0.7 (3.88)	78.7 (5.28)	-0.3 (5.75)	79.2 (6.22)	-0.4 (4.68)
		Median	80.0	1.0	80.0	-1.0	80.0	-1.0
		Min, Max	65, 90	-6, 12	66, 90	-17, 25	65, 101	-10, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	80.0 (5.53)		79.0 (5.45)		80.0 (6.73)	
		Median	80.0		78.0		78.5	
		Min, Max	72, 95		70, 91		70, 106	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	78.8 (4.17)		79.2 (5.06)		79.7 (4.85)	
		Median	79.0		79.0		79.0	
		Min, Max	72, 93		70, 92		71, 90	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	79.1 (5.21)	0.2 (3.38)	77.9 (5.99)	-1.3 (3.56)	80.0 (5.16)	0.3 (3.16)
		Median	78.0	0.5	78.0	-1.0	79.5	0.0
		Min, Max	68, 92	-6, 12	60, 90	-10, 6	70, 91	-10, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	79.2 (4.81)	0.3 (3.51)	78.3 (5.87)	-0.9 (3.88)	80.5 (6.11)	0.8 (3.78)
		Median	80.0	0.0	78.0	-1.0	78.0	1.0
		Min, Max	70, 90	-9, 11	60, 90	-16, 7	72, 94	-13, 13
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	79.3 (4.15)	0.7 (3.47)	78.0 (6.45)	-1.1 (4.43)	79.4 (5.53)	-0.3 (4.30)
		Median	78.0	1.0	78.0	-1.0	80.0	0.0
		Min, Max	68, 89	-10, 12	62, 94	-9, 15	65, 92	-15, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	78.7 (4.08)	0.1 (3.40)	78.8 (5.54)	-0.2 (4.76)	79.4 (4.48)	-0.3 (4.57)
		Median	80.0	0.0	78.0	1.0	79.0	0.0
		Min, Max	68, 86	-10, 7	68, 94	-14, 12	70, 88	-15, 11
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	77.9 (5.02)	-0.7 (3.84)	77.8 (4.99)	-1.2 (4.51)	78.9 (5.51)	-0.8 (4.52)
		Median	78.0	0.0	78.0	0.0	78.0	0.0
		Min, Max	64, 90	-10, 8	60, 88	-13, 7	69, 90	-13, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	78.6 (5.11)	0.1 (4.00)	78.6 (4.81)	-0.4 (3.71)	80.0 (6.94)	0.3 (5.47)
		Median	78.0	1.0	78.0	0.0	79.0	0.0
		Min, Max	66, 94	-9, 12	68, 92	-12, 8	68, 98	-11, 14
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	78.4 (5.34)	-0.1 (4.49)	78.4 (4.81)	-0.7 (3.93)	77.6 (6.64)	-2.1 (5.11)
		Median	78.0	0.0	78.0	-1.0	78.0	-1.0
		Min, Max	67, 94	-10, 13	66, 90	-11, 10	60, 98	-17, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	79.3 (4.86)	0.8 (3.92)	79.7 (4.96)	0.8 (5.48)	78.7 (6.13)	-1.1 (4.91)
		Median	78.0	0.0	79.0	0.0	78.0	-1.0
		Min, Max	70, 94	-7, 12	67, 92	-10, 20	60, 94	-16, 8
Day 43		n	49	49	56	56	48	48
		Mean (SD)	78.4 (6.36)	-0.1 (4.84)	78.9 (5.21)	-0.0 (4.27)	80.0 (6.38)	0.3 (5.47)
		Median	78.0	0.0	78.0	-0.5	80.0	0.5
		Min, Max	60, 96	-13, 14	66, 90	-11, 10	70, 101	-14, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	78.4 (5.79)		78.2 (6.41)		79.0 (7.47)	
		Median	80.0		80.0		80.0	
		Min, Max	68, 94		68, 95		68, 107	
Baseline		n	50		60		50	
		Mean (SD)	77.4 (4.50)		78.0 (5.05)		78.0 (4.69)	
		Median	79.0		79.0		78.0	
		Min, Max	70, 89		64, 90		70, 89	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	77.6 (5.47)	0.2 (3.38)	77.4 (5.95)	-0.6 (3.71)	79.0 (5.20)	0.9 (3.07)
		Median	80.0	0.0	78.0	0.0	80.0	1.0
		Min, Max	66, 90	-6, 12	60, 94	-14, 9	70, 89	-8, 8
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	78.0 (5.32)	0.6 (3.45)	77.3 (5.60)	-0.7 (3.43)	79.4 (6.24)	1.4 (3.86)
		Median	79.0	0.0	78.0	-1.0	80.0	1.0
		Min, Max	68, 92	-8, 14	60, 94	-12, 9	70, 94	-6, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	77.4 (5.15)	0.3 (3.64)	77.6 (6.34)	-0.3 (3.49)	78.7 (5.05)	0.7 (3.98)
		Median	78.0	0.0	78.0	0.0	78.0	0.0
		Min, Max	65, 87	-9, 10	60, 92	-9, 10	68, 91	-5, 11
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	77.4 (5.20)	0.2 (3.02)	77.7 (5.67)	-0.2 (4.58)	78.6 (5.63)	0.6 (3.90)
		Median	78.0	0.0	78.0	0.0	80.0	0.0
		Min, Max	66, 90	-8, 12	66, 95	-12, 16	65, 90	-7, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	76.8 (5.13)	-0.3 (3.30)	77.3 (5.28)	-0.6 (3.68)	78.6 (5.18)	0.6 (3.85)
		Median	78.0	-1.0	78.0	0.0	78.0	1.0
		Min, Max	68, 92	-9, 12	60, 86	-10, 7	70, 90	-8, 15
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	77.2 (5.48)	0.1 (3.50)	77.5 (5.56)	-0.3 (4.79)	78.8 (7.26)	0.8 (4.95)
		Median	78.0	0.0	78.0	0.0	78.0	0.0
		Min, Max	65, 91	-9, 11	67, 95	-18, 9	69, 98	-9, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	77.3 (5.61)	0.2 (4.19)	77.8 (5.56)	-0.1 (4.51)	77.6 (6.08)	-0.3 (4.12)
		Median	78.0	0.0	78.0	-1.0	78.0	0.0
		Min, Max	65, 95	-9, 15	65, 92	-9, 20	65, 97	-10, 12
Day 29		n	49	49	56	56	49	49
		Mean (SD)	78.1 (5.44)	1.0 (4.30)	78.1 (4.81)	0.3 (5.36)	78.1 (5.38)	0.1 (4.45)
		Median	80.0	1.0	78.0	-0.5	78.0	0.0
		Min, Max	70, 91	-9, 11	69, 92	-9, 16	68, 96	-13, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	77.9 (6.28)	0.8 (5.36)	77.8 (7.04)	-0.0 (6.90)	78.6 (6.18)	0.5 (5.23)
		Median	79.0	0.0	78.0	-1.0	78.0	0.0
		Min, Max	70, 101	-9, 21	50, 94	-28, 26	70, 104	-10, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	36.7 (0.28)		36.7 (0.33)		36.7 (0.30)	
		Median	36.8		36.8		36.8	
		Min, Max	36, 37		35, 37		36, 37	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Baseline		n	50		60		50	
		Mean (SD)	36.6 (0.23)		36.7 (0.33)		36.7 (0.33)	
		Median	36.7		36.7		36.7	
		Min, Max	36, 37		35, 37		36, 37	
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	36.7 (0.24)	0.1 (0.17)	36.6 (0.34)	-0.0 (0.20)	36.6 (0.39)	-0.0 (0.16)
		Median	36.8	0.0	36.7	-0.0	36.8	0.0
		Min, Max	36, 37	-0, 1	36, 37	-1, 1	35, 37	-1, 0

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	36.7 (0.29)	0.1 (0.28)	36.7 (0.34)	0.0 (0.24)	36.6 (0.33)	0.0 (0.24)
		Median	36.8	0.1	36.7	0.0	36.7	0.0
		Min, Max	36, 37	-1, 1	35, 37	-1, 1	36, 37	-1, 1
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	36.7 (0.27)	0.1 (0.27)	36.7 (0.32)	0.0 (0.27)	36.7 (0.32)	0.0 (0.23)
		Median	36.8	0.1	36.8	0.0	36.7	0.0
		Min, Max	36, 37	-1, 1	36, 37	-1, 1	35, 37	-1, 0

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	36.6 (0.40)	-0.0 (0.30)	36.6 (0.30)	-0.0 (0.24)	36.6 (0.33)	-0.0 (0.18)
		Median	36.7	0.0	36.7	0.0	36.7	-0.0
		Min, Max	35, 37	-1, 0	36, 37	-1, 1	36, 37	-1, 1
	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	36.7 (0.28)	0.0 (0.26)	36.7 (0.33)	0.0 (0.23)	36.7 (0.31)	-0.0 (0.19)
		Median	36.8	0.0	36.8	0.0	36.7	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	36.6 (0.36)	-0.0 (0.33)	36.7 (0.28)	0.0 (0.26)	36.6 (0.35)	0.0 (0.20)
		Median	36.7	0.0	36.7	0.0	36.8	0.0
		Min, Max	35, 37	-1, 1	36, 37	-1, 1	36, 37	-1, 0
	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	36.7 (0.35)	0.0 (0.35)	36.7 (0.27)	0.0 (0.23)	36.6 (0.33)	-0.0 (0.22)
		Median	36.8	0.1	36.8	0.0	36.7	-0.0
		Min, Max	36, 37	-1, 1	36, 37	-1, 1	36, 37	-1, 0

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 29		n	49	49	56	56	49	49
		Mean (SD)	36.8 (0.31)	0.1 (0.31)	36.8 (0.29)	0.1 (0.26)	36.7 (0.31)	0.0 (0.25)
		Median	36.8	0.1	36.8	0.1	36.7	-0.0
		Min, Max	36, 37	-1, 1	36, 37	-1, 1	36, 37	-1, 1
Day 43		n	49	49	56	56	48	48
		Mean (SD)	36.7 (0.26)	0.0 (0.28)	36.7 (0.31)	0.1 (0.27)	36.7 (0.24)	0.0 (0.25)
		Median	36.7	0.0	36.8	0.1	36.7	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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	93.5 (12.60)		90.6 (11.45)		91.5 (13.75)	
		Median	92.0		88.5		90.2	
		Min, Max	69, 126		62, 115		64, 150	
Day 43		n	49	49	56	56	48	48
		Mean (SD)	94.0 (12.45)	0.1 (0.97)	91.3 (12.15)	0.3 (3.49)	90.6 (11.17)	0.6 (3.92)
		Median	92.0	0.0	89.3	0.0	90.2	0.0
		Min, Max	69, 127	-3, 5	62, 119	-13, 20	64, 114	-5, 25

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening		n	50		60		50	
		Mean (SD)	66.6 (15.67)		65.9 (12.27)		69.9 (17.31)	
		Median	66.5		64.7		65.9	
		Min, Max	34, 120		44, 91		42, 143	
Baseline		n	50		60		50	
		Mean (SD)	66.6 (15.56)		66.2 (12.63)		69.9 (17.33)	
		Median	66.6		64.8		65.8	
		Min, Max	34, 120		45, 91		42, 143	

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 1	1 hour Post Dose	n	50	50	60	60	50	50
		Mean (SD)	66.6 (15.56)	0.1 (0.17)	66.3 (12.63)	0.1 (0.23)	69.9 (17.34)	-0.0 (0.17)
		Median	66.6	0.0	64.8	0.0	65.8	0.0
		Min, Max	34, 120	-0, 1	45, 91	-0, 1	42, 143	-1, 0
	4 hour Post Dose	n	50	50	60	60	49	49
		Mean (SD)	66.6 (15.56)	0.0 (0.13)	66.3 (12.65)	0.0 (0.16)	69.4 (17.09)	0.0 (0.16)
		Median	66.6	0.0	64.8	0.0	65.3	0.0
		Min, Max	34, 120	-0, 1	45, 91	-0, 1	42, 143	-1, 0

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	Pre-dose	n	49	49	59	59	49	49
		Mean (SD)	67.2 (14.93)	-0.0 (0.58)	66.5 (12.63)	0.1 (0.47)	69.5 (17.13)	0.1 (0.48)
		Median	67.0	0.0	65.6	0.0	65.4	0.0
		Min, Max	42, 120	-1, 2	44, 92	-1, 2	42, 144	-1, 2
	1 hour Post Dose	n	49	49	59	59	47	47
		Mean (SD)	67.2 (14.93)	0.0 (0.57)	66.6 (12.65)	0.1 (0.53)	69.8 (17.58)	-0.0 (1.16)
		Median	67.0	0.0	65.6	0.0	66.2	0.0
		Min, Max	42, 120	-1, 2	44, 92	-1, 2	42, 144	-7, 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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 8	4 hour Post Dose	n	49	49	58	58	47	47
		Mean (SD)	67.2 (14.92)	-0.0 (0.58)	66.7 (12.72)	0.1 (0.51)	69.8 (17.58)	-0.1 (1.17)
		Median	67.0	0.0	66.1	0.0	66.2	0.0
		Min, Max	42, 120	-1, 2	44, 92	-1, 2	42, 144	-7, 2
Day 15	Pre-dose	n	49	49	57	57	49	49
		Mean (SD)	67.2 (14.80)	0.0 (0.77)	67.0 (12.52)	0.1 (0.64)	69.4 (17.34)	0.0 (1.40)
		Median	66.9	0.0	66.3	0.0	66.0	0.0
		Min, Max	42, 120	-3, 3	44, 91	-2, 2	41, 144	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 15	1 hour Post Dose	n	49	49	56	56	47	47
		Mean (SD)	67.3 (14.79)	0.1 (0.74)	66.8 (12.39)	0.2 (0.69)	69.8 (17.57)	0.0 (1.33)
		Median	66.9	0.0	66.3	0.0	66.1	0.0
		Min, Max	42, 120	-2, 3	45, 92	-2, 3	42, 144	-8, 3
Day 29		n	49	49	56	56	49	49
		Mean (SD)	67.3 (14.89)	0.1 (0.87)	67.1 (12.67)	0.2 (0.89)	69.5 (17.22)	0.1 (1.42)
		Median	66.6	0.0	66.6	0.1	66.3	0.1
		Min, Max	42, 120	-2, 3	44, 92	-3, 3	41, 143	-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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Visit	Time Point	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Day 43		n	49	49	56	56	48	48
		Mean (SD)	67.4 (14.93)	0.2 (0.95)	67.2 (12.72)	0.3 (1.04)	68.2 (13.24)	0.4 (0.83)
		Median	66.6	0.0	66.4	0.4	65.8	0.2
		Min, Max	41, 120	-3, 3	45, 92	-3, 3	42, 96	-1, 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.

Table 14.3.3.2
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Diastolic Blood Pressure(mmHg)	Day 43/Early Withdrawal		Value <= 50 and >= 15 decrease from Baseline	0(0.0)	1 (1.7)	0(0.0)
Pulse Rate(bpm)	Day 1	Post-dose 4h	Value >= 120 and >= 15 increase from Baseline	0(0.0)	0(0.0)	1 (2.0)
Respiration Rate(Breaths/minute)	Day 1	Post-dose 4h	RR > 25 per minute	0(0.0)	0(0.0)	1 (2.0)
	Day 8	Post-dose 1h	RR < 12 per minute	0(0.0)	1 (1.7)	0(0.0)
		Post-dose 4h	RR < 12 per minute	0(0.0)	1 (1.7)	0(0.0)

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.
Refer to Appendix 2 of the Statistical Analysis Plan.

Table 14.3.3.2
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Respiration Rate(Breaths/minute)	Day 15	Pre-dose	RR < 12 per minute	0(0.0)	1 (1.7)	0(0.0)
		Pre-dose	RR > 25 per minute	0(0.0)	1 (1.7)	0(0.0)
	Day 43/Early Withdrawal		RR > 25 per minute	0(0.0)	0(0.0)	1 (2.0)
Systolic Blood Pressure(mmHg)	Day 8	Pre-dose	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0(0.0)	0(0.0)
		Post-dose 1h	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0(0.0)	0(0.0)

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.
Refer to Appendix 2 of the Statistical Analysis Plan.

Table 14.3.3.2
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Systolic Blood Pressure(mmHg)	Day 8	Post-dose 4h	Value <= 90 and >= 20 decrease from Baseline	1 (2.0)	0(0.0)	0(0.0)
Weight(kg)	Day 8	Post-dose 1h	>= 7% decrease from Baseline	0(0.0)	0(0.0)	1 (2.0)
		Post-dose 4h	>= 7% decrease from Baseline	0(0.0)	0(0.0)	1 (2.0)
	Day 15	Pre-dose	>= 7% decrease from Baseline	0(0.0)	0(0.0)	1 (2.0)
		Post-dose 1h	>= 7% decrease from Baseline	0(0.0)	0(0.0)	1 (2.0)

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.
Refer to Appendix 2 of the Statistical Analysis Plan.

Table 14.3.3.2
Incidence of Clinically Notable Abnormalities for Vital Signs
Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Weight(kg)	Day 29	Pre-dose	>= 7% decrease from Baseline	0(0.0)	0(0.0)	1 (2.0)

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.
Refer to Appendix 2 of the Statistical Analysis Plan.

Table 14.3.4
Physical Examination: Treatment Emergent Abnormalities
Safety Population

Result	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) 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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Screening		n	50		59		48	
			Mean (SD)	81.8 (14.18)		78.9 (12.95)		77.8 (12.62)	
			Median	81.5		78.0		77.0	
			Min, Max	59, 115		50, 107		56, 103	
	Baseline		n	50		59		49	
			Mean (SD)	78.7 (12.25)		76.3 (11.42)		78.4 (13.48)	
			Median	76.7		74.0		78.0	
			Min, Max	54, 115		53, 109		54, 102	

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	80.5 (12.64)	1.7 (7.19)	77.3 (12.54)	1.0 (8.92)	81.2 (13.42)	2.8 (10.28)
			Median	81.0	0.8	75.0	0.3	83.0	0.7
			Min, Max	56, 115	-15, 20	55, 108	-20, 25	55, 113	-26, 27
		4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	81.4 (12.32)	2.7 (8.32)	78.2 (12.81)	1.9 (7.56)	80.6 (15.30)	2.9 (12.49)
			Median	79.5	0.0	76.0	0.3	81.0	1.3
			Min, Max	60, 115	-20, 23	51, 108	-15, 24	51, 130	-31, 34

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	80.3 (14.88)	1.5 (11.62)	78.0 (13.08)	1.7 (10.03)	76.6 (12.23)	-0.9 (8.54)
			Median	82.5	2.8	76.0	0.0	77.0	-0.3
			Min, Max	50, 128	-26, 37	55, 107	-19, 28	44, 100	-22, 19
		1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	80.7 (12.69)	1.9 (10.28)	79.7 (13.09)	3.8 (11.09)	81.0 (15.05)	3.2 (11.86)
			Median	82.0	0.7	78.0	4.7	83.5	0.7
			Min, Max	55, 124	-21, 38	54, 104	-21, 26	46, 108	-16, 33

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Day 15		n	49	49	56	56	47	46
			Mean (SD)	76.8 (13.83)	-2.0 (11.07)	77.3 (12.63)	1.3 (11.25)	77.0 (14.56)	-1.2 (12.23)
			Median	78.0	-1.7	78.0	-0.2	78.0	-1.8
			Min, Max	50, 112	-21, 27	48, 104	-22, 25	50, 112	-39, 37
	Day 29		n	49	49	55	55	49	48
			Mean (SD)	78.4 (14.89)	-0.4 (12.57)	78.6 (12.73)	3.2 (10.73)	75.8 (12.69)	-2.1 (12.61)
			Median	74.0	-0.7	77.0	3.3	77.0	-1.3
			Min, Max	50, 110	-33, 35	58, 112	-19, 34	48, 102	-32, 22

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
ECG Mean Heart Rate(bpm)	Day 43		n	49	49	55	55	47	46
			Mean (SD)	76.8 (14.07)	-2.0 (11.71)	75.0 (10.60)	-0.4 (10.04)	76.1 (13.18)	-1.6 (11.95)
			Median	74.0	-1.0	74.0	0.7	76.0	-0.8
			Min, Max	55, 109	-32, 35	55, 103	-24, 22	51, 108	-37, 25
PR Interval, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	150.0 (19.63)		149.8 (18.15)		156.3 (21.24)	
			Median	143.0		151.0		157.0	
			Min, Max	123, 197		113, 193		113, 241	

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate (ms)	Baseline		n	50		59		49	
			Mean (SD)	151.7 (19.34)		148.7 (17.32)		154.0 (15.95)	
			Median	144.5		149.7		154.0	
			Min, Max	121, 194		113, 181		109, 188	
	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	151.8 (19.03)	0.0 (7.52)	148.7 (18.53)	0.0 (7.03)	150.9 (17.86)	-2.7 (9.11)
			Median	147.0	0.0	148.0	0.3	153.0	-2.7
			Min, Max	123, 193	-27, 17	110, 187	-17, 18	108, 197	-37, 22

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate (ms)	Day 1	4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	152.5 (20.40)	0.8 (7.08)	149.4 (19.25)	0.7 (8.48)	156.3 (18.67)	2.7 (9.14)
			Median	145.5	0.8	145.0	2.3	156.5	2.3
			Min, Max	119, 205	-17, 20	106, 191	-24, 15	111, 195	-37, 26
	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	152.9 (20.97)	0.8 (11.02)	151.2 (18.46)	2.3 (10.03)	154.0 (17.88)	1.1 (10.41)
			Median	147.5	2.3	149.0	1.3	154.0	1.7
			Min, Max	111, 205	-35, 22	115, 196	-17, 47	110, 185	-35, 20

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate (ms)	Day 8	1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	151.1 (20.21)	-1.0 (12.52)	151.2 (18.23)	1.9 (10.52)	153.7 (16.89)	0.8 (8.70)
			Median	145.0	-0.5	149.0	0.7	155.0	1.7
			Min, Max	122, 201	-47, 26	116, 198	-21, 46	111, 193	-33, 19
	Day 15		n	49	49	56	56	47	46
			Mean (SD)	149.8 (21.30)	-2.2 (11.78)	151.0 (18.13)	1.8 (12.43)	157.3 (20.57)	3.2 (15.89)
			Median	144.0	-2.3	151.0	-0.5	156.0	1.8
			Min, Max	120, 206	-40, 28	109, 190	-21, 48	112, 244	-22, 88

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
PR Interval, Aggregate (ms)	Day 29		n	49	49	55	55	49	48
			Mean (SD)	150.4 (19.48)	-1.5 (11.03)	151.0 (16.42)	2.1 (10.41)	157.9 (21.96)	4.0 (17.08)
			Median	144.0	-1.0	151.0	1.3	155.0	1.8
			Min, Max	121, 197	-40, 20	111, 184	-20, 28	118, 252	-40, 96
	Day 43		n	49	49	55	55	47	46
			Mean (SD)	153.1 (19.20)	1.2 (10.71)	149.2 (16.86)	0.3 (9.17)	154.5 (21.93)	0.7 (17.70)
			Median	149.0	1.0	146.0	0.3	155.0	1.2
			Min, Max	124, 198	-21, 39	115, 184	-17, 35	111, 239	-39, 83

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	86.3 (7.52)		90.2 (10.50)		88.2 (8.09)	
			Median	85.0		88.0		87.0	
			Min, Max	73, 103		77, 143		73, 107	
	Baseline		n	50		59		49	
			Mean (SD)	87.3 (6.66)		90.2 (10.52)		88.7 (5.94)	
			Median	86.5		87.7		88.7	
			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. Percentages are based on the total number of subjects in each group (N) under Safety Population, SD = Standard Deviation, Min = Minimum, Max = Maximum.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate (ms)	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	86.7 (8.05)	-0.6 (5.97)	88.7 (10.86)	-1.5 (5.13)	88.7 (7.36)	0.4 (5.22)
			Median	85.0	-0.8	87.0	-1.0	87.0	0.2
			Min, Max	75, 107	-17, 12	73, 151	-14, 10	73, 105	-9, 13
		4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	86.5 (8.65)	-0.8 (6.13)	89.1 (11.02)	-1.1 (4.64)	87.3 (6.50)	-1.0 (5.05)
			Median	85.5	0.3	87.0	-1.7	86.0	-2.0
			Min, Max	73, 107	-13, 12	72, 149	-10, 10	74, 102	-11, 12

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate (ms)	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	86.0 (8.75)	-1.4 (7.46)	87.9 (10.72)	-1.9 (5.12)	86.8 (8.13)	-1.8 (6.44)
			Median	84.0	-2.3	86.0	-2.7	86.0	-1.7
			Min, Max	69, 105	-15, 23	71, 144	-16, 9	73, 107	-18, 15
		1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	88.1 (6.97)	0.7 (6.46)	89.4 (11.25)	-0.8 (6.36)	88.1 (8.60)	-0.5 (5.61)
			Median	87.5	0.0	87.0	-1.0	88.5	-0.7
			Min, Max	75, 106	-11, 19	66, 148	-16, 18	73, 106	-10, 13

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate (ms)	Day 15		n	49	49	56	56	47	46
			Mean (SD)	86.8 (7.42)	-0.6 (6.45)	89.6 (10.94)	-0.6 (5.75)	86.9 (8.58)	-1.9 (7.41)
			Median	85.0	-1.7	87.5	-1.0	85.0	-2.7
			Min, Max	74, 103	-12, 17	75, 151	-16, 16	69, 107	-18, 18
	Day 29		n	49	49	55	55	49	48
			Mean (SD)	85.8 (7.08)	-1.5 (6.54)	89.9 (10.61)	-0.2 (5.00)	88.0 (7.58)	-0.5 (6.03)
			Median	86.0	-3.0	87.0	-0.3	88.0	-0.3
			Min, Max	67, 103	-13, 16	80, 148	-11, 14	75, 107	-12, 14

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QRS Duration, Aggregate (ms)	Day 43		n	49	49	55	55	47	46
			Mean (SD)	87.1 (7.27)	-0.2 (6.69)	90.7 (10.36)	0.5 (6.71)	88.4 (8.72)	-0.0 (7.58)
			Median	86.0	-2.0	89.0	0.3	88.0	1.0
			Min, Max	73, 104	-14, 18	71, 140	-15, 17	73, 105	-13, 21
QT Interval, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	358.5 (32.56)		356.5 (25.92)		361.3 (27.41)	
			Median	361.0		357.0		360.5	
			Min, Max	292, 447		313, 441		313, 423	

Source: Listing 16.2.11.1
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.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
Programmer:SK
Date of Extraction:05FEB2023

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate (ms)	Baseline		n	50		59		49	
			Mean (SD)	360.3 (26.50)		360.4 (25.91)		361.3 (29.95)	
			Median	358.0		359.7		359.7	
			Min, Max	298, 421		299, 423		314, 451	
	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	357.4 (27.55)	-2.9 (12.74)	356.7 (27.11)	-3.7 (15.67)	354.4 (24.94)	-7.2 (18.01)
			Median	352.5	-1.8	355.0	-1.0	352.0	-5.3
			Min, Max	301, 428	-29, 28	294, 423	-50, 35	309, 434	-48, 37

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate (ms)	Day 1	4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	355.9 (25.80)	-4.4 (15.10)	354.5 (25.13)	-5.9 (15.11)	355.7 (31.21)	-6.5 (21.66)
			Median	355.5	-1.5	353.0	-5.0	346.5	-8.0
			Min, Max	296, 413	-36, 28	307, 420	-52, 17	295, 442	-53, 43
	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	361.9 (31.52)	1.9 (23.51)	358.1 (30.24)	-2.5 (19.87)	361.9 (27.36)	-1.1 (20.85)
			Median	358.5	-1.2	354.5	1.0	356.0	3.2
			Min, Max	275, 430	-47, 93	307, 429	-45, 50	322, 425	-74, 33

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate (ms)	Day 8	1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	358.6 (28.96)	-1.3 (20.93)	354.4 (28.42)	-6.6 (20.63)	353.4 (29.36)	-7.5 (24.09)
			Median	353.5	-0.2	352.5	-7.2	344.5	-3.7
			Min, Max	278, 442	-55, 80	303, 418	-47, 52	287, 419	-71, 33
	Day 15		n	49	49	56	56	47	46
			Mean (SD)	365.4 (29.82)	5.3 (23.10)	359.9 (27.57)	-1.3 (20.03)	362.7 (32.15)	1.5 (22.99)
			Median	357.0	5.3	355.0	-3.7	362.0	3.8
			Min, Max	309, 441	-59, 52	305, 430	-46, 51	309, 451	-60, 45

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QT Interval, Aggregate (ms)	Day 29		n	49	49	55	55	49	48
			Mean (SD)	364.1 (31.34)	4.1 (27.18)	360.7 (31.49)	-1.7 (23.38)	366.9 (30.66)	4.8 (27.52)
			Median	362.0	1.0	361.0	-0.7	367.0	2.8
			Min, Max	298, 424	-72, 74	303, 423	-63, 44	307, 447	-70, 72
	Day 43		n	49	49	55	55	47	46
			Mean (SD)	367.9 (28.04)	7.8 (22.68)	364.2 (28.19)	1.9 (22.02)	363.8 (27.83)	1.1 (25.35)
			Median	365.0	8.3	361.0	1.3	364.0	2.7
			Min, Max	309, 423	-39, 53	300, 430	-44, 51	312, 428	-61, 70

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	414.6 (22.97)		405.7 (26.81)		408.2 (19.17)	
			Median	416.5		404.0		407.5	
			Min, Max	362, 465		338, 471		359, 455	
	Baseline		n	50		59		49	
			Mean (SD)	409.6 (19.65)		403.7 (22.92)		408.8 (15.84)	
			Median	408.5		403.7		410.7	
			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. Percentages are based on the total number of subjects in each group (N) under Safety Population, SD = Standard Deviation, Min = Minimum, Max = Maximum.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate (ms)	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	410.5 (19.51)	0.9 (14.42)	401.9 (24.58)	-1.8 (14.25)	408.8 (18.04)	-0.2 (14.20)
			Median	413.0	1.8	399.0	-2.0	409.0	-2.2
			Min, Max	368, 451	-42, 31	355, 481	-46, 35	370, 453	-41, 27
		4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	411.6 (19.15)	2.0 (11.50)	401.6 (23.68)	-2.1 (12.12)	407.7 (18.56)	-0.4 (16.61)
			Median	410.0	0.7	400.0	-0.3	410.5	0.3
			Min, Max	370, 459	-32, 28	351, 481	-31, 19	375, 456	-46, 36

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate (ms)	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	414.2 (22.60)	4.9 (17.42)	405.2 (26.73)	0.9 (15.64)	405.6 (17.11)	-2.8 (15.86)
			Median	414.5	5.2	404.5	1.0	405.0	-3.2
			Min, Max	353, 455	-35, 44	353, 487	-50, 42	354, 447	-46, 43
		1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	412.8 (20.84)	3.5 (18.51)	405.6 (27.73)	2.0 (16.88)	406.3 (19.90)	-0.8 (19.22)
			Median	413.0	2.8	405.5	2.7	406.5	-5.3
			Min, Max	366, 460	-67, 50	343, 494	-31, 39	360, 442	-39, 50

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate (ms)	Day 15		n	49	49	56	56	47	46
			Mean (SD)	409.4 (20.42)	0.0 (13.77)	405.6 (25.45)	1.5 (18.16)	406.5 (17.55)	-1.8 (16.62)
			Median	409.0	-2.3	406.0	3.0	408.0	0.8
			Min, Max	362, 453	-27, 37	349, 463	-56, 58	355, 444	-56, 32
	Day 29		n	49	49	55	55	49	48
			Mean (SD)	411.6 (21.93)	2.2 (18.01)	409.6 (24.29)	5.6 (15.86)	407.9 (17.53)	-0.5 (13.06)
			Median	406.0	4.0	410.0	6.0	407.0	-1.7
			Min, Max	365, 462	-41, 33	335, 456	-23, 42	369, 452	-34, 27

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcB Interval, Aggregate (ms)	Day 43		n	49	49	55	55	47	46
			Mean (SD)	412.4 (24.73)	3.0 (16.73)	405.2 (24.67)	1.1 (16.40)	406.5 (25.87)	-2.1 (18.62)
			Median	412.0	3.7	405.0	2.3	407.0	-2.2
			Min, Max	357, 467	-40, 54	340, 461	-43, 46	350, 464	-44, 45
QTcF Interval, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	394.6 (22.36)		388.3 (21.78)		391.5 (17.26)	
			Median	387.5		386.0		391.5	
			Min, Max	350, 459		338, 442		355, 426	

Source: Listing 16.2.11.1
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.

Reference Datasets:ADSL,ADEG
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Date of Extraction:05FEB2023

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate (ms)	Baseline		n	50		59		49	
			Mean (SD)	392.1 (17.71)		388.5 (20.26)		391.9 (15.39)	
			Median	391.7		386.7		389.3	
			Min, Max	360, 428		336, 447		368, 436	
	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	391.7 (17.88)	-0.4 (11.25)	386.0 (21.24)	-2.5 (10.17)	389.4 (14.22)	-2.8 (10.04)
			Median	388.5	-0.7	384.0	-2.3	389.0	-2.2
			Min, Max	361, 430	-34, 20	353, 448	-26, 25	361, 429	-30, 19

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate (ms)	Day 1	4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	391.8 (17.27)	-0.3 (9.20)	385.0 (19.39)	-3.5 (10.20)	389.1 (16.51)	-2.8 (12.00)
			Median	389.5	0.3	385.0	-2.7	389.0	-3.7
			Min, Max	357, 433	-26, 18	341, 447	-26, 17	360, 434	-46, 15
	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	395.6 (20.59)	3.8 (15.26)	388.6 (23.84)	-0.4 (13.31)	390.2 (15.19)	-2.1 (14.07)
			Median	394.0	3.2	389.0	0.3	389.0	0.2
			Min, Max	346, 441	-39, 63	343, 457	-40, 29	361, 435	-51, 32

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate (ms)	Day 8	1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	393.6 (19.68)	1.8 (15.81)	387.4 (23.86)	-1.2 (13.58)	387.5 (15.80)	-3.2 (16.27)
			Median	393.5	1.2	385.0	-2.7	384.0	-4.0
			Min, Max	354, 439	-63, 59	336, 453	-23, 39	350, 422	-49, 35
	Day 15		n	49	49	56	56	47	46
			Mean (SD)	393.7 (17.43)	1.9 (12.73)	389.5 (21.40)	0.5 (13.60)	391.1 (16.63)	-0.5 (13.08)
			Median	391.0	1.3	387.5	1.2	388.0	0.0
			Min, Max	366, 436	-32, 26	342, 445	-37, 38	356, 427	-34, 22

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
QTcF Interval, Aggregate (ms)	Day 29		n	49	49	55	55	49	48
			Mean (SD)	394.7 (19.02)	2.8 (17.08)	392.3 (22.98)	2.8 (14.72)	393.3 (16.77)	1.4 (12.99)
			Median	396.0	4.3	392.0	0.3	390.0	2.2
			Min, Max	362, 442	-35, 46	328, 439	-23, 34	362, 435	-43, 37
	Day 43		n	49	49	55	55	47	46
			Mean (SD)	396.7 (20.10)	4.8 (13.49)	390.8 (22.83)	1.3 (14.88)	391.5 (21.44)	-0.9 (15.81)
			Median	397.0	4.0	392.0	0.7	391.0	-0.7
			Min, Max	359, 446	-20, 47	337, 443	-31, 45	345, 445	-50, 41

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate (ms)	Screening		n	50		59		48	
			Mean (SD)	755.4 (128.98)		782.6 (133.39)		791.2 (127.75)	
			Median	735.5		769.0		782.5	
			Min, Max	521, 1010		560, 1193		581, 1067	
	Baseline		n	50		59		49	
			Mean (SD)	781.6 (121.45)		804.7 (117.90)		789.7 (142.02)	
			Median	784.8		815.3		768.3	
			Min, Max	523, 1104		548, 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. Percentages are based on the total number of subjects in each group (N) under Safety Population, SD = Standard Deviation, Min = Minimum, Max = Maximum.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate (ms)	Day 1	1 hour Post Dose	n	50	50	59	59	49	48
			Mean (SD)	764.9 (123.61)	-16.7 (69.75)	796.3 (125.90)	-8.4 (99.90)	760.0 (131.77)	-30.9 (106.28)
			Median	739.5	-9.0	803.0	-5.3	725.0	-8.2
			Min, Max	524, 1065	-166, 158	557, 1099	-307, 246	532, 1092	-292, 231
		4 hours Post Dose	n	50	50	59	59	48	47
			Mean (SD)	753.7 (113.55)	-27.9 (78.60)	788.3 (128.77)	-16.5 (77.20)	772.1 (153.39)	-24.1 (124.54)
			Median	755.5	-3.7	785.0	-3.0	742.0	-8.0
			Min, Max	523, 1003	-261, 150	553, 1171	-253, 161	461, 1186	-278, 342

Source: Listing 16.2.11.1
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.

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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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate (ms)	Day 8	Pre-dose	n	48	48	58	57	47	46
			Mean (SD)	772.9 (142.99)	-8.5 (111.89)	789.8 (129.53)	-12.3 (96.18)	805.2 (145.62)	6.3 (103.14)
			Median	729.0	-27.7	788.0	-2.7	775.0	5.8
			Min, Max	470, 1193	-292, 227	559, 1083	-225, 214	597, 1349	-228, 311
		1 hour Post Dose	n	48	48	58	58	44	43
			Mean (SD)	762.0 (120.35)	-19.4 (97.72)	772.4 (126.62)	-35.4 (106.39)	769.9 (165.83)	-24.2 (122.12)
			Median	735.5	-13.2	770.5	-42.5	719.0	-1.3
			Min, Max	483, 1091	-298, 169	579, 1109	-231, 197	553, 1299	-340, 261

Source: Listing 16.2.11.1
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.

Reference Datasets:ADSL,ADEG
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Tables\Table 14.3.5.1.sas
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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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate (ms)	Day 15		n	49	49	56	56	47	46
			Mean (SD)	806.9 (153.36)	25.5 (110.07)	798.6 (144.04)	-8.6 (120.18)	806.2 (155.39)	15.3 (126.59)
			Median	767.0	12.3	769.0	-1.5	774.0	16.5
			Min, Max	535, 1208	-238, 221	575, 1239	-258, 285	535, 1204	-368, 429
	Day 29		n	49	49	55	55	49	48
			Mean (SD)	793.2 (154.18)	11.8 (122.35)	782.6 (126.82)	-29.4 (104.83)	816.9 (152.09)	22.3 (133.49)
			Median	807.0	2.0	783.0	-31.7	783.0	12.7
			Min, Max	544, 1199	-256, 305	534, 1037	-321, 179	589, 1253	-258, 409

Source: Listing 16.2.11.1
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.

Table 14.3.5.1
Summary of Change from Baseline in Electrocardiogram (ECG) Parameters
Safety Population

				Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Parameter	Visit	Timepoint	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
RR Interval, Aggregate (ms)	Day 43		n	49	49	55	55	47	46
			Mean (SD)	806.7 (141.53)	25.2 (117.12)	815.3 (113.49)	3.4 (101.65)	812.1 (142.61)	15.9 (131.88)
			Median	809.0	9.0	811.0	-10.0	788.0	7.2
			Min, Max	549, 1091	-279, 394	581, 1087	-211, 238	558, 1167	-328, 383

Source: Listing 16.2.11.1
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.

Table 14.3.5.2
Electrocardiogram (ECG): Treatment Emergent Abnormalities as Assessed by Central Reader
Safety Population

Result	Evenamide 7.5 mg BID) (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%	Evenamide 30 mg BID (N=50) n(%)
Abnormal	5(10.0)	6(10.0)	5(10.0)

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Abnormal CS	0(0.0)	0(0.0)	0(0.0)
Abnormal NCS	12(24.0)	9(15.0)	9(18.0)

Source: Listing 16.2.11.1
CS = Clinically Significant, NCS = Not Clinically Significant, N - Total number of subjects in the Safety population, n - number of subjects in the specified category. 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 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
QTcB Interval (msec)	Day 1	1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	1(2.0)	0(0.0)	1(2.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	1(2.0)	1(1.7)	0(0.0)
		4 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	2(4.0)	0(0.0)	1(2.0)
		4 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	0(0.0)	0(0.0)	2(4.0)
	Day 8	Pre dose	Absolute interval	> 450 msec and <= 480 msec	2(4.0)	1(1.7)	0(0.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
QTcB Interval (msec)	Day 8	Pre dose	Change from baseline	> 30 msec and <= 60 msec	4(8.0)	1(1.7)	1(2.0)
		1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	1(2.0)	0(0.0)	0(0.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	4(8.0)	5(8.3)	3(6.0)
	Day 15		Absolute interval	> 450 msec and <= 480 msec	0(0.0)	1(1.7)	0(0.0)
			Change from baseline	> 30 msec and <= 60 msec	1(2.0)	2(3.3)	1(2.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
QTcB Interval (msec)	Day 29		Absolute interval	> 450 msec and <= 480 msec	2(4.0)	0(0.0)	1(2.0)
			Change from baseline	> 30 msec and <= 60 msec	2(4.0)	3(5.0)	0(0.0)
	Day 43		Absolute interval	> 450 msec and <= 480 msec	1(2.0)	0(0.0)	3(6.0)
			Change from baseline	> 30 msec and <= 60 msec	2(4.0)	3(5.0)	1(2.0)
QTcF Interval (msec)	Day 8	Pre dose	Absolute interval	> 450 msec and <= 480 msec	0(0.0)	1(1.7)	0(0.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
QTcF Interval (msec)	Day 8	Pre dose	Change from baseline	> 30 msec and <= 60 msec	0(0.0)	0(0.0)	1(2.0)
		Pre dose	Change from baseline	> 60 msec	1(2.0)	0(0.0)	0(0.0)
		1 Hour Post dose	Absolute interval	> 450 msec and <= 480 msec	0(0.0)	1(1.7)	0(0.0)
		1 Hour Post dose	Change from baseline	> 30 msec and <= 60 msec	2(4.0)	1(1.7)	1(2.0)
	Day 15		Change from baseline	> 30 msec and <= 60 msec	0(0.0)	1(1.7)	0(0.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
QTcF Interval (msec)	Day 29		Change from baseline	> 30 msec and <= 60 msec	2(4.0)	2(3.3)	1(2.0)
	Day 43		Change from baseline	> 30 msec and <= 60 msec	3(6.0)	2(3.3)	1(2.0)
QRS Duration (msec)	Day 8	Pre dose	Change from baseline	More than 25% change from baseline	1(2.0)	0(0.0)	0(0.0)
	Day 43		Change from baseline	More than 25% change from baseline	0(0.0)	0(0.0)	1(2.0)
PR Interval (msec)	Day 1	4 Hour Post dose	Absolute interval	> 200 msec	1(2.0)	0(0.0)	0(0.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
PR Interval (msec)	Day 8	Pre dose	Absolute interval	> 200 msec	1(2.0)	0(0.0)	0(0.0)
		Pre dose	Change from baseline	More than 25% change from baseline	0(0.0)	1(1.7)	0(0.0)
		1 Hour Post dose	Absolute interval	> 200 msec	1(2.0)	0(0.0)	0(0.0)
		1 Hour Post dose	Change from baseline	More than 25% change from baseline	0(0.0)	1(1.7)	0(0.0)
	Day 15		Absolute interval	> 200 msec	1(2.0)	0(0.0)	1(2.0)

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.

Table 14.3.5.4
Electrocardiogram (ECG) Treatment Emergent Parameters Categorical Analysis
Safety Population

Parameter	Visit	Timepoint	Criteria	Category	Evenamide 7.5 mg BID (N=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
PR Interval (msec)	Day 15		Change from baseline	More than 25% change from baseline	0(0.0)	2(3.3)	1(2.0)
	Day 29		Absolute interval	> 200 msec	0(0.0)	0(0.0)	1(2.0)
			Change from baseline	More than 25% change from baseline	0(0.0)	0(0.0)	1(2.0)
	Day 43		Absolute interval	> 200 msec	0(0.0)	0(0.0)	1(2.0)
			Change from baseline	More than 25% change from baseline	1(2.0)	1(1.7)	2(4.0)

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.

Table 14.3.6
Neurological Examination: Treatment Emergent Abnormalities
Safety Population

Result	Evenamide 7.5 mg BID (N=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)
Abnormal, NCS	0(0.0)	0(0.0)	1(2.0)
Abnormal, CS	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=50) n (%)	Evenamide 15 mg BID (N=60) n (%)	Evenamide 30 mg BID (N=50) n (%)
Abnormal, NCS	1(2.0)	0(0.0)	1(2.0)
Abnormal, CS	0(0.0)	0(0.0)	1(2.0)

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.
Subject with multiple abnormal post-baseline findings on any body system are 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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Rigidity:Upper Limbs	Baseline	No rigidity	49(98.0)	60(100.0)	48(96.0)
			Minimal	1(2.0)	0(0.00)	2(4.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Rigidity:Upper Limbs	Day 43	No rigidity	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Rigidity:Lower Limbs	Baseline	No rigidity	49(98.0)	60(100.0)	48(96.0)
			Minimal	1(2.0)	0(0.00)	2(4.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Rigidity:Lower Limbs	Day 43	No rigidity	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Rigidity:Neck	Baseline	No rigidity	49(98.0)	60(100.0)	49(98.0)
			Minimal	1(2.0)	0(0.00)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Rigidity:Neck	Day 43	No rigidity	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Tremor:Face/jaw/chin/ lips/head	Baseline	No tremor	49(98.0)	59(98.3)	49(98.0)
			Minimal	1(2.0)	1(1.7)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Tremor:Face/jaw/chin/ lips/head	Day 43	No tremor	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Tremor:Upper limbs/hands	Baseline	No tremor	48(96.0)	59(98.3)	48(96.0)
			Minimal	1(2.0)	1(1.7)	1(2.0)
			Mild	1(2.0)	0(0.00)	1(2.0)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Tremor:Upper limbs/hands	Day 43	No tremor	49(98.0)	55(91.7)	44(88.0)
			Minimal	0(0.00)	1(1.7)	4(8.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Tremor:Lower limbs/ feet	Baseline	No tremor	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Tremor:Lower limbs/ feet	Day 43	No tremor	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Reduced facial expression/speech	Baseline	Normal	47(94.0)	59(98.3)	45(90.0)
			Minimal	2(4.0)	1(1.7)	5(10.0)
			Mild	1(2.0)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Reduced facial expression/speech	Day 43	Normal	48(96.0)	56(93.3)	44(88.0)
			Minimal	1(2.0)	0(0.00)	3(6.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	1(2.0)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Impaired Gait/ Posture	Baseline	Normal	49(98.0)	60(100.0)	48(96.0)
			Minimal	1(2.0)	0(0.00)	2(4.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Impaired Gait/ Posture	Day 43	Normal	49(98.0)	56(93.3)	47(94.0)
			Minimal	0(0.00)	0(0.00)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Postural Instability	Baseline	No postural instability	50(100.0)	59(98.3)	49(98.0)
			Minimal	0(0.00)	1(1.7)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Postural Instability	Day 43	No postural instability	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Bradykinesia/ Hypokinesia	Baseline	No slowness of movement	48(96.0)	59(98.3)	45(90.0)
			Minimal	2(4.0)	1(1.7)	5(10.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Parkinsonism	Bradykinesia/ Hypokinesia	Day 43	No slowness of movement	49(98.0)	56(93.3)	44(88.0)
			Minimal	0(0.00)	0(0.00)	4(8.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Tongue	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Tongue	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Jaw	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Jaw	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Eyes/upper face/lower face/larynx	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Eyes/upper face/lower face/larynx	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Shoulders/upper limbs/hands	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Shoulders/upper limbs/hands	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Hips/lower limbs/feet	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Hips/lower limbs/feet	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dystonia	Trunk/neck	Baseline	None	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dystonia	Trunk/neck	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Tongue	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Tongue	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Jaw	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Jaw	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Eyes/upper face/lower face	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Eyes/upper face/lower face	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Shoulders/upper limbs/hands	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Shoulders/upper limbs/hands	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Hips/lower limbs/feet	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Hips/lower limbs/feet	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Dyskinesia	Trunk/neck	Baseline	Absent	50(100.0)	60(100.0)	50(100.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Dyskinesia	Trunk/neck	Day 43	Absent	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Akathisia	Subjective	Baseline	None	50(100.0)	59(98.3)	49(98.0)
			Minimal	0(0.00)	1(1.7)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Akathisia	Subjective	Day 43	None	49(98.0)	55(91.7)	48(96.0)
			Minimal	0(0.00)	1(1.7)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Akathisia	Objective	Baseline	None	48(96.0)	60(100.0)	49(98.0)
			Minimal	2(4.0)	0(0.00)	1(2.0)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				
Akathisia	Objective	Day 43	None	49(98.0)	56(93.3)	48(96.0)
			Minimal	0(0.00)	0(0.00)	0(0.00)
			Mild	0(0.00)	0(0.00)	0(0.00)
			Moderate	0(0.00)	0(0.00)	0(0.00)
			Severe	0(0.00)	0(0.00)	0(0.00)
			Extreme	0(0.00)	0(0.00)	0(0.00)
		.				

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Parkinsonism	Baseline	n	50		60		50	
		Mean (SD)	0.3 (1.13)		0.1 (0.33)		0.4 (1.20)	
		Median	0.0		0.0		0.0	
		Min,Max	0,6		0,2		0,6	
Parkinsonism	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.14)	-0.2 (0.77)	0.0 (0.13)	-0.1 (0.32)	0.3 (0.95)	0.0 (0.95)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,1	-5,0	0,1	-2,0	0,4	-3,4

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Dystonia	Baseline	n	50		60		50	
		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	
Dystonia	Day 43	n	49	49	56	56	48	48
		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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Dyskinesia	Baseline	n	50		60		50	
		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	
Dyskinesia	Day 43	n	49	49	56	56	48	48
		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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Akathisia	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.20)		0.0 (0.13)		0.0 (0.20)	
		Median	0.0		0.0		0.0	
		Min,Max	0,1		0,1		0,1	
Akathisia	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.00)	-0.0 (0.14)	0.0 (0.13)	0.0 (0.19)	0.0 (0.00)	-0.0 (0.20)
		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

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.

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=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Total Score	Baseline	n	50		60		50	
		Mean (SD)	0.3 (1.22)		0.1 (0.44)		0.5 (1.23)	
		Median	0.0		0.0		0.0	
		Min,Max	0,6		0,3		0,6	
Total Score	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.14)	-0.2 (0.78)	0.0 (0.27)	-0.1 (0.46)	0.3 (0.95)	-0.0 (0.94)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min,Max	0,1	-5,0	0,2	-3,1	0,4	-3,4

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Baseline	Absent	47(94.00)	57(95.00)	44(88.00)
Parkinsonism		Mild	1(2.00)	0(0.0)	0(0.0)
Parkinsonism		Minimal	2(4.00)	3(5.00)	6(12.00)
Dyskinesia		Absent	50(100.0)	60(100.0)	50(100.0)
Dystonia		Absent	50(100.0)	60(100.0)	50(100.0)
Akathisia		Absent	49(98.00)	60(100.0)	49(98.00)
Akathisia		Minimal	1(2.00)	0(0.0)	1(2.00)

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.

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=50) n(%)	Evenamide 15 mg BID (N=60) n(%)	Evenamide 30 mg BID (N=50) n(%)
Parkinsonism	Day 43	Absent	49(98.00)	55(91.67)	43(86.00)
Parkinsonism		Minimal	0(0.0)	1(1.67)	5(10.00)
Dyskinesia		Absent	49(98.00)	56(93.33)	48(96.00)
Dystonia		Absent	49(98.00)	56(93.33)	48(96.00)
Akathisia		Absent	49(98.00)	56(93.33)	48(96.00)

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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Depression	Screening	n	50		60		50	
		Mean (SD)	0.1 (0.35)		0.3 (0.44)		0.3 (0.44)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.1 (0.35)		0.3 (0.44)		0.2 (0.42)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.1 (0.31)	-0.0 (0.29)	0.2 (0.39)	-0.1 (0.26)	0.2 (0.38)	-0.0 (0.25)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 1	-1, 1	0, 1	-1, 0	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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Hopelessness	Screening	n	50		60		50	
		Mean (SD)	0.0 (0.20)		0.1 (0.32)		0.2 (0.37)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.20)		0.1 (0.32)		0.1 (0.33)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.00)	-0.0 (0.20)	0.1 (0.35)	0.0 (0.13)	0.1 (0.33)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 0	-1, 0	0, 1	0, 1	0, 1	0, 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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Self Depreciation	Screening	n	50		60		50	
		Mean (SD)	0.1 (0.35)		0.1 (0.28)		0.1 (0.27)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.1 (0.24)		0.1 (0.25)		0.1 (0.39)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 2	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.20)	-0.0 (0.14)	0.1 (0.23)	-0.0 (0.13)	0.1 (0.28)	-0.0 (0.14)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 1	-1, 0	0, 1	-1, 0	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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Guilty Ideas of Reference	Screening	n	50		60		50	
		Mean (SD)	0.1 (0.24)		0.1 (0.28)		0.1 (0.36)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 2	
	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.00)		0.1 (0.22)		0.1 (0.27)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 0		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.14)	0.0 (0.14)	0.1 (0.23)	0.0 (0.19)	0.0 (0.20)	0.0 (0.00)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 1	0, 1	0, 1	-1, 1	0, 1	0, 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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Pathological Guilt	Screening	n	50		60		50	
		Mean (SD)	0.0 (0.20)		0.0 (0.13)		0.1 (0.24)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.14)		0.0 (0.13)		0.1 (0.36)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 2	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.00)	-0.0 (0.14)	0.0 (0.13)	0.0 (0.00)	0.0 (0.20)	-0.0 (0.14)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 0	-1, 0	0, 1	0, 0	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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Morning Depression	Screening	n	50		60		50	
		Mean (SD)	0.0 (0.00)		0.1 (0.22)		0.1 (0.30)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 0		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.00)		0.1 (0.22)		0.1 (0.27)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 0		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.14)	0.0 (0.14)	0.0 (0.19)	-0.0 (0.13)	0.0 (0.14)	-0.1 (0.24)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 1	0, 1	0, 1	-1, 0	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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Early Wakening	Screening	n	50		60		50	
		Mean (SD)	0.0 (0.14)		0.1 (0.25)		0.0 (0.14)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.1 (0.24)		0.0 (0.18)		0.0 (0.14)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.00)	-0.1 (0.24)	0.0 (0.13)	-0.0 (0.13)	0.0 (0.00)	-0.0 (0.14)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 0	-1, 0	0, 1	-1, 0	0, 0	-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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Suicide	Screening	n	50		60		50	
		Mean (SD)	0.0 (0.00)		0.0 (0.00)		0.0 (0.20)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 0		0, 0		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.0 (0.00)		0.0 (0.00)		0.0 (0.14)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 0		0, 0		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.14)	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, 1	0, 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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Observed Depression	Screening	n	50		60		50	
		Mean (SD)	0.1 (0.27)		0.1 (0.30)		0.1 (0.27)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Baseline	n	50		60		50	
		Mean (SD)	0.1 (0.27)		0.0 (0.18)		0.1 (0.27)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 1		0, 1		0, 1	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.1 (0.24)	-0.0 (0.14)	0.0 (0.13)	0.0 (0.19)	0.1 (0.24)	-0.0 (0.14)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 1	-1, 0	0, 1	-1, 1	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.

Table 14.3.9
Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Scores and Total
Safety Population

			Evenamide 7.5 mg BID (N=50)		Evenamide 15 mg BID (N=60)		Evenamide 30 mg BID (N=50)	
Scale Category	Visit	Statistics	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Total Score	Screening	n	50		60		50	
		Mean (SD)	0.5 (1.03)		0.8 (1.44)		0.9 (1.71)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Baseline	n	50		60		50	
		Mean (SD)	0.4 (0.97)		0.6 (1.29)		0.8 (1.65)	
		Median	0.0		0.0		0.0	
		Min, Max	0, 4		0, 6		0, 6	
	Day 43	n	49	49	56	56	48	48
		Mean (SD)	0.2 (0.78)	-0.2 (0.72)	0.5 (1.26)	-0.1 (0.56)	0.6 (1.40)	-0.2 (0.60)
		Median	0.0	0.0	0.0	0.0	0.0	0.0
		Min, Max	0, 4	-3, 1	0, 6	-2, 2	0, 6	-2, 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.

Table 14.3.10
Summary of Seizure Checklist Findings
Safety Population

Seizure Checklist
No data to display

Table 14.2.1.1c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
Using Overall Comparison (Primary Estimand) mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Screening	n	156	
	Mean (SD)	79.6 (5.20)	
	Median	79.5	
	Min, Max	70, 89	
Baseline	n	156	
	Mean (SD)	79.5 (5.04)	
	Median	80	
	Min, Max	70, 89	

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.
p-value = Paired t-test.

Table 14.2.1.1c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
Using Overall Comparison (Primary Estimand) mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Day 8	n	154	154
	Mean (SD)	77.9 (5.42)	-1.6 (2.84)
	Median	78	-1
	Min, Max	65, 94	-16, 5
Day 15	n	153	153
	Mean (SD)	75.4 (6.40)	-4.1 (3.99)
	Median	75	-3
	Min, Max	60, 91	-17, 3

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.
p-value = Paired t-test.

Table 14.2.1.1c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score
Using Overall Comparison (Primary Estimand) mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Day 29	n	153	153
	Mean (SD)	72.8 (7.54)	-6.8 (5.54)
	Median	73	-6
	Min, Max	54, 90	-28, 4
Day 43	n	152	152
	Mean (SD)	70.0 (8.30)	-9.5 (7.13)
	Median	70	-9
	Min, Max	48, 91	-34, 12
	95% CI		(-10.60, -8.32)
	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.
p-value = Paired t-test.

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\Adhoc\Prog\Table 14.2.1.1c.sas
Programmer:AG
Date of Extraction:05FEB2023 Final- 25APR2023:11:23

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
Positive Scale	Baseline	n	156	
		Mean (SD)	23.7 (3.30)	
		Median	24	
		Min, Max	17, 36	
	Day 8	n	154	154
		Mean (SD)	23.1 (3.40)	-0.6 (1.21)
		Median	23	0
		Min, Max	14, 32	-5, 2

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
Positive Scale	Day 15	n	153	153
		Mean (SD)	21.9 (3.74)	-1.8 (2.03)
		Median	22	-1
		Min, Max	11, 35	-9, 2
	Day 29	n	153	153
		Mean (SD)	20.7 (4.06)	-2.9 (2.76)
		Median	21	-2
		Min, Max	10, 35	-15, 3

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

				Evenamide (N=156)
Scale	Visit	Statistic	Observed	Change from Baseline
Positive Scale	Day 43	n	152	152
		Mean (SD)	19.6 (4.39)	-4.0 (3.39)
		Median	19.5	-4
		Min, Max	10, 35	-15, 3
		95% CI		(-4.57, -3.48)
		p-value		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
Negative Scale	Baseline	n	156	
		Mean (SD)	19.7 (3.37)	
		Median	20	
		Min, Max	10, 31	
	Day 8	n	154	154
		Mean (SD)	19.4 (3.31)	-0.3 (0.83)
		Median	20	0
		Min, Max	10, 29	-6, 1

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
Negative Scale	Day 15	n	153	153
		Mean (SD)	19.0 (3.20)	-0.8 (1.55)
		Median	19	0
		Min, Max	10, 28	-7, 4
	Day 29	n	153	153
		Mean (SD)	18.5 (3.09)	-1.4 (2.04)
		Median	19	-1
		Min, Max	11, 26	-10, 6

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
Negative Scale	Day 43	n	152	152
		Mean (SD)	17.9 (3.20)	-1.9 (2.55)
		Median	18	-1
		Min, Max	10, 26	-11, 7
		95% CI		(-2.35, -1.53)
		p-value		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
General Psychopathology Scale	Baseline	n	156	
		Mean (SD)	36.1 (3.71)	
		Median	36	
		Min, Max	28, 49	
	Day 8	n	154	154
		Mean (SD)	35.3 (3.73)	-0.7 (1.61)
		Median	35	0
		Min, Max	27, 49	-9, 3

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

			Evenamide (N=156)	
Scale	Visit	Statistic	Observed	Change from Baseline
General Psychopathology Scale	Day 15	n	153	153
		Mean (SD)	34.5 (4.07)	-1.5 (1.99)
		Median	34	-1
		Min, Max	23, 49	-10, 3
	Day 29	n	153	153
		Mean (SD)	33.6 (4.36)	-2.5 (2.44)
		Median	33	-2
		Min, Max	24, 48	-12, 2

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.2c
Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Subscales –
Overall Comparison mITT Population

				Evenamide (N=156)
Scale	Visit	Statistic	Observed	Change from Baseline
General Psychopathology Scale	Day 43	n	152	152
		Mean (SD)	32.5 (4.27)	-3.5 (3.13)
		Median	32	-3
		Min, Max	23, 46	-14, 4
		95% CI		(-4.00, -2.99)
		p-value		<.001

Source: Listing 16.2.6.1.1
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.

Table 14.2.1.4c
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Score at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Day 43	n	156
	Mean (SD)	70.1 (8.30)
	Median	70
	Min, Max	48, 91
	Mean change from Baseline (SD)	-9.4 (7.07)
	95% CI	(-10.56, -8.31)
	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. 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.

Table 14.2.1.5c
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Day 43
Paired t-test Using LOCF Supportive Estimand
mITT Population

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	79.5 (5.04)
	Median	80.0
	Min, Max	70, 89
Day 43	n	156
	Mean (SD)	70.3 (8.39)
	Median	70.0
	Min, Max	48, 91
	Mean Change From Baseline (SD)	-9.3 (7.14)
	95% CI	(-10.40, -8.14)
	p-value	<.001

Source: Listing 16.2.6.1.2
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. 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.

Table 14.2.1.6c
Sensitivity Analysis on Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Day 43- Comparison of Different Models
mITT Population

Models	Statistic	Evenamide (N=156)
Primary Estimand	Mean Change from Baseline (SD)	-9.5 (7.13)
	95% CI	(-10.60, -8.32)
	p-value	<.001
LOCF@	Mean Change from Baseline (SD)	-9.3 (7.14)
	95% CI	(-10.40, -8.14)
	p-value	<.001
MI	Mean change from Baseline (SD)	-9.4 (7.07)
	95% CI	(-10.56, -8.31)
	p-value	<.001

Source: Listing 16.2.6.1.2
N - Total number of subjects in the mITT Population, SD = Standard Deviation. p-value = Paired t-test.
LOCF = Last observation-carried forward, MI = Multiple Imputation, CI = Confidence Interval, The results obtained in each model are compared in this table.
@ In case subject has not taken any rescue medication and not added any further efficacy data, LOCF will be considered as supportive.

Table 14.2.2.1c
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S)-
Overall Comparison mITT Population

			Evenamide (N=156)
Visit	Statistic	Observed	Change from Baseline
Screening	n	156	
	Mean (SD)	4.5 (0.58)	
	Median	4	
	Min, Max	4, 6	
Baseline	n	156	
	Mean (SD)	4.5 (0.58)	
	Median	4	
	Min, Max	4, 6	

Source: Listing 16.2.6.2
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.

Table 14.2.2.1c
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S)-
Overall Comparison mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Day 8	n	154	154
	Mean (SD)	4.4 (0.60)	-0.1 (0.33)
	Median	4	0
	Min, Max	3, 6	-2, 0
Day 15	n	153	153
	Mean (SD)	4.2 (0.65)	-0.3 (0.52)
	Median	4	0
	Min, Max	2, 6	-3, 0

Source: Listing 16.2.6.2
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.

Table 14.2.2.1c
Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S)-
Overall Comparison mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Day 29	n	153	153
	Mean (SD)	4.0 (0.71)	-0.5 (0.62)
	Median	4	0
	Min, Max	2, 6	-3, 0
Day 43	n	152	152
	Mean (SD)	3.8 (0.74)	-0.7 (0.71)
	Median	4	-1
	Min, Max	2, 6	-3, 1
	95% CI		(-0.84, -0.61)
	p-value		<.001

Source: Listing 16.2.6.2
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.

Reference Datasets:ADSL, CGI-S
Program Path:D:\Studies\study_014\CSR_014\Adhoc\Prog\Table 14.2.2.1c.sas
Programmer:AG
Date of Extraction:05FEB2023 Final- 25APR2023:11:26

Table 14.2.2.2c
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 - Paired t-test Using Multiple Imputation
mITT Population

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	4.5 (0.58)
	Median	4.0
	Min, Max	4, 6
Day 43	n	156
	Mean (SD)	3.8 (0.74)
	Median	4.0
	Min, Max	2, 6
	Mean change from Baseline (SD)	-0.7 (0.70)
	95% CI	(-0.83, -0.61)
	p-value	<.001

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation, CI = Confidence Interval. Min = Minimum, Max = Maximum.
Results are obtained from the data, which has imputed missing values by Monotone Regression Method. The imputations were averaged prior to calculating descriptive statistics. p-value = Paired t-test.

Table 14.2.2.3c
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43 – Paired t-test Using LOCF
mITT Population

Visit	Statistic	Evenamide (N=156)
Baseline	n	156
	Mean (SD)	4.5 (0.58)
	Median	4.0
	Min, Max	4, 6
Day 43	n	156
	Mean (SD)	3.8 (0.74)
	Median	4.0
	Min, Max	2, 6
	Mean change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.82, -0.59)
	p-value	<.001

Source: Listing 16.2.6.2
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.
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.

Table 14.2.2.4c
Sensitivity Analysis on Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) at Day 43- Comparison of Different Models
mITT Population

Models	Statistic	Evenamide (N=156)
Primary Estimand	Mean Change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.84, -0.61)
	p-value	<.001
LOCF@	Mean Change from Baseline (SD)	-0.7 (0.71)
	95% CI	(-0.82, -0.59)
	p-value	<.001
MI	Mean Change from Baseline (SD)	-0.7 (0.70)
	95% CI	(-0.83, -0.61)
	p-value	<.001

Source: Listing 16.2.6.2
N - Total number of subjects in the mITT Population, MI = Multiple Imputation, LOCF = Last observation-carried forward, CI = Confidence Interval, p-value = Paired t-test, SD = Standard Deviation.
@ In case subject has not taken any rescue medication and not added any further efficacy data, LOCF will be considered as supportive.

Table 14.2.3.1c
Clinical Global Impression - Change from Baseline (CGI-C)-
Overall Comparison mITT Population

Visit	Statistic	Evenamide (N=156)
Day 8	n	154
	Mean (SD)	3.8 (0.48)
	Median	4
	Min, max	2, 5
Day 15	n	153
	Mean (SD)	3.5 (0.56)
	Median	3
	Min, max	2, 5

Source: Listing 16.2.6.3
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

Table 14.2.3.1c
Clinical Global Impression - Change from Baseline (CGI-C)-
Overall Comparison mITT Population

Visit	Statistic	Evenamide (N=156)
Day 29	n	153
	Mean (SD)	3.3 (0.64)
	Median	3
	Min, max	2, 5
Day 43	n	152
	Mean (SD)	3.0 (0.72)
	Median	3
	Min, max	2, 5

Source: Listing 16.2.6.3
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

Table 14.2.4c
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Overall Comparison mITT Population

			Evenamide (N=156)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Social Contacts	Baseline	n	156	
		Mean (SD)	1.3 (0.93)	
		Median	1.5	
		Min, Max	0, 4	
	Day 43	n	152	152
		Mean (SD)	1.6 (1.01)	0.2 (0.56)
		Median	1.75	0
		Min, Max	0, 4	-2, 2.5

Source: Listing 16.2.6.4
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.

Reference Datasets:ADSL,LOF
Program Path:D:\Studies\study_014\CSR_014\Adhoc\Prog\Table 14.2.4c.sas
Programmer:AG
Date of Extraction:05FEB2023 Final- 25APR2023:11:33

Table 14.2.4c
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Overall Comparison mITT Population

			Evenamide (N=156)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Work	Baseline	n	156	
		Mean (SD)	1.2 (0.98)	
		Median	2	
		Min, Max	0, 3	
	Day 43	n	152	152
		Mean (SD)	1.3 (0.98)	0.1 (0.58)
		Median	2	0
		Min, Max	0, 4	-2, 2

Source: Listing 16.2.6.4
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.

Table 14.2.4c
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Overall Comparison mITT Population

			Evenamide (N=156)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Symptomatology	Baseline	n	156	
		Mean (SD)	2.8 (0.45)	
		Median	3	
		Min, Max	0.5, 4	
	Day 43	n	152	152
		Mean (SD)	3.0 (0.49)	0.2 (0.47)
		Median	3	0
		Min, Max	0.5, 3.5	-2, 2.5

Source: Listing 16.2.6.4
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.

Table 14.2.4c
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Overall Comparison mITT Population

			Evenamide (N=156)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Function	Baseline	n	156	
		Mean (SD)	2.4 (0.48)	
		Median	2.7	
		Min, Max	0.7, 4	
	Day 43	n	152	152
		Mean (SD)	2.5 (0.47)	0.1 (0.27)
		Median	2.7	0
		Min, Max	0.7, 4	-0.7, 1.4

Source: Listing 16.2.6.4
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.

Reference Datasets:ADSL,LOF
Program Path:D:\Studies\study_014\CSR_014\Adhoc\Prog\Table 14.2.4c.sas
Programmer:AG
Date of Extraction:05FEB2023

Table 14.2.4c
Change from Baseline in Strauss-Carpenter-Level of Functioning Scale(LOF) Total Score and Sub-scale Scores at Day 43- Overall Comparison mITT Population

			Evenamide (N=156)	
Sub-scale	Visit	Statistic	Observed	Change from Baseline
Total Score	Baseline	n	156	
		Mean (SD)	17.9 (4.05)	
		Median	19	
		Min, Max	3, 30	
	Day 43	n	152	152
		Mean (SD)	19.3 (4.17)	1.3 (2.73)
		Median	20	1
		Min, Max	3, 35	-11, 13
		95% CI		(0.88 ,1.76)
		p-value		<.001

Source: Listing 16.2.6.4
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.

Reference Datasets:ADSL,LOF
Program Path:D:\Studies\study_014\CSR_014\Adhoc\Prog\Table 14.2.4c.sas
Programmer:AG
Date of Extraction:05FEB2023 Final- 25APR2023:11:33

Table 14.2.5c
Change from Baseline in Medication Satisfaction Questionnaire (MSQ)-
Overall Comparison mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	156	
	Mean (SD)	4 (0.78)	
	Median	4	
	Min, Max	2, 6	
Day 15	n	153	153
	Mean (SD)	4.5 (0.78)	0.5 (0.84)
	Median	5	0
	Min, Max	2, 7	-2, 3

Source: Listing 16.2.6.5
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
p-value = Paired t-test, Change from Baseline = Post Dose – Baseline.

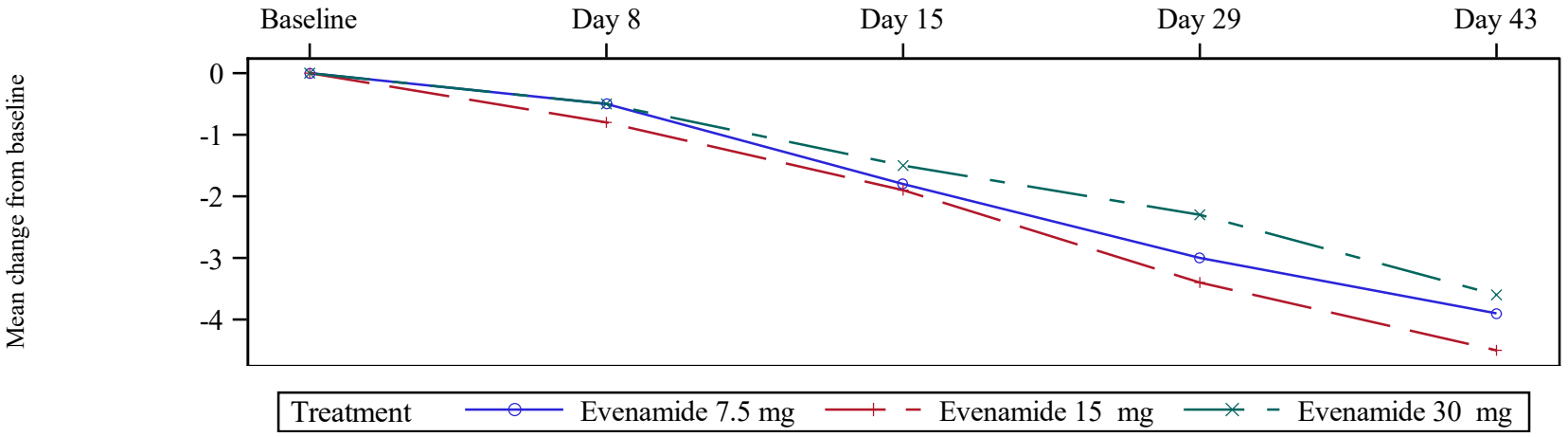
Table 14.2.5c
Change from Baseline in Medication Satisfaction Questionnaire (MSQ)-
Overall Comparison mITT Population

		Evenamide (N=156)	
Visit	Statistic	Observed	Change from Baseline
Day 43	n	152	152
	Mean (SD)	4.8 (0.8)	0.9 (1.06)
	Median	5	1
	Min, Max	2, 6	-4, 3
	95% CI		(0.71, 1.05)
	p-value		<.001

Source: Listing 16.2.6.5
N - Total number of subjects in the mITT Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum, CI = Confidence Interval, mITT = Modified intent-to-treat
p-value = Paired t-test, Change from Baseline = Post Dose – Baseline.

Figure 14.2.1.1
Mean Change from Baseline by Visit in PANSS
mITT Population

Total Positive Score



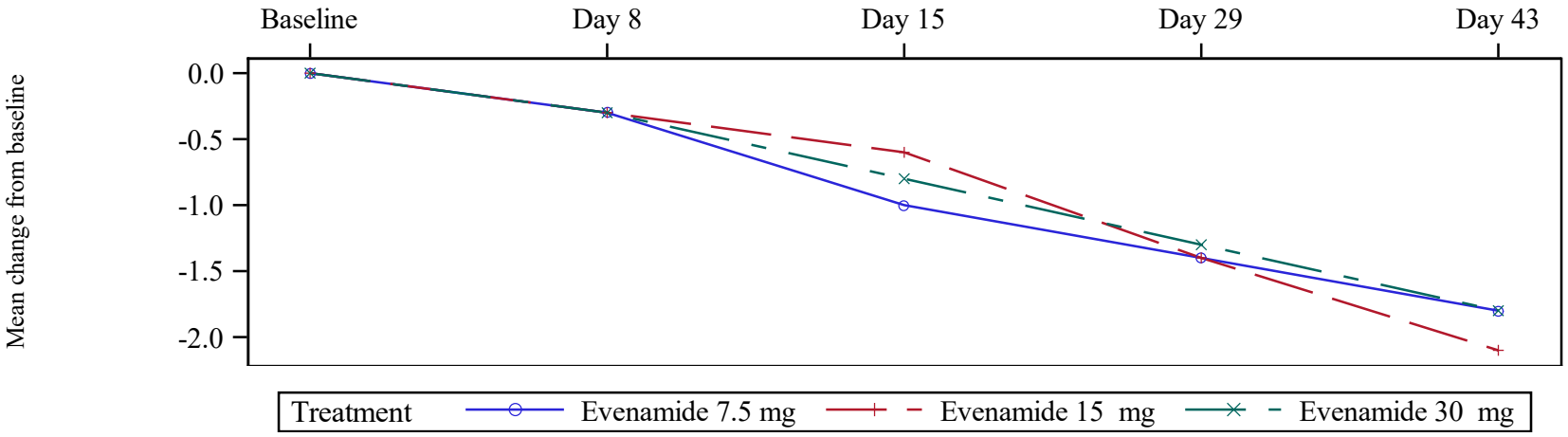
	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.5(1.25)	-1.8(1.81)	-3(2.9)	-3.9(3.52)
Evenamide 15 mg	0(0)	-0.8(1.21)	-1.9(2.23)	-3.4(2.8)	-4.5(3.75)
Evenamide 30 mg	0(0)	-0.5(1.16)	-1.5(2)	-2.3(2.5)	-3.6(2.77)

Source: Listing 16.2.6.1.1, Table 14.2.1.1

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.1.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:17

Figure 14.2.1.1
Mean Change from Baseline by Visit in PANSS
mITT Population

Total Negative Score



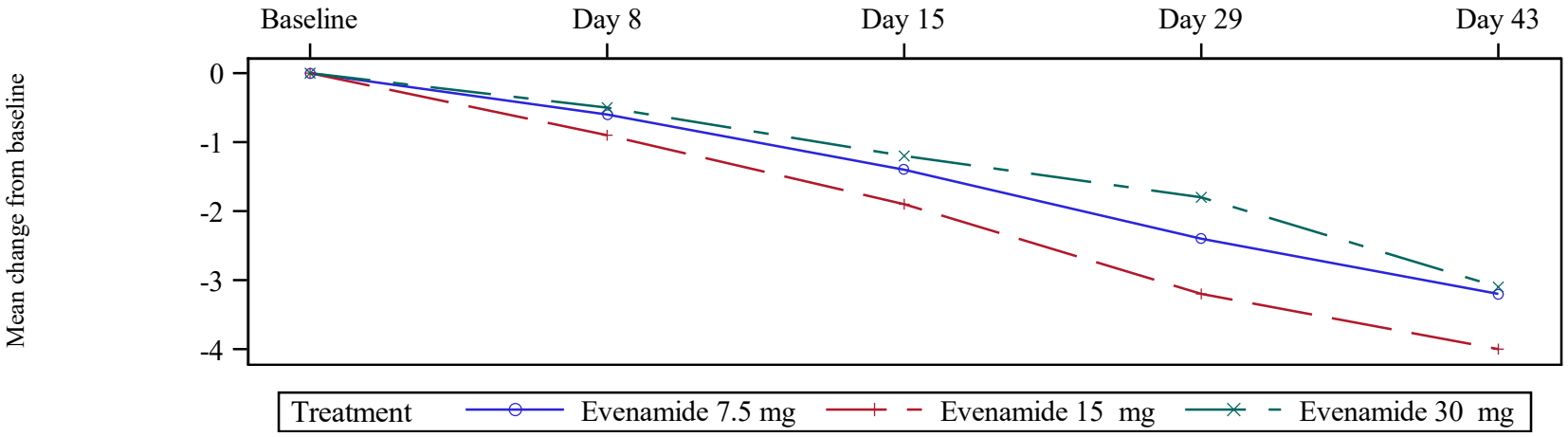
	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.3(0.67)	-1(1.8)	-1.4(2.51)	-1.8(2.71)
Evenamide 15 mg	0(0)	-0.3(0.94)	-0.6(1.55)	-1.4(1.99)	-2.1(2.74)
Evenamide 30 mg	0(0)	-0.3(0.84)	-0.8(1.29)	-1.3(1.55)	-1.8(2.18)

Source: Listing 16.2.6.1.1, Table 14.2.1.1

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.1.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:17

Figure 14.2.1.1
Mean Change from Baseline by Visit in PANSS
mITT Population

Total General Psychopathology Score



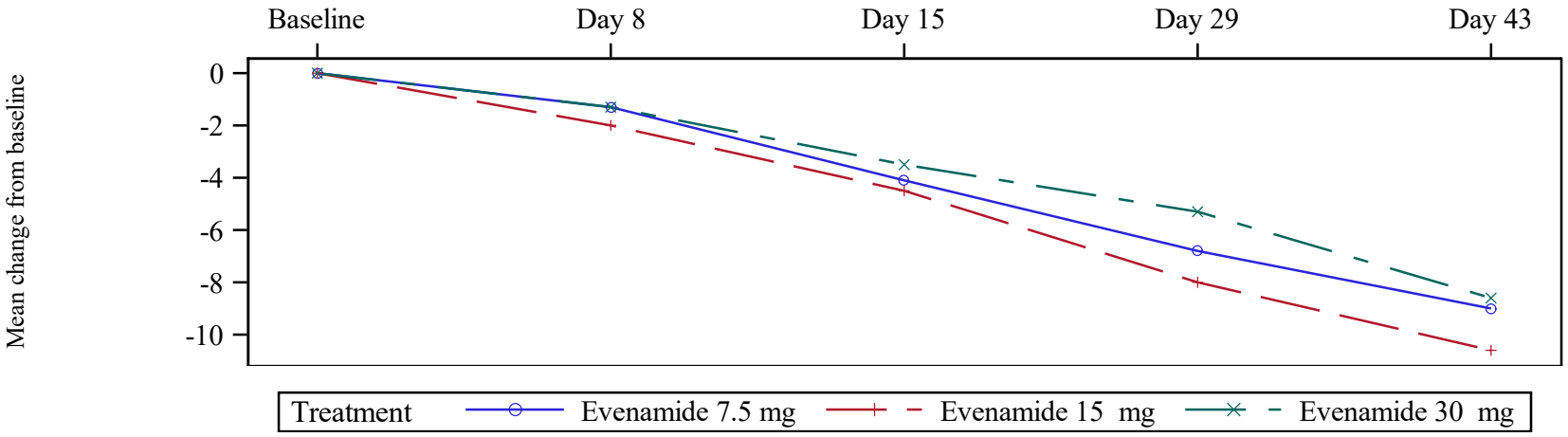
	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.6(1.05)	-1.4(1.67)	-2.4(2.13)	-3.2(3.05)
Evenamide 15 mg	0(0)	-0.9(1.74)	-1.9(2.19)	-3.2(2.61)	-4(3.34)
Evenamide 30 mg	0(0)	-0.5(1.88)	-1.2(1.98)	-1.8(2.32)	-3.1(2.94)

Source: Listing 16.2.6.1.1, Table 14.2.1.1

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.1.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:17

Figure 14.2.1.1
Mean Change from Baseline by Visit in PANSS
mITT Population

Total Score

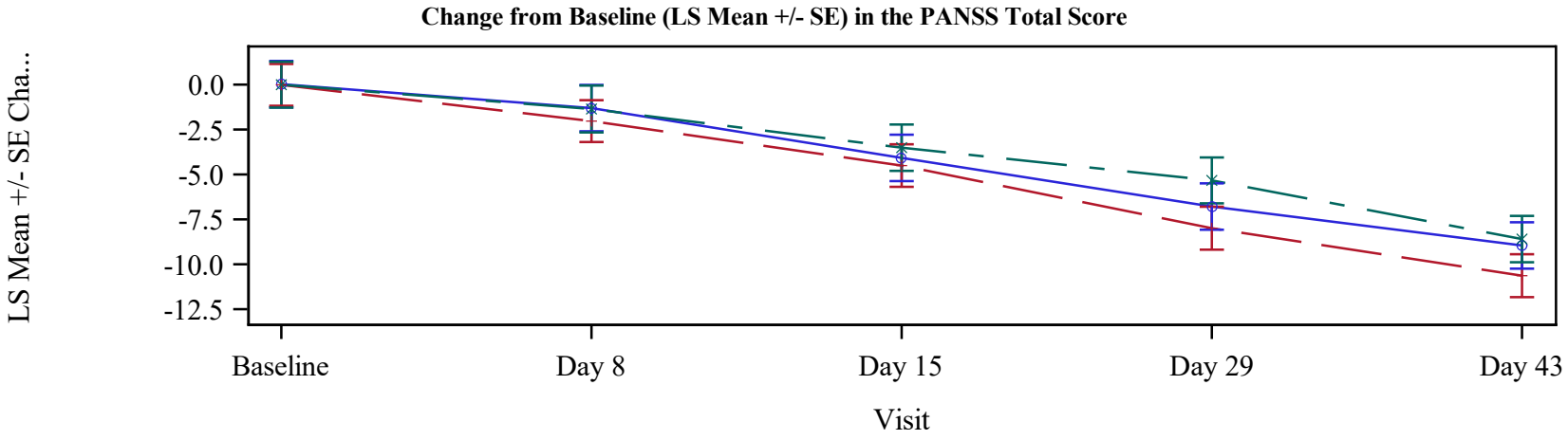


	Mean (SD)				
Evenamide 7.5 mg	0(0)	-1.3(2.37)	-4.1(3.63)	-6.8(5.8)	-9(7.4)
Evenamide 15 mg	0(0)	-2(2.94)	-4.5(4.13)	-8(5.42)	-10.6(7.49)
Evenamide 30 mg	0(0)	-1.3(3.12)	-3.5(4.17)	-5.3(5.16)	-8.6(6.35)

Source: Listing 16.2.6.1.1, Table 14.2.1.1

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.1.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:17

Figure 14.2.1.2
Change from Baseline (LS Mean +/- SE) in the PANSS Total Score Mixed Model
mITT Population

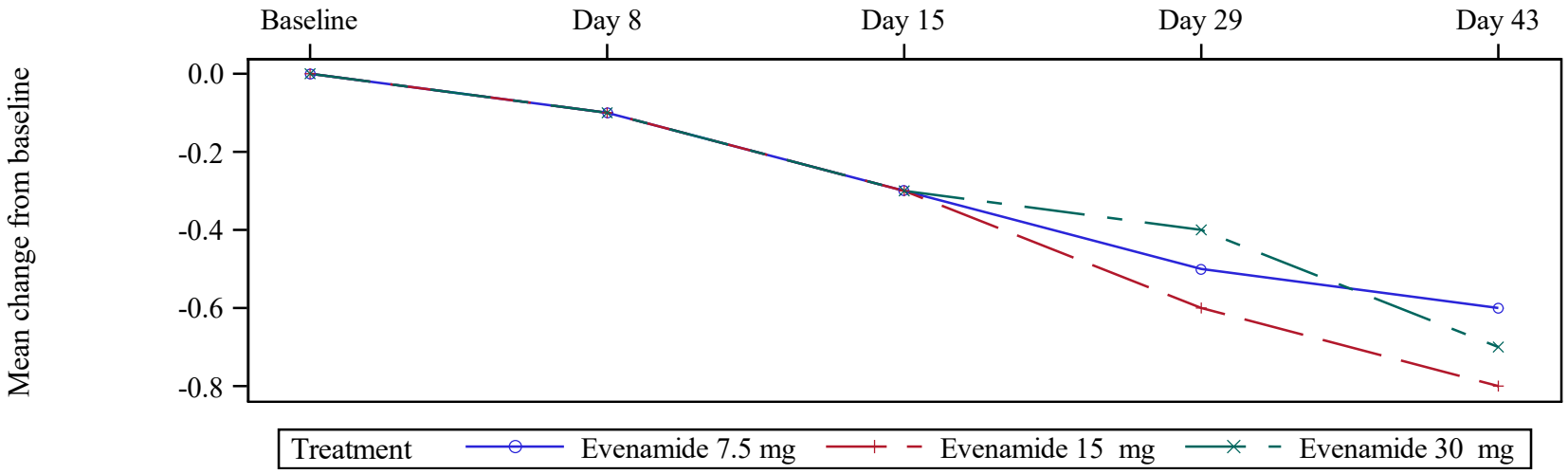


Number of Subjects					
Evenamide 7.5 mg	48	48	48	48	48
Evenamide 15 mg	59	59	57	56	56
Evenamide 30 mg	49	47	48	49	48

Source: Listing 16.2.6.1.1, Table 14.2.1.1

Reference Datasets:ADSL,PANSS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.1.2
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:18

Figure 14.2.2.1
Mean Change from Baseline by Visit in Clinical Global Impression
- Severity of Illness (CGI-S)
mITT Population

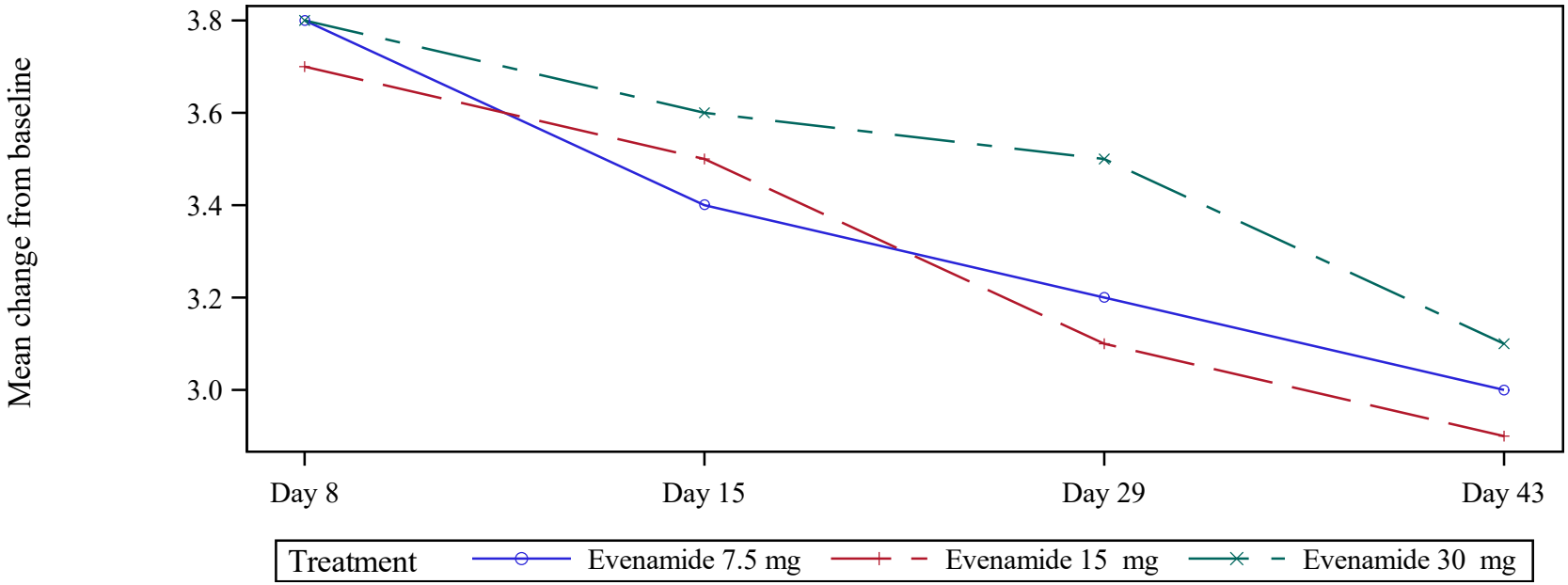


	Mean (SD)				
Evenamide 7.5 mg	0(0)	-0.1(0.35)	-0.3(0.49)	-0.5(0.65)	-0.6(0.79)
Evenamide 15 mg	0(0)	-0.1(0.33)	-0.3(0.57)	-0.6(0.62)	-0.8(0.72)
Evenamide 30 mg	0(0)	-0.1(0.31)	-0.3(0.49)	-0.4(0.58)	-0.7(0.62)

Source: Listing 16.2.6.2, Table 14.2.2.2

Reference Datasets:ADSL,CGIS
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.2.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:13:32

Figure 14.2.3.1
Mean Rating of Change from Baseline by Visit in
Clinical Global Impression - Change from Baseline (CGI-C)
mITT Population

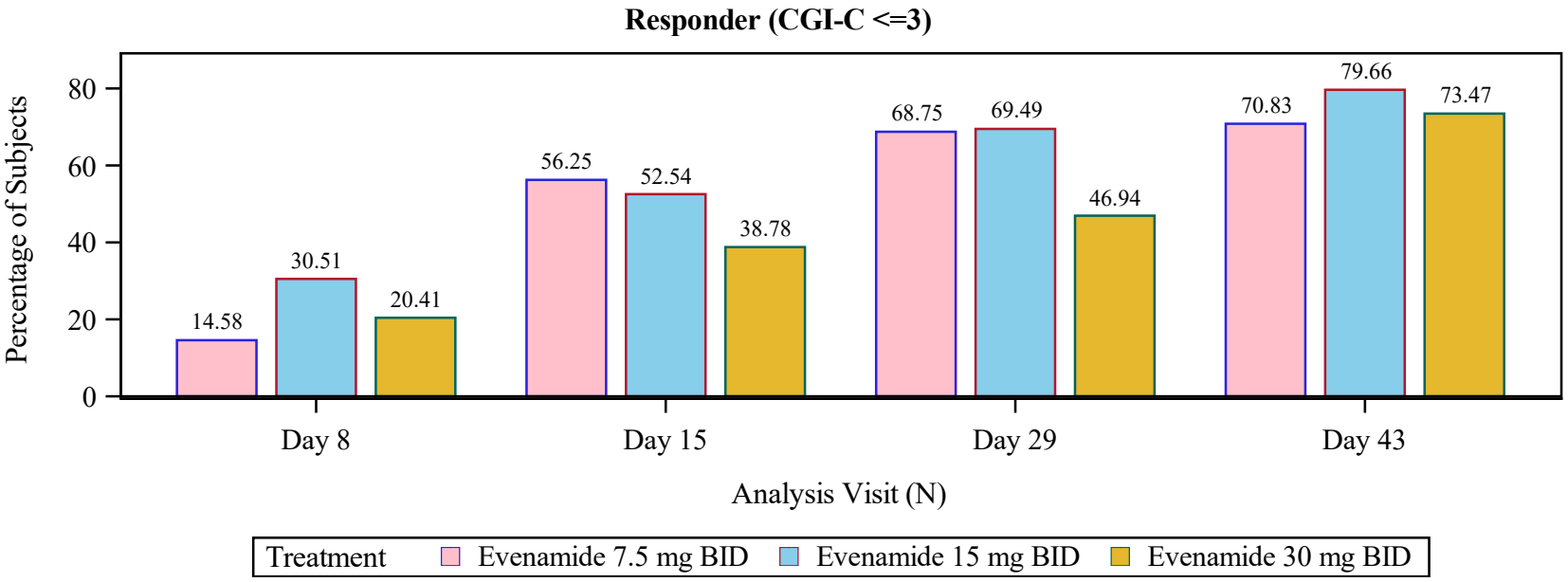


	Mean (SD)			
Evenamide 7.5 mg	3.8(0.43)	3.4(0.5)	3.2(0.62)	3(0.8)
Evenamide 15 mg	3.7(0.49)	3.5(0.6)	3.1(0.63)	2.9(0.72)
Evenamide 30 mg	3.8(0.51)	3.6(0.57)	3.5(0.62)	3.1(0.65)

Source: Listing 16.2.6.3, Table 14.2.3.2

Reference Datasets:ADSL,CGIC
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figure 14.2.3.1
Programmer:VM
Date of Extraction:05FEB2023 Final- 13FEB2023:14:19

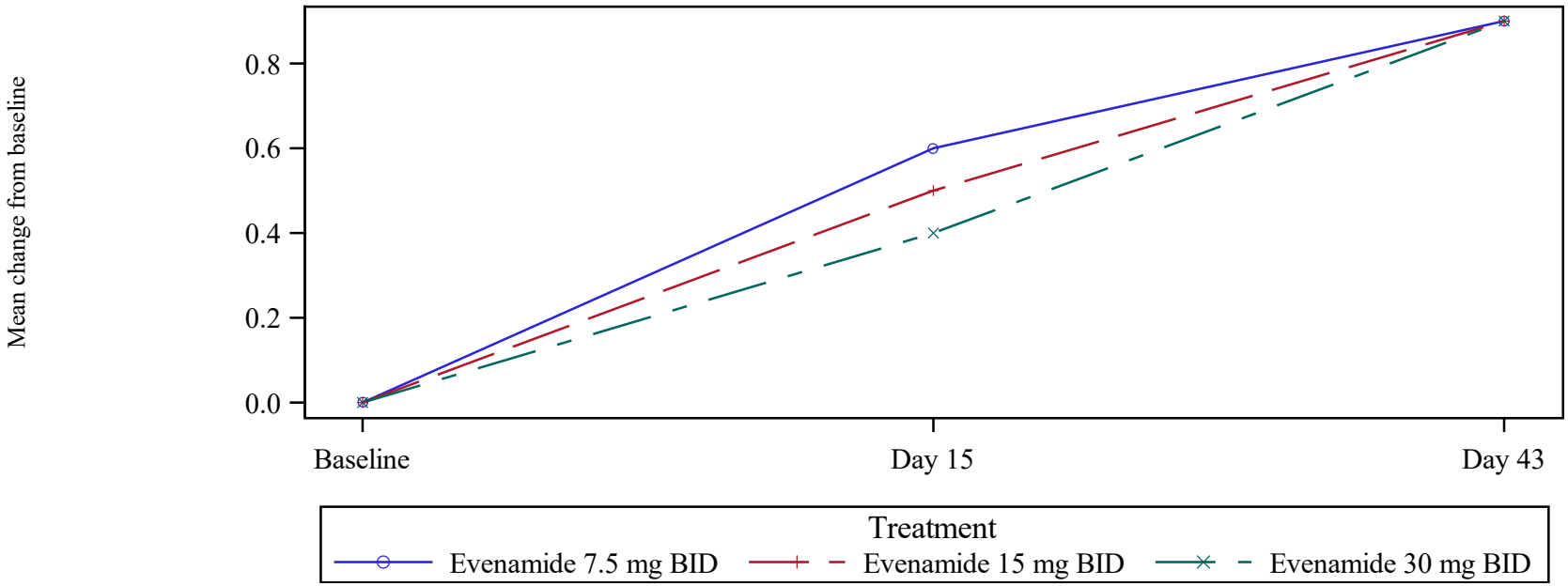
Figure 14.2.3.2
Bar Chart for Clinical Global Impression – Change from Baseline (CGI-C) Responder Analysis
mITT Population



Source: Listing 16.2.6.3, Table 14.2.3.2
Percentage of Subjects= No. of subjects in Responder (CGI-C <=3) at each dose group under mITT Population.
Patients with CGI-C Score of 1, 2 or 3.

Reference Datasets:ADSL,CGIC
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figures\Figure 14.2.3.2
Programmer:AG
Date of Extraction:05FEB2023 Final- 09JUN2023:16:58

Figure 14.2.4.1
Mean Change from Baseline by avisit in
Medication Satisfaction Questionnaire (MSQ)
mITT Population



	Mean (SD)		
Evenamide 7.5 mg BID	0(0)	0.6(0.79)	0.9(1.16)
Evenamide 15 mg BID	0(0)	0.5(0.91)	0.9(1.13)
Evenamide 30 mg BID	0(0)	0.4(0.84)	0.9(0.88)

Source: Listing 16.2.6.5, Table 14.2.5.2

Reference Datasets:ADSL,MSQ
Program Path:D:\Studies\study_014\CSR_014\development_programs\TFL_progs\Figure 14.2.4.1
Programmer:AG
Date of Extraction:05FEB2023 Final- 09JUN2023:17:07