Addendum to the Clinical Study Report

1. TITLE PAGE

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

This document represents an Addendum to the Study 015 clinical study report (CSR), and reports results from the study treatment period beyond Week 46 up to and including Week 94.

Investigational Medicinal Product	Evenamide (NW-3509)
Indication studied	Treatment-Resistant Schizophrenia
Protocol number	NW-3509/015/II/2019
EudraCT number	2020-000439-32
Development Phase	Phase II
First subject rolled over	18-Feb-2022 (Study 015 beyond Week 46)
Last subject completed	11-Oct-2024
Company/Sponsor signatory	Ravi Anand MD, Chief Medical Officer Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano), Italy
Study Duration	18-Feb-2022 to 11-Oct-2024
Date of Report	30-Jan-2025

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

2. SYNOPSIS

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

Title of Study:

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

Investigators: A total of 6 Principal Investigators in India took part to the study beyond Week 46.

Study Centers: The Study 015 beyond Week 46 was conducted at 6 centers in India.

Publication (Reference): None

Phase of Development: II

Study Period: 18-Feb-2022 to 11-Oct-2024 (for the Study 015 beyond Week 46)

Study Objectives:

Primary:

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

Secondary:

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

Study Design and Methods:

Study 015 is a 94-week (46-week initial period + 48-week additional period), open-label, multi-center, extension of the 6-week Study NW-3509/014/II/2019 (Study 014) designed to evaluate the long-term safety, tolerability, and preliminary efficacy of evenamide as add-on treatment in patients with TRS on a stable therapeutic dose of an antipsychotic.

The study design and methods, as well as analyses of efficacy and safety of Study 015 up to the nominal visit Week 46, have been described in a precedent Clinical Study Report (CSR NW3509-015-II-2019 Version 1.0 dated 08 Jul 2024), and therefore will not be included in this report.

Patients from India who completed the Week 46 visit in Study 015 and, according to the Investigator's opinion were benefitting from treatment with evenamide and had no safety concerns that would put them at risk, were eligible to continue treatment for an additional 24 weeks, for a total of 70 weeks of treatment in this study (Additional Period I). Patients who completed the Week 70 visit, and were deemed eligible by the Investigator, could continue treatment for an additional 24 weeks, for a total of 94 weeks of treatment (Additional Period II). Eligible patients signed a dedicated informed consent form (ICF) for each additional treatment period.

Patients were randomized to one of 3 evenamide dose groups (7.5 mg *BID*, 15 mg *BID* and 30 mg *BID*) in the antecedent Study 014. As per protocol *Amendment 4.1, dated 30th November 2021*, patients randomized to the 7.5 mg *BID* dose in Study 015 had their dose increased to 15 mg *BID* upon entry into or during Study 015, and no patient received the 7.5 mg *BID* dose beyond Week 46.

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

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

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

** Starting dose in Additional Period I.*

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

**** The 7.5 mg BID dose was discontinued, and any patients who were receiving a dose of 7.5 mg BID were switched to 15 mg BID; all patients in the 7.5 mg randomized dose group received the 15 mg BID dose in the additional treatment periods.*

Baseline (Day 0 of Study 014):

Study 014 baseline values were used for assessing changes from baseline for safety and efficacy parameters for the additional treatment periods of this extension study.

48-Week Additional Treatment Period:

After all final Study 015 (Week 46) evaluations, patients continuing in the first 24-week additional treatment period (up to Week 70) were given a supply of study medication at their current dose to cover the period until the next scheduled visit. Patients were instructed to take their first dose in the evening at their residence, at least 6 hours after the last dose in Study 015 that they received in the morning in the clinic.

The patients were required to return to the clinic for scheduled interim visits at Weeks 58 and 70 (Additional Period I), and Weeks 82 and 94 (Additional Period II). During these visits, selected safety and efficacy (e.g. PANSS, CGI-S/C and LOF) evaluations were performed. If no safety or tolerability issues were detected, the patients continued receiving their current dose. The patients received a telephone contact from the Investigator/site staff at Weeks 52 and 64 (Additional Period I), and Weeks 76 and 88 (Additional Period II), to inquire regarding any safety or tolerability issues that they may have experienced, and use of any concomitant medications.

Throughout the treatment period, at each scheduled visit or telephone contact, careful open-ended questioning was used to evaluate whether the patient had experienced symptoms and/or signs suggestive of neurological side-effects, severe sedation, seizures, or any other symptoms that were dose-limiting, e.g., hypotension. In case the patient reported any of these symptoms, the patient was asked to contact the Principal Investigator, who decided, based on the symptoms/signs that had been identified, whether the patient had to come in for an evaluation, whether their dosing regimen required modification, and/or whether a concomitant medication was added. In cases where further evaluation of the patient confirmed symptoms or signs suggestive of treatment

toxicity, the Investigator decided on the appropriate therapeutic and diagnostic measures. These may have included hospitalization, performance of a full neurological examination, EEG, ECG, etc.

All safety and efficacy evaluations were performed at the final visit at Week 70 for Additional Period I, and at Week 94 for Additional Period II (or at early discontinuation). For patients who discontinued prematurely, as well as those who discontinued after completing 70 weeks in Additional Period I, and those who completed a total of 94 weeks of treatment, a safety follow-up visit was performed one week after their final dose of study medication, during which an assessment of vital signs and adverse events was performed. In addition, the occurrence of any SAEs within 30 days after the final dose was reported (this information was collected through a telephone contact).

Study Population:

Subjects initially randomized in Study 014 who had completed Study 015 (Week 46) and signed the informed consent form (ICF) for the additional extension periods I and/or II until Week 70 and Week 94, respectively. The treatment periods beyond Week 46 were available for sites in India only.

Diagnosis and Main Criteria for Eligibility:

Inclusion and exclusion criteria for entry into Study 015 are listed in the prior CSR (Study 015 up to Week 46).

Patients who completed 46 weeks of treatment underwent a global assessment by the Investigator. If in the Investigator's opinion, the patient was benefitting from treatment with evenamide and had no safety concerns that would have put the patient at risk, he/she was eligible to continue treatment for an additional 24 weeks, for a total of 70 weeks of treatment in this study (Additional Period I). Patients who completed 70 weeks of treatment underwent a similar assessment by the Investigator, and if there was evidence of benefit from the study treatment and no safety concerns, the patient was eligible to continue treatment for an additional 24 weeks, for a total of 94 weeks of treatment in this study (Additional Period II).

Identity of Investigational Medicinal Product, Mode of Administration and Batch Number:

The study medication (hard gelatin capsules of evenamide) was administered orally twice daily (*BID*) as 15 mg and 30 mg dosage strengths. Information on the batches for each of the dosage strengths of evenamide capsules used in the study is provided in Synopsis Table 2.

Synopsis Table 2: Investigational Medicinal Product, Mode of Administration and Batch Numbers

Investigational Product Name	Formulation	Route	Manufacturing Authorization Holder	Strength	Batch Numbers
Evenamide (NW-3509)	Hard gelatin capsules	Oral	Newron Pharmaceuticals S.p.A.	7.5 mg	Not applicable as it was not used in the study beyond Week 46
				15 mg	17244/11 17244/17 17244/24 17244/40 17244/42
				30 mg	17244/25 17244/41 17244/43

Study medication (15 mg and 30 mg evenamide) was provided in 30 ml HDPE bottles. A 12-week supply of study medication was dispensed at the appropriate dose level for each patient at each scheduled visit.

Duration of Treatment:

The treatment period of Study 015 lasted up to 94 weeks including the initial 46 weeks, Additional Period I (24 weeks) and Additional Period II (24 weeks). In addition, patients had a safety follow-up visit 7 days after the last dose and a SAE follow-up assessment after 30 days.

Comparator, Dose and Mode of Administration: None

Criteria for Evaluation and Endpoints:

Safety Evaluations – Primary Safety Objective

Safety was assessed by the following measures:

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

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

Preliminary Efficacy Evaluations

Preliminary efficacy was assessed by the following measures:

Primary efficacy endpoint

- PANSS total score - mean change from baseline to endpoint

Secondary efficacy endpoints

- 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 – Negative 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 – proportion of patients with improvement from baseline to endpoint (≥20% on PANSS Total and ≥4-points on PANSS Positive Symptoms)
- CGI-S – proportion of patients with improvement from baseline to endpoint ("at least 2-category improvement" and "at least 1-category improvement").

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

Independent Safety Monitoring Board

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

Statistical Methods:

***Sample Size*:**

The extension periods beyond Week 46 were available for sites in India only, and they included all the patients continuing from the prior treatment periods considered eligible by the Investigator. No formal calculation of the sample size was performed.

Patient Characteristics:

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

Analysis Populations:

The Safety population consisted of all subjects who signed the ICF of the extension period beyond Week 46 and took at least one dose of study medication in this additional extension period of the study (Study 015 beyond Week 46).

Efficacy analyses have been carried out using the Modified Intent-to-Treat (mITT) population, Modified Intent-to-Treat Completers 1 (mITT-C1) population and Modified Intent-to-Treat Completers 2 (mITT-C2) population. The modified Intent-to-Treat (mITT) population comprised patients who received at least one dose of the study medication in this additional extension period of the study (Study 015 beyond Week 46), who had a valid Study 014 baseline, and had at least one post-baseline assessment for the primary efficacy measure, the PANSS total score, in the extension Study 015 beyond Week 46. The mITT-C1 completers population included subjects in the mITT population who have completed treatment through the Week 70 visit. The mITT-C2 completers population included subjects in the mITT population who have completed treatment through the Week 94 visit. Efficacy analyses were limited to the overall evenamide group, including all doses of evenamide combined.

Safety Analysis:

The Safety population was used for the analysis of all safety variables. The safety analysis for patients continuing in the additional treatment period in Study 015 included all safety data collected from the time of

the first dose of study medication in this extension period (beyond Week 46) and used the baseline values of all safety parameters from Study 014 as the baseline values. All AEs were summarized by body system and preferred term. The incidence (%) of SAEs, AEs that were newly occurring or worsened after administration of study medication in this extension study (i.e., treatment-emergent AEs [TEAEs]), and AEs leading to discontinuation (ADOs), were also summarized; the severity of each AE and relatedness to study medication was assessed and presented. Changes from baseline (Study 014) at each visit and at endpoint (Week 70, or Week 94, or early discontinuation) for vital signs, ECG and laboratory values, and findings on the physical/neurological examinations and standard eye examination, were summarized, with abnormal and clinically notable values/findings identified. Mean changes from baseline (Study 014) in the total score and sub-scale scores on the ESRS-A, and total score on the CDSS, were presented. Safety analyses included both dose-wise analyses and overall analyses combining all doses in a single evenamide treatment group.

Preliminary Efficacy Analysis:

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) were provided for all continuous long-term efficacy measures for actual values and changes from baseline (Study 014) at each time-point. The changes from baseline (Study 014) to endpoint (Week 70, or Week 94, or early discontinuation) for each of the continuous measures were analyzed and presented. For categorical variables, the number and percentage of patients in each category were presented at each time-point.

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

Mean values and mean changes from baseline (Study 014) to endpoint (Week 70, or Week 94, or early discontinuation) on the PANSS total score were presented. The mean score at each visit and at endpoint (Week 70, or Week 94, or early discontinuation) for the CGI-S and CGI-C were presented. The distribution of patients by each category of change and the proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3) on the CGI-C was provided. Mean values and mean changes from baseline (Study 014) to endpoint on the total scores on the PANSS – Positive Symptoms sub-scale, LOF, CGI-S, PANSS – General Psychopathology sub-scale, and PANSS – Negative Symptoms sub-scale were presented.

Summary – Results and Conclusions:

Subject Population and Study Disposition:

Ninety-six (96) subjects who completed Study 015 up to Week 46 (for a total duration of 1-year considering the 6 weeks of the core Study 014) rolled over in the Additional Period I, and 92 of these completed this first additional period up to Week 70.

The Sponsor had submitted to the DCGI the protocol Amendment 4.2 on 30th December 2022 to provide the opportunity for subjects to roll over into an additional treatment period (Additional Period II) from Week 70 to Week 94. This amendment was approved by the DCGI on 23rd November 2023, however, at that time, 73% of patients had already completed the first additional treatment period through Week 70, and had discontinued the study medication, and therefore, were not eligible to participate in the Additional Period II.

Eleven (11) subjects participated in the Additional Period II, and 9 of these completed this period through Week 94. No demographic or baseline characteristics differed notably between the treatment groups in the safety population.

After Protocol Amendment 4.1, subjects randomized to 7.5 mg *BID* had their dose of evenamide increased to 15 mg *BID*. Dose up-titration from 7.5 mg *BID* to 15 mg *BID* occurred for a total of 31 patients: for 21 cases the dose up-titration occurred at Week 46; while for the remaining 10 cases the dose was already up-titrated before Week 46. Therefore, the 7.5 mg *BID* randomized dose group can also be considered with the 15 mg *BID* dose group as per dose administered for this additional extension period.

The following populations were defined for analysis purposes:

Rolled over population: 96 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 31, 15 mg *BID* - 34, and 30 mg *BID* – 31] in Additional Period I; and 11 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 0, 15 mg *BID* - 4, and 30 mg *BID* – 7] in Additional Period II.

Safety Population: 96 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 31, 15 mg *BID* - 34, and 30 mg *BID* – 31]

mITT population: 93 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 28, 15 mg *BID* – 34, and30 mg *BID* - 31)]

mITT population-C1: 91 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 27, 15 mg *BID* – 33, and30 mg *BID* – 31]

mITT population-C2: 9 subjects [7.5 mg *BID (up-titrated to 15 mg BID)* - 0, 15 mg *BID* – 3, and 30 mg *BID* – 6]

Safety Results:

Treatment for up to 48 weeks in the Study 015 beyond Week 46 with evenamide at doses up to 30 mg *BID* was well-tolerated. A total of 6 (6.3%) subjects reported at least one TEAE, which included 3 (9.7%), 3 (8.8%) and 0 (0.0%) subjects in the evenamide 7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID* treated groups, respectively.

Of the 6 TEAEs reported, 4 (4.2%) were of mild severity [reported by 2 (6.5%) subjects in evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 2 (5.9%) subjects in evenamide 15 mg *BID* treated groups], 2 (2.1%) were of moderate severity [reported by 1 (3.2%) subject in evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 1 (2.9%) subject in the evenamide 15 mg *BID* treated groups], and none were of severe intensity.

The most frequently reported TEAE by PT was 'Hyponatraemia' with 2 (2.1%) subjects overall [2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group]. The other reported TEAEs by PT were 'Body temperature increased' with 1 (1.0%) subject overall [1 (2.9%) subject in the evenamide 15 mg *BID* treated group], 'Liver function test increased' with 1 (1.0%) subject overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group], 'Restlessness' with 1 (1.0%) subject overall [1 (2.9%) subject in the evenamide 15 mg *BID* treated group], 'Schizophrenia' with 1 (1.0%) subject overall [1 (2.9%) subject in the evenamide 15 mg *BID* treated group], 'Anaemia' with 1 (1.0%) subject overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group] and 'Seizure' with 1 (1.0%) subject overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group].

Overall, only one (1.0%) subject reported a Treatment-Related TEAE, which was in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group [1 (3.2%) subject] and reported under the preferred term 'Anaemia' in the SOC 'Blood and lymphatic system disorders'. This treatment-related TEAE was also of mild severity. None of the subjects experienced Any Serious and Treatment-Related TEAE in the Study 015 beyond Week 46.

Overall, 1 (1.0%) subject reported one Serious TEAE in the Study 015 beyond Week 46 and that one subject was from the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group [1 (3.2%) subject]. This SAE was a case of dilutional hyponatremia leading to a seizure that occurred 26 days after the subject had taken his last dose of evenamide (15 mg *BID*). The Investigator considered the event as 'not related' to evenamide, but due to the ingestion of a large volume of water, which was treated by administration of 100 mL i.v. bolus of 3 percent saline.

None of the subjects in any of the three treatment groups had a TEAE leading to study drug discontinuation in the Study 015 beyond Week 46. No death was reported in this Study 015 beyond Week 46.

There were no overdoses/ medication errors reported in this Study 015 beyond Week 46.

Very few clinical laboratory test results were deemed clinically significant by the Principal Investigator, and no patterns of laboratory abnormalities were noted in any of the three treatment groups.

The numbers of clinically notable vital sign abnormalities were low across all the treatment groups and no clinically meaningful trends were observed in the clinically notable abnormalities in any of the three treatment groups.

There were no abnormalities in any of the ECG parameters that were considered clinically significant by the Investigators in any of the three treatment groups. Analysis of categorical changes in the ECG did not indicate any pattern of effects of evenamide, including on the QTcF interval.

No safety concerns were noted on physical, neurological, or standard eye examinations, EPS (assessed by ESRS-A) or depressive symptoms (assessed by the CDSS) in any of the three treatment groups.

The treatment with evenamide beyond 1-year and up to 100 weeks, considering the initial treatment period of 6 weeks in Study 014, continued to be associated with an innocuous safety profile, based on the absence of any pattern of safety abnormality detected on any of the safety measures, including vital signs, laboratory tests, ECGs, physical, neurological, and standard eye examinations, extrapyramidal symptoms (assessed by the ESRS-A), changes in depressive symptoms (assessed by the CDSS), and the review of treatment-emergent adverse events.

Overall, the results for the safety parameters assessed in the study indicated that evenamide given orally at all doses [7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID*] as add-on treatment to first and second generation antipsychotics (excluding clozapine) in patients with treatment-resistant schizophrenia was well tolerated, without any major safety concern.

Efficacy Results:

Positive and Negative Syndrome Scale (PANSS)

A steady improvement in the PANSS total score was recorded at all study visits compared to baseline in the overall combined evenamide dose group for the mITT population, as well as for the mITT-C1 and mITT-C2 populations, reflecting a continuation of improvement in the symptoms of schizophrenia. Improvements were also observed on all three PANSS Subscales (Positive Syndrome, Negative Syndrome, and General Psychopathology).

In the overall combined evenamide dose group, the mean (SD) of PANSS total score recorded was 78.8 (5.05), 65.1 (10.02), 64.2 (10.16), 53.0 (7.14) and 53.3 (5.69) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline in the PANSS Total score recorded was -13.7 (9.00), -14.5 (9.32), -23.8 (7.97) and -23.7 (6.53) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

These results were confirmed by the Supportive Estimand Hypothetical Policy analysis of the mITT Population in the overall combined evenamide dose group.

Moreover, these results were supported by the proportion of patients in the mITT population achieving a clinically meaningful level of improvement on the PANSS (Total score reduction ≥20%, as described by Rosenheck et al., 1997 and Meltzer et al., 2008, and ≥4 points improvement on PANSS Positive Symptoms sub-scale score), which increased over time in each additional treatment period.

The proportion of responders, based on a ≥ 20% reduction in the PANSS total score from baseline, increased over time in each additional treatment period. In Additional Period I, the number (%) of 'responders' in the overall combined evenamide dose group for the mITT population was 37 (39.8%) and 38 (40.9%) at Week 58 and Week 70/End of Study, respectively. In Additional Period II, the number (%) of responders in the overall combined evenamide dose group for the mITT population was 7 (63.6%) and 9 (81.8%) at Week 82 and Week 94/End of Study, respectively.

Global Impression - Severity of illness (CGI-S)

A steady decrease (improvement) in the CGI-S score of the mITT Population in the overall combined evenamide dose group was observed at all study visits (Week 58, 70/End of Study, 82 and 94/End of Study) compared to baseline. In the overall combined evenamide dose group, the mean (SD) of CGI-S score recorded was 4.5 (0.62), 3.5 (0.73), 3.5 (0.75), 3.1 (0.33) and 3.0 (0.45) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD)

change from baseline in the CGI-S showed a steady decrease in the overall combined evenamide dose group with -1.0 (0.70), -1.0 (0.72), -1.0 (0.00) and -1.1 (0.30) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

Results of responders analysis on the CGI-S showed an increasing proportion of patients meeting the responder criteria (at least 1- or 2-category improvement) in each additional treatment period. In the Additional Period I, the number (%) of responders improving by at least 2 categories on the CGI-S (reduction of CGI-S from baseline of ≥ 2) in the overall combined evenamide dose group was 20 (21.5%) and 20 (21.5%) at Week 58 and Week 70/End of Study, respectively. In the Additional Period II, the number (%) of responders (reduction of CGI-S from baseline of ≥ 2) in the overall combined evenamide dose group was 0 (0.0%) and 1 (9.1%) at Week 82 and Week 94/End of Study, respectively. A similar trend was observed in the analysis of responders improving by at least 1 category (CGI-S score reduction from baseline of ≥ 1) wherein the number (%) of responders in the overall combined evenamide dose group was 76 (81.7%) and 77 (82.8%) at Week 58 and Week 70/End of Study, respectively in the Additional Period I and 9 (81.8%) and 11 (100.0%) at Week 82 and Week 94/End of Study, respectively in the Additional Period II.

Global Impression - Change from baseline (CGI-C)

The mean rating on the CGI-C showed a decrease by visit in the overall evenamide dose group for the mITT population. Furthermore, an increasing proportion of patients over time were considered responders in each additional period, based on the definitions of at least "minimally improved" and at least "much improved" on the CGI-C. In the overall combined evenamide dose group, the mean (SD) of CGI-C score observed was 2.7 (0.83), 2.7 (0.79), 2.1 (0.78) and 2.2 (0.60) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

The number (%) of subjects rated as "improved" (score ≤ 3, i.e. any improvement) on the CGI-C in the overall combined dose group was 79 (84.9%), 81 (87.1%), 9 (81.8%) and 11 (100.0%) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively, increasing at each visit in each additional period. A similar trend was observed in the analysis of responders rated at least "much improved" (CGI-C score ≤ 2) in the overall combined evenamide dose group.

Strauss-Carpenter Level of Functioning (LOF) scale

An increase in the LOF Total Score was observed at Weeks 70 and 94 compared to baseline in the overall combined evenamide dose group, indicating improvement in functionality of subjects after treatment with evenamide in addition to their background antipsychotic. At baseline, the LOF mean (SD) total score recorded was 18.3 (3.84), which improved to 20.5 (4.07), 20.6 (3.89), 20.6 (2.46) and 21.6 (3.83) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline in the LOF total score observed in the overall combined evenamide dose group was 2.2 (3.69), 2.3 (3.81), 3.1 (2.26) and 3.4 (2.91) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. There was a continuous increase in the mean change from baseline in the LOF Total Score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study, indicating improvement in functionality of subjects after treatment.

Improvement was also observed in the LOF Subscales (Social Contact, Work, Symptomatology and Function Subscales) at Weeks 70 and 94 compared to baseline in the overall combined evenamide dose group.

Though improvements were observed in various efficacy scales, the efficacy data should not be considered statistically conclusive for the data beyond Week 46, considering the fact that a small number of subjects (n=96) rolled over in the Additional Period I up to Week 70 (24 Weeks), which was further reduced (n=11) in the Additional Period II up to Week 94 (24 Weeks). The major reason for this limited roll-over was that, by the time the regulatory approvals were obtained for Protocol Amendments 4.1 dated 30 November 2021 and 4.2 dated 08 July 2022, which allowed enrollment of patients in the additional treatment periods, many of the subjects had already completed Week 46 or Week 70 and had discontinued study medication before getting a chance to be enrolled in the Additional Period I and Additional Period II, respectively.

The long-term treatment with evenamide [7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID*] as add-on to first and second generation antipsychotics (excluding clozapine) in patients with TRS was associated

with an improvement in symptoms of schizophrenia assessed by the PANSS (total score and subscales), a decrease in disease severity assessed by the CGI-S score, overall improvement from baseline assessed by the CGI-C, and enhancement in functionality of patients assessed by the LOF. These beneficial effects, which increased over time, were observed in patients with TRS not responding adequately to their stable, therapeutic dose of a single antipsychotic medication.

Conclusions:

Long-term safety results from the Additional Period I and Additional Period II in Study 015 beyond Week 46, suggest that evenamide was well tolerated at the doses of 7.5 mg (up-titrated to 15 mg *BID*), 15 mg, and 30 mg *BID* up to Week 94, for an overall duration of treatment up to 100 weeks, including 6 weeks of the core Study 014. Long-term treatment with evenamide was devoid of any pattern of newly emergent or worsening abnormalities on any of the safety measures including TEAEs, laboratory tests, vital signs, ECG, physical, neurological and eye examinations, extrapyramidal symptoms (ESRS-A), and depressive symptoms (CDSS). In addition, no dropouts due to adverse events were reported in the treatment period beyond Week 46.

All efficacy measures showed improvement over time up to 94 weeks in the mean change from baseline (Study 014) in the overall combined evenamide dose group. Similarly, the responder rates for the PANSS Total Score (≥20% improvement from baseline), as well as for the CGI-S (1- or 2-category improvement from baseline), and CGI-C ("any improvement" and at least "much improved") increased by visit in each additional treatment period. These results, although collected in an open-label trial, with no control group, either active or placebo, and with subjects from a single country (i.e. India), continue to show a long-lasting improvement confirming the benefits observed during the first year of treatment (Studies 014 and 015 up to Week 46).

This study was conducted in compliance with International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

3. TABLE OF CONTENTS

3.1. LIST OF IN-TEXT TABLES

3.2. LIST OF IN-TEXT FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADO	Adverse Dropout (Discontinuation Due to Adverse Event)
AE	Adverse Event
ALT	Alanine-Aminotransferase
AST	Aspartate-Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
BMI	Body Mass Index
CAM	Current Antipsychotic Medications
CDSS	Calgary Depression Scale for Schizophrenia
CGI-C	Clinical Global Impression – Change from Baseline
CGI-S	Clinical Global Impression – Severity of Illness
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
DCGI	Drugs Controller General of India
DSM-5	Diagnostic And Statistical Manual of Mental Disorders – 5th Edition
ECG	Electrocardiogram
EEG	Electroencephalogram
EPS	Extrapyramidal Symptoms
ESRS-A	Extrapyramidal Symptom Rating Scale – Abbreviated Version
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
hr	Hour(S)
HS	*Hora Somni* (At Bedtime)
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISMB	Independent Safety Monitoring Board
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein

LOF	Strauss-Carpenter Level of Functioning Scale
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
min	Minimum
mITT	Modified Intent-to-Treat
NCS	Not Clinically Significant
OC	Observed Cases
OD	Once Daily
OTC	Over The Counter
PANSS	Positive And Negative Syndrome Scale
PAM	Prior Antipsychotic Medications
PD	Protocol Deviation
PI	Principal Investigator
P.O.	Per Os
PT	Preferred Term
qd	Every Day
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of units
SOC	System Organ Class
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Event
THC	Tetrahydrocannabinol
TID	Three Times a Day
TRS	Treatment-Resistant Schizophrenia
TSH	Thyroid Stimulating Hormone
VGSC	Voltage-Gated Sodium Channels
WBC	White Blood Cells

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

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

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

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

All subjects reconsented to the changes related to the discontinuation of the 7.5 mg *BID* dose and extension of the study for an additional 48 weeks (24 weeks of Additional Period I as per *Amendment 4.1, dated 30th November 2021* and 24 weeks of Additional Period II as per *Amendment 4.2, dated 08th July 2022*) before continuing in Study 015 beyond Week 46.

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 before the ICF was signed. The informed consent procedure was done according to the guidelines provided in the Declaration of Helsinki and the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP).

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

The Investigator assured Newron Pharmaceuticals SpA that Informed Consent was obtained by signing the Investigator Statement (Appendix 3 of the study protocol provided in Appendix 16.1.1).

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

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Study 015 beyond Week 46 was conducted at 6 sites in India. A list of principal investigators (PI), sub-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. All people involved at the clinical centers were qualified to perform their roles. The study administrative structure is described in Table 6-1.

Table 6-1 Study Administrative Structure

Sponsor Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano) Italy Tel: +39-02-6103461	**Contract Research Organization (CRO)** CliniRx Tangent Research India Pvt Ltd Patriot House, 4th Floor, 3 BSZ Marg, New Delhi-110002 India
ISMB Committee Members **R. Krishnan, M.D. (Chairman of the ISMB)** CEO of the Rush University System for Health Rush University Medical Center Rush Ambulatory Behavioral Health 1645 W. Jackson Blvd. Suite 600 Chicago, IL 60612 Phone: +1 312 942 5372 Fax: +1 312 942 4224 Email: RangaKrishnan@rush.edu	**Adverse Event Reporting** **Rodolfo Giuliani** Head of Medical Affairs and Drug Safety Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (MI), Italy Tel: + 39 02 61034631 Fax: + 39 02 61034637 Email: rodolfo.giuliani@newron.com Drug Safety Newron Pharmaceuticals S.p.A. drugsafety@newron.com

Robert W. Buchanan, M.D. Professor of Psychiatry University of Maryland Psychiatry Research Center 701 West Pratt Street Baltimore, MD 21201 Phone: +1 410 402-7876 Fax: +1 410 402 7198 Email: rwbuchanan@som.umaryland.edu **Richard G. Trohman, M.D**. Professor of Medicine and Director of Electrophysiology Division of Cardiology Rush University Medical Center 1653 W. Congress Parkway. Chicago, IL 60612 Phone: +1 312 674 4003 Fax: +1 312 674 4013 Email: raymondnarh@rush.edu	**AWINSA LIFE SCIENCES** Sanjeev Miglani Medical Director 513B, Sector-22, Gurugram, 122015, India Email: newronsafety@awinsals.com
List of Vendors	
Central ECG Services Clario eResearchTechnology, Inc. 1818 Market Street, Suite 1000, Philadelphia, Pennsylvania 19103, USA	**Clinical Laboratory Services** Central Laboratory for India Metropolis Healthcare Ltd. 250 D, Udyog Bhavan, Hind Cycle Lane Worli, Mumbai-400030
Study Monitoring, Medical Monitoring, Data Management, Biostatistics, CSR preparation CliniRx Research Pvt Ltd Patriot House, 4th Floor; 3, Bahadur Shah Zafar Marg New Delhi-110002, India	**Pharmacovigilance:** AWINSA Life Sciences 513 B Sector 22 Pocket B 122015, Gurgaon India sanjeev.miglani@awinsals.com
Drug Supply Management Thermo Fisher FISHER CLINICAL SERVICES GMBH Steinbühlweg 69, CH-4123 Allschwil, Switzerland	

7. INTRODUCTION

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. NW-3509 normalizes glutamate release induced by aberrant sodium channel activity, without affecting basal glutamate levels, due to its inhibition of VGSCs. 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).

Additional information on the pre-clinical and clinical pharmacology, toxicology and clinical studies conducted to date for evenamide is included in the study protocol in Appendix 16.1.1, in the main clinical study report (CSR) of Study 015 covering the treatment period until Week 46, and in the Investigator's Brochure.

8. STUDY OBJECTIVES

The objectives of the study were as follows:

8.1. Primary objective

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

8.2. Secondary objectives

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

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan - Description

Study 015 is a 94-week (46-week initial period + 48-week additional period), open-label, multi-center, extension of Study NW-3509/014/II/2019 (Study 014) designed to evaluate the

long-term safety, tolerability, and preliminary efficacy of evenamide as add-on treatment in patients with TRS on a stable therapeutic dose of a single antipsychotic.

The study design and methods, as well as analyses of efficacy and safety of Study 015 up to the nominal visit Week 46, have been described in a precedent Clinical Study Report (CSR NW3509-015-II-2019 Version 1.0 dated 08 Jul 2024), and therefore will not be included in this report. Patients randomized in Study 014 who completed 6 weeks of open-label treatment, were not experiencing moderate/severe side effects, and not showing severe worsening of their symptoms of schizophrenia, and met other entry criteria for this study were eligible to receive evenamide in this open-label extension study (Study 015).

Patients from India who completed 46 weeks of treatment in Study 015 and, according to the Investigator's opinion were benefitting from treatment with evenamide and had no safety concerns that would put the patients at risk, were eligible to continue treatment for an additional 24 weeks, for a total of 70 weeks of treatment in this study. Patients who completed 70 weeks of treatment, and were deemed eligible by the Investigator, were eligible to continue the treatment for an additional 24 weeks, for a total of 94 weeks of treatment.

Patients were required to return to the clinic for scheduled interim visits at Weeks 58 and 70 (Additional Period I), and Weeks 82 and 94 (Additional Period II). During these visits selected safety and efficacy (PANSS, CGI-S/C and LOF) evaluations were performed. If no safety or tolerability issues were detected, the patients continued receiving their current dose. Patients received a telephone contact from the Investigator/site staff at Weeks 52 and 64 (Additional Period I), and Weeks 76 and 88 (Additional Period II), to inquire regarding any safety or tolerability issues that they may have experienced, and use of any concomitant medications.

All safety and efficacy evaluations were to be performed at the final visit at Week 70 for Additional Period I, and at Week 94 for Additional Period II (or at early discontinuation during the additional period). For patients who discontinued prematurely, as well as those who discontinued after completing 70 weeks in Additional Period I, and those who completed a total of 94 weeks of treatment, a safety follow-up visit was performed one week after their final dose of study medication, during which an assessment of vital signs and adverse events was performed. In addition, the occurrence of any SAEs within 30 days after the final dose was reported (this information could be collected through a telephone contact).

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

Table 9-1 Summary of Study Design

Period	Pre-Treatment		Study 014 and Study 015 Initial Treatment Period	Study 015 beyond Week-46 Additional Treatment Periods I and II				Post-Treatment	
Visit	**Screening**	**Baseline**	**Week 46**	**Week 58**	**Week 70****	**Week 82**	**Final[$] (Week 94 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	-21 to -1	0/1 (pre-dose)	365	449	533	617	701	7 days after last dose	30 days after last dose
Duration	3-21 days	0/1	322 days	84 days	84 days	84 days	84 days	7 days	30 days
Treatment/ Procedures	Informed consent; Screening evaluations performed; I/E criteria assessed; urine drug screen; serum pregnancy tests in women of child-bearing potential	Patient checked into clinic; Baseline safety and efficacy evaluations; repeated urine drug screen; alcohol breath test; urine/serum pregnancy tests in women of child-bearing potential; confirm I/E criteria met	First dose of evenamide for additional treatment period taken at Week 46.	Selected safety and all efficacy assessments.	All final safety and efficacy assessments; serum prolactin; urine drug screen; serum pregnancy test.	Selected safety and all efficacy assessments.	Last dose of study medication; all final safety and efficacy assessments; serum prolactin; urine drug screen; serum pregnancy test.	Safety evaluations (vital signs and AEs) performed 7 days after last dose of study medication	Contacted patient 30 days after last dose of study medication to assess occurrence of any SAEs
Telephone Contact			Week 52 (AEs and Conc. Medication)	Week 64 (AEs and Conc. Medication)	Week 76 (AEs and Conc. Medication)	Week 88 (AEs and Conc. Medication)		If patient did not return for scheduled visit, contacted to assess AEs	Information collected via telephone contact

[$]*Final evaluation for patients who discontinued prematurely.*
**Performed for patients who discontinued prematurely, as well as those who discontinued after completing 70 weeks of treatment in Additional Period I, and those who completed 94 weeks of treatment in Additional Period II.*
***This visit served as the final evaluation for patients who completed 70 weeks of treatment in Additional Period I and did not continue in Additional Period II.*
***Abbreviations:** AEs: adverse events; BID: twice daily; Conc.: concomitant; d/c: discontinuation; I/E: inclusion/exclusion; SAEs: serious adverse events*

9.2. Discussion of Study Design, Including Choice of Control Groups

Study 014 (core study) and Study 015 were both phase 2, open-label trials, with no placebo control, mainly designed to collect long-term data on safety and tolerability, and preliminary evidence of efficacy of evenamide at three different doses. An open-label study design was chosen for this extension study, as this allowed the treating physicians to be aware to the patient's allocation to treatment and adjust the patient's dose in case of tolerability issues.

The assessment of efficacy was performed by trained raters (all psychiatrists) blinded to the dose of evenamide.

Initially, Study 014 included evenamide 7.5 mg *BID* and 15 mg *BID.* The ISMB, after the review of safety and efficacy results of the first 50 patients randomized to treatment, allowed the introduction of evenamide 30 mg *BID* and the dose of evenamide 7.5 mg *BID* was removed through protocol *Amendment 4 dated 18th June 2021*. The randomization ratio was adjusted to have an approximately equal number of patients randomized to the three treatment groups.

Patients treated with evenamide 7.5 mg *BID* in Studies 014 and 015 were up-titrated to evenamide 15 mg *BID* starting from the subsequent scheduled visit. A total of 13 patients were up-titrated to evenamide 15 mg *BID* from evenamide 7.5 mg *BID* during Study 015 and the remaining 21 subjects at Week 46 (last visit of the first year of treatment). Therefore, all the subjects who participated in the treatment periods beyond Week 46 were receiving evenamide 15 mg *BID* or 30 mg *BID*. The dose could be reduced to once daily dosing at any time if intolerance developed, and patients could have entered Study 015 at these reduced doses.

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

9.3. Selection of Study Population

Patients from Indian sites who completed 46 weeks of treatment in Study 015 underwent a global assessment by the Investigator. If in the Investigator's opinion, the patient was benefitting from treatment with evenamide and had no safety concerns that would put the

patient at risk, he/she was eligible to continue treatment for an additional 24 weeks in Additional Period I, for a total of 70 weeks of treatment in this study. Patients completing 70 weeks of treatment underwent a similar assessment for determining eligibility to continue treatment for another 24 weeks in Additional Period II, for a total of 94 weeks of treatment.

The same subject number assigned to each patient in Study 014 was used throughout Study 015 (initial period plus additional treatment periods) to identify the patient. The subject number was entered in the eCRF and the same appeared in the header of each eCRF page.

9.3.1. Inclusion Criteria

See prior CSR (Study 015 up to Week 46) for Study 015 Inclusion/Exclusion Criteria.

9.3.2. Exclusion Criteria

See prior CSR (Study 015 up to Week 46) for Study 015 Inclusion/Exclusion Criteria.

9.3.3. Removal of Patients from Therapy or Assessment

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

Interrupting or permanently discontinuing a subject's treatment with the study medication was 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 Week 70 (subjects who continued in Additional Period I), or Week 94 (subjects who continued in Additional Period II) are 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 required hospitalization;
- The subject experienced an AE sufficiently severe, in the opinion of the investigator, that it contraindicated continuing in the study;
- The subject wished to withdraw; in this instance, a specific reason (e.g., subject was unwilling to attend the scheduled clinic visits) was to be recorded by the Investigator;
- The subject was afflicted with a systemic illness, unrelated to the study medication, during the study treatment period, for which a prohibited concomitant medication was required and could put the patient at risk for further participation in the study;
- The subject was not adhering to the protocol requirements, and continued participation posed a significant risk to the subject's health;
- The subject was lost to follow-up, i.e., the subject did not return to the clinic and attempts to contact the subject were unsuccessful. For the subject 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.

Record of Study Participants

The investigator maintained a confidential record of all study participants, including all patients who completed the Study 015 until Week 46 and were considered for this additional extension period, but were not actually enrolled. The confidential record included sufficient information so that it was possible to contact the study patient.

9.4. Treatments

9.4.1. Treatments Administered

The investigational product (IP) (evenamide) was provided by the Sponsor in the form of capsules at dosage strengths of 7.5 mg (discontinued and up-titrated to 15 mg), 15 mg and 30 mg, for oral administration. The IP, together with relevant documentation, was supplied to the pharmacy or designated location, as applicable, at the investigational site. All the subjects who agreed to participate in the additional treatment period beyond Week 46 received evenamide 15 mg *BID* or evenamide 30 mg *BID*.

The bottles of study medication were unblinded and had the dosage strength specified on the label. The appropriate doses were dispensed at Week 46 according to the dose that the patient was receiving at the end of Study 015. The Principal Investigator, study coordinator, nurses, and other site staff, as well as the patients, were aware of what was administered to the patient; however, the blinded safety and efficacy rater was not aware of the treatment assignment (blinded rater), i.e., dose of evenamide. Special care was taken so that the blinded rater was not accidentally unblinded during the study, including ensuring that he/she was not present during dosing in the clinic, and did not see the medication bottle or notes in the chart that would have revealed the treatment assignment.

The oral doses of evenamide taken by the patient according to their treatment assignment in Study 014 are summarized in Table 9-2.

The study medication was administered as capsules of 15 and 30 mg dosage strengths of evenamide in Study 015 beyond Week 46. Doses were administered as 1 capsule *BID* given at approximately 8:00 AM and 8:00 PM (these dosing times were flexible; however, the two doses were supposed to be taken at least 6 hours apart). Patients were instructed to take one capsule from the bottle of study medication at each dosing time.

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

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

** Starting dose in Additional Period I*

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

**** The 7.5 mg BID dose was discontinued, and any patients who were receiving a dose of 7.5 mg BID were switched to 15 mg BID; all patients in the 7.5. mg randomized dose group received the 15 mg BID dose in the additional treatment periods.*

Dosing during the 48-week Additional Treatment Period

As per protocol amendment 4.1, patients randomized to the 7.5 mg *BID* dose in Study 015 had their dose increased to 15 mg *BID* upon entry into Study 015, or at their next scheduled visit if they were already enrolled in Study 015.

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

Overdose

If the investigational site staff administering the study medication or the Study Pharmacist (based on pill counting) reported that a subject inadvertently took more than the requisite number of capsules or a higher dose than was assigned, this was considered an overdose and was to be reported immediately to the Investigator. Any instance of overdose whether symptomatic or not, was to be communicated to the CRO and Sponsor within 24 hours and fully documented as an SAE. Only symptomatic overdoses were submitted to Regulatory Authorities as expedited safety reports. Details of any signs or symptoms and their management were recorded, including details of any antidote(s) administered.

9.4.2. Identity of Investigational Product(s)

The supplies for the study consisted of evenamide capsules with each different dosage (15 mg 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-3509/015/II/2019
- Investigator's name and contact information (provided on a separate label based on country-specific requirements)
- Quantity of capsules
- Evenamide dosage strength (15 mg or 30 mg)
- Expiry date
- Storage conditions (typically room temperature, which is between 15°C and 25°C)
- Cautions required by regulatory authorities
- Name of the study sponsor and contact information
- Patient's subject number (entered by site)
- Date of dispensing (entered by site)

Capsules containing evenamide were dispensed for the planned doses of 15 mg or 30 mg, which were administered orally twice daily (or once daily if the patient has had a dose reduction). The packaging of the medication for each dose level is presented in Table 9-3. Each patient received 12 bottles, each containing 16 capsules (designated for one week of dosing), at Week 46, 58, 70 and 82.

Two extra capsules were provided in each bottle for each week of *BID* dosing in case of lost or damaged medication, or a delay in the patient returning for a scheduled visit. This extra medication was sufficient to cover the allowable window on each scheduled visit; however, if it was known that a patient was delayed further in returning for his/her visit, and might run out of medication, additional medication was to be dispensed to the patient to cover this period. Patients who had their dose reduced to once-daily dosing received half the number of bottles of study medication that was used for twice daily dosing at the current dose and were instructed to take only one capsule per day in the morning.

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

Study Day/Week	Randomized Doses (*BID* dosing)				Dose Reductions (*OD* dosing)			
	No. of Bottles*	Evenamide			No. of Bottles*	Evenamide		
		7.5 mg *BID***	15 mg *BID*	30 mg *BID*		7.5 mg *OD***	15 mg *OD*	30 mg *OD*
Week 46	12	192 caps x 15 mg	192 caps x 15 mg	192 caps x 30 mg	6	96 caps x 15 mg	96 caps x 15 mg	96 caps x 30 mg
Week 58	12	192 caps x 15 mg	192 caps x 15 mg	192 caps x 30 mg	6	96 caps x 15 mg	96 caps x 15 mg	96 caps x 30 mg
Week 70	12	192 caps x 15 mg	192 caps x 15 mg	192 caps x 30 mg	6	96 caps x 15 mg	96 caps x 15 mg	96 caps x 30 mg
Week 82	12	192 caps x 15 mg	192 caps x 15 mg	192 caps x 30 mg	6	96 caps x 15 mg	96 caps x 15 mg	96 caps x 30 mg

*16 capsules/bottle

*** The 7.5 mg dosage strength had been discontinued and was no longer dispensed, however patients randomized in this group received the 15 mg dosage strength in the additional treatment periods.*

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

9.4.3. Method of Assigning Subjects to Treatment Groups

Subject Number

The same subject number assigned to each patient in the antecedent study (Study 014) was used throughout Study 015 to identify the patient. The subject number was entered in the eCRF and appeared in the header of each eCRF page.

Patient Randomization

Patients who rolled over into the additional treatment periods in Study 015 beyond Week 46 continued with the same dose they had been receiving at the completion of Week 46 in Study 015, except for subjects randomized to 7.5 mg *BID*, who had their dose of evenamide increased to 15 mg *BID*. Dose up-titration from 7.5 mg *BID* to 15 mg *BID* occurred for a total of 34 patients: for 21 cases the up-titration occurred at Week 46; while for the remaining 13 cases the dose was already up-titrated before Week 46. Therefore, the 7.5 mg *BID* randomized dose group can also be considered with the 15 mg *BID* dose group as per dose administered.

9.4.4. Selection of doses in the Study

The rationale for doses of evenamide used in Study 015 was already provided in the Clinical Study Report (CSR) Section 9.4.4.

9.4.5. Timing of Dosing for Each Patient

Twice daily (*BID*) dosing has been used in the current study, with a decrease to once daily (*OD*) dosing permitted if intolerance develops. Further information is available in prior CSR (Study 015 up to Week 46).

9.4.6. Blinding

This was an open-label, rater-blinded study; therefore, the patient, the principal investigator and study staff, except for the blinded rater assessing safety and efficacy, were aware of the patient's treatment assignment. If the blinded rater accidentally became aware of the treatment assignment for an individual patient, the Investigator was to document this in the patient's records, and to also provide a reason for the unblinding and the extent of the unblinding.

9.4.7. Prior and Concomitant Therapy

9.4.7.1. Background Antipsychotics

Any medication, in addition to the study medication, that was administered during the study from the time of signing of the consent form through to the evaluations on Week 70 or Week 94 must have been recorded in the eCRF (including over the counter [OTC] medications). Patients and their caregivers were instructed to contact the Investigator for approval prior to taking any medications, including OTC medications, while residing at home or in a residential care facility and prior to their evaluation on Week 70 or Week 94.

Restrictions on concomitant medications being taken during the treatment period of the study followed those specified in the Exclusion criteria in the study protocol for Study 014.

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

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

In addition, quetiapine, at a maximum dose of 150 mg *hs*, was permitted as a soporific in patients who had been taking it throughout Study 014. Patients were also allowed to start quetiapine (at doses up to 150 mg *hs*) for sleep post-baseline in Study 015. This might be

provided as a maintenance dose, if needed. Also, valproic acid was permitted, if used as a maintenance treatment. Drugs that could increase the risk of seizures, e.g. bupropion, were not allowed to be administered.

9.4.7.2. Rescue medication

As per protocol, "Rescue medication" is every pharmacological intervention used by the investigator to treat "an exacerbation of schizophrenia". This treatment could be, as per protocol, a dose increases of the current antipsychotic medication, a prohibited medication, or an addition of a different antipsychotic medication.

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

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

If the dose of the patient's antipsychotic was increased by more than 25%, or the rescue medication administered was a drug prohibited by the protocol (e.g., a mood stabilizer), and use of the medication was not temporary (5 days or less), all final (Week 70 or Week 94) efficacy evaluations were to be performed prior to the start of dosing with the new treatment.

At screening and during the treatment period, a patient was required to be on a stable dose of only one antipsychotic medication, which can be recognized from its start date (preceding the screening date). If a new antipsychotic was initiated, with a start date after baseline, that was considered "rescue medication" and had an indication of "worsening psychosis" or "worsening of schizophrenia symptoms".

A table was provided to summarize the doses of rescue medication taken during the study (Table 14.1.4.3). A subject data listing of the rescue medication details was also presented for the Safety Population. Since this was an exploratory study, data collected after initiation of rescue medication was not censored for any efficacy analyses purposes.

9.4.8. Treatment Compliance

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

The compliance related methodological details are captured in Section 9.7.1.18.1 of this report.

9.5. Safety and Efficacy Variables

9.5.1. Safety and Efficacy Measurements Assessed and Flow Chart

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

Table 9-4 Schedule of Evaluations

Period	Pre-Treatment		Study 014 and Study 015 - Initial Treatment Period	Treatment Phase								Post-Treatment	
Study	Study 014			Study 015 beyond Week 46								Study 015	
				Additional Period I				Additional Period II					
Visit Name	Screening Days-21 to-3	Baseline[A] Day 0	Week 46	Week 52	Week 58	Week 64	Week 70	Week 76	Week 82	Week 88	End of Study (Week 94)[D]	7-day Safety follow-up[E]	30-day Safety follow-up[F]
Visit Day			365	407	449	491	533	575	617	659	701	708	731
Visit Number	1	2	12	13	14	15	16	17	18	19	20	21	22
Assessment													
Informed Consent	X												
Inclusion/Exclusion Criteria	X						X[K]						
Randomization													
Demography/Background Information	X												
Medical History and Current Medical conditions	X												
Psychiatric History	X												
Vital Signs[B]	X	X			X		X		X		X	X	
Physical Examination	X	X					X				X		
Neurological Examination	X	X					X				X		
ECG 12-lead[C]	X	X			X		X				X		
Standard Eye Examination	X	X					X				X		
Laboratory (Hematology, Biochemistry, Urinalysis)	X	X			X		X				X		
Virology (Hepatitis B/C, HIV)	X												
Thyroid Function Tests (TSH, free T4 and free T3)	X												
Serum prolactin		X					X				X		
Alcohol Breath Test		X											
Screen Urine Drug	X	X					X				X		
Serum Pregnancy Test[I]	X	X					X				X		
ESRS-A		X			X		X		X		X		
Study drug dispensing and accountability			X[T]		X		X[J]		X		X[J]		
Concomitant Medication and Significant Non-Drug Therapies (CAM, PAM, and CM)	X	X		X	X	X	X	X	X	X	X		
Adverse Events			X	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[G]	X[F]
PANSS	X	X			X		X		X		X		
CGI-S	X	X			X		X		X		X		
CGI-C					X		X		X		X		
LOF		X			X		X		X		X		
GAF	X	X											

Period	Pre-Treatment		Study 014 and Study 015 - Initial Treatment Period	Treatment Phase								Post-Treatment	
Study	Study 014			Study 015 beyond Week 46								Study 015	
				Additional Period I				Additional Period II					
Visit Name	Screening Days-21 to-3	Baseline[A] Day 0	Week 46	Week 52	Week 58	Week 64	Week 70	Week 76	Week 82	Week 88	End of Study (Week 94)[D]	7-day Safety follow-up[E]	30-day Safety follow-up[F]
CDSS	X	X					X				X		
Telephone Contact				X[H]		X[H]		X[H]		X[H]		(X)[E]	X
Study Completion			(X)[L]				(X)[M]				X		

[A] Following completion of baseline evaluations on Day 0, subjects meeting all eligibility criteria were randomized and dosed on Day 1. Thus, the baseline (Day 0) evaluations and Day 1 post-dose evaluations were performed on the same day, if possible.
[B] Vital signs were performed at baseline (Day 0) in triplicate, and at Weeks 58, 70, 82 and 94, and at the 7-day safety follow-up visit. Vital signs taken once in 3 positions (sitting for 5 minutes, within 1 minute of standing and after 3 minutes of standing). Waist circumference was measured at baseline of Study 014 and at Weeks 70 and 94. Height that was measured at screening of Study 014 was used for calculating BMI.
[C] A 12-lead ECG was performed at baseline (Day 0) and at Weeks 58, 70 and 94.
[D] All Week 94 evaluations were performed when a subject discontinued from the study prematurely.
[E] Performed 7 (±2) days after the last dose of study medication for patients who discontinued prematurely, as well as those who discontinued after completing 46 weeks of treatment in the initial treatment period or 70 weeks of treatment in Additional Period I, and those who completed 94 weeks of treatment in Additional Period II. If the patient did not attend the clinic visit, a call was made to the patient (or caregiver) to encourage attendance; or if unavailable, to collect adverse event information via the telephone.
[F] The patient was contacted minimally 30 days after the last dose of study medication to assess the occurrence of any SAEs. This information can be collected through telephone contact.
[H] Patients being treated as outpatients were contacted by telephone at Weeks 52, 64, 76 and 88; adverse events and concomitant medication use was assessed. If the patient reported significant intolerance, a dose reduction was performed, and he/she was asked to return to the hospital for an unscheduled visit for evaluation and appropriate workup.
[I] Serum pregnancy test was performed for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or were surgically sterilized, at Baseline and Weeks 70 and 94.
[J] At Week 70, if it was the final visit, and Week 94, only accountability of returned study medication was performed. No additional study medication was dispensed.
[K] Patients who completed 46 weeks of treatment and, in the Investigator's opinion, were benefitting from treatment with evenamide and had no safety concerns that would put them at risk, were eligible to continue treatment for an additional 24 weeks in Additional Period I. Patients who completed Additional Period I and were doing well, were eligible for an additional 24 weeks of treatment in Additional Period II.
[L] The Week 46 visit was the final evaluation for patients who did not continue treatment in Additional Period I.
[M] The Week 70 visit was the final evaluation for patients who did not continue treatment in Additional Period II.
[S] First dose date of study 015 beyond Week 46 is 014 Day 1.
[T] First drug dispensation in Study 015 beyond Week 46.
Some parameters, e.g., Alcohol Breath Test, Virology (Hepatitis B/C, HIV), Thyroid Function Tests (TSH, free T4 and free T3), GAF is not part of the 015 Schedule of Evaluations, but is added in the above Table 9-4, because 014 screening and baseline information was included.

9.5.1.1. Safety Assessments

The assessment of safety was based on the following:

- Adverse events (AEs) - subjective reporting and objective observation, including symptoms and signs suggestive of seizures (see Appendix 4 of study protocol)
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, body temperature, respiratory rate, BMI, waist circumference),
- Laboratory evaluations (hematology, blood chemistry, and urinalysis; HbA1c; 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)
- 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 at baseline, and at each visit of the study. Every untoward medical event was collected from the time when the patient signed the informed consent till the end of the safety follow-up period, i.e., 7 days post final dose of study drug. All AEs were recorded in the CRF. In addition, the patients were followed up for 30 days after their last dose of study medication for the occurrence of any serious AE.

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

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

9.5.1.1.2. Reporting of Overdose

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

The details regarding reporting of overdose are mentioned in Section 9.4.1.

9.5.1.1.3. Management of Pregnancy

Women of child-bearing potential, who were not using an adequate contraception method, as determined by their Health Care Provider, were not eligible for the study. The use of contraception was to be initiated at least 28 days before the first dose (in Study 014) and continued until 30 days after stopping study medication. As a further precaution, a serum pregnancy test was performed for all women of child-bearing potential, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or who had been surgically sterilized, at baseline, Week 46,Week 70 and Week 94, or at early discontinuation. Additional serum or urine pregnancy tests were performed, as needed, based on local requirements.

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

9.5.1.1.4. Vital Signs

Vital signs assessments were performed at all scheduled evaluations (Weeks 58, 70, 82, and 94 and safety follow-ups, as applicable). Vital signs included body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. In addition, waist circumference was measured at Week 70 and 94, or at early discontinuation visit. Height, measured at the screening visit in Study 014, was used to calculate BMI. For all vital signs assessments, pulse and blood pressure was measured after the subject had been in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing.

Orthostatic Hypotension(s) (OH) was derived as OH = Supine – Standing.

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

9.5.1.1.5. Clinical Laboratory Evaluations

Blood and urine samples were collected at the visits specified in the schedule of evaluations (see Section 9.5.1). Evaluations of the hematology, blood chemistry and urinalysis analytes listed in Table 9-5 were performed at Week 58, Week 70/End of Study and Week 94/End of Study or early discontinuation. In addition, measurement of serum prolactin was performed at Baseline and final visit, i.e., Week 70 and Week 94. A serum pregnancy test was performed at Baseline, Week 46 (prior to rolling over into the additional extension period), Week 70 and Week 94, or at early discontinuation, for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or had been surgically sterilized.

A urine drug screen was performed at Baseline, Week 70 and Week 94, or at early discontinuation. The following substances were analyzed in the urine drug screen (performed at the study site): amphetamines, barbiturates, benzodiazepines, THC, cocaine, methylenedioxy-methamphetamine, opiates, oxycodone, phencyclidine, and propoxyphene). Additional urine drug screens were performed during the study if substance abuse was suspected.

Table 9-5 Summary of Laboratory Analytes

Laboratory Analytes			
Hematology	**Blood Chemistry**		**Urinalysis**
Hematocrit	Sodium	Triglycerides	pH
Hemoglobin	Potassium	Aspartate aminotransferase	Specific gravity
Red blood cell count	Chloride	Alanine aminotransferase	Protein
White blood cell count	Bicarbonate	Alkaline phosphatase	Glucose
Differential White blood cell count	Calcium	Gamma-glutamyl transferase	Ketones
Platelets	Glucose	Lactate dehydrogenase	Red blood cells, white blood cells, casts
	Blood urea nitrogen	Total cholesterol	Nitrites
	Creatinine	High-density lipoprotein, Low-density lipoprotein, Very low-density lipoprotein	Bilirubin
	Total bilirubin	Creatine phosphokinase	Hemoglobin
	Albumin	Total protein	
Special Diagnostic Tests • Urine drug screen (Baseline [Baseline of Study 014] and final visit, i.e. Week 70 and Week 94) • Serum prolactin (baseline and final visit, i.e. Week 70 and Week 94) • Serum pregnancy tests (Baseline and final visit, i.e. Week 70 and Week 94) – for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or had been surgically sterilized.			

The Investigator was to review post-dose laboratory values within 24 hours of receipt of the laboratory report. After the review was completed, the Investigator signed and dated each laboratory report.

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

analytical problems (e.g., machine not accurately calibrated, technical problems with equipment or reagents, or deterioration of analyte).

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

9.5.1.1.6. Electrocardiogram (ECG)

All the subjects had a standard 12-lead ECG performed as mentioned in the schedule of evaluations (Table 9-4, Section 9.5.1).

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.

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

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

9.5.1.1.7. Physical Examinations

A physical examination was performed at Baseline (014 Baseline), Week 70 and Week 94, 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 Baseline (014 Baseline), Week 70 and Week 94, 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) was performed at Week 70 and Week 94, or at early discontinuation. The examination was performed by a physician at the site who had the appropriate experience and training. If a clinically significant abnormality was noted that required expert follow-up, an Ophthalmologist or Optometrist was to be consulted.

9.5.1.1.10. 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 every 12 weeks (Weeks 58, 70, 82, and 94, 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 was scored between 0 and 3 based on operational criteria. A total score of 6 or above was considered predictive of a major depressive episode. Internal reliability, as well as inter-rater reliability, was high (Addington et al., 1993). In the current study, the CDSS was performed at Weeks 70 and 94, or at early discontinuation to assess changes from baseline in depressive symptoms.

9.5.1.1.12. Seizure Checklist

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

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

9.5.1.1.13. 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 develop 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 baseline, 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 (ISMB)

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

The ISMB comprised at least 3 voting members. All these members are highly experienced clinicians. 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 safety data available from the subjects in the evenamide clinical studies 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.

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

9.5.1.2. Efficacy Assessments

Patients were instructed to take the morning dose of study medication at their residence on the day of each scheduled clinic visit. Patients took their concomitant antipsychotic and other medications at their residence according to their usual schedule. To ensure consistency of ratings for key efficacy measures, e.g. PANSS and CGI-C/S, these assessments were performed at the approximately the same time relative to the morning dose of study medication, if possible, during the scheduled clinic visits at Weeks 58, 70, 82 and 94, or at early discontinuation.

Efficacy-related Endpoints

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

Primary efficacy endpoint

- PANSS total score - mean change from baseline to endpoint

Secondary efficacy endpoints

- 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 – Negative 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 – proportion of patients with improvement from baseline to endpoint (≥20% on PANSS Total and ≥4-points on PANSS Positive Symptoms)

- CGI-S – proportion of patients with improvement from baseline to endpoint ("at least 2-category improvement" and "at least 1-category improvement").

9.5.1.2.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al., 1987) is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The 30 symptoms are each rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale, which has been shown to be sensitive to medication treatment, provides a balanced representation of positive and negative symptoms, and gauges their relationship to one another and to global psychopathology. In addition to a total score, this assessment yields separate sub-scores on a Positive Syndrome Scale, a Negative Syndrome Scale, and a General Psychopathology Index. The PANSS interview process typically takes between 30 and 40 minutes to complete. The PANSS was conducted at Weeks 58, 70, 82 and 94 or at early discontinuation and was used as the primary efficacy measure in the trial. The same physician (an MD, clinical psychologist, or other clinician with extensive training and experience) performed the ratings of the PANSS, CGI-C and CGI-S.

9.5.1.2.2. Clinical Global Impression (CGI)

The CGI (Guy, 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.

The CGI rating scale permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S is performed, in which the Investigator rates the severity of a subject's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). At subsequent visits, the Investigator assesses the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at baseline in Study 014 using the CGI-C, a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating "no change". The CGI-S and CGI-C assessments were conducted at Weeks 58, 70, 82 and 94, or at early discontinuation, as applicable.

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

9.5.1.2.3. Strauss-Carpenter Level of Functioning (LOF) Scale

The LOF has been widely used as an instrument to evaluate clinical outcome in patients with schizophrenia (Strauss and Carpenter, 1977). The LOF is a semi-structured, clinician-administered scale containing nine items and requires approximately 15 to 20 minutes for completion. The individual items fall into four domains, with higher scores on a 5-point scale (0 - 4) reflecting better functioning. The subscales are: Social contacts (frequency and quality of social contacts), Work (quantity and quality of useful work), Symptomatology (absence of symptoms and recent hospitalization), and Function (ability to meet basic needs, fullness of life, and overall level of function). Subscale scores were calculated as the mean scores for items in each scale. A total score was calculated as the sum of the raw scores across the nine items. Inter-rater reliability has been demonstrated, and the instrument has been shown to be sensitive to subtle changes in functioning and treatment effects over time. The LOF was conducted at Weeks 58, 70, 82 and 94, or at early discontinuation.

9.5.1.2.4. Rater Training

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

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

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

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

9.5.2. Appropriateness of Measurements

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

of efficacy was a secondary objective of this study. The efficacy of evenamide in treating the symptoms of schizophrenia was assessed using the PANSS, CGI-S, CGI-C, and LOF.

9.5.3. Primary Efficacy Variable

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

9.6. Data Quality Assurance

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

9.6.1.2. Study Monitoring

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

- To verify that written informed consent was obtained prior to each subject's participation in the study,
- To assess the progress of the study,

- To review the compliance with the study protocol
- To determine whether all AEs were appropriately reported,
- To determine whether the Investigator was maintaining the essential documents,
- To discuss any emergent problem,
- To check the eCRF for accuracy and completeness,
- To validate the contents of the eCRFs against source documents,
- To assess the status of drug storage, dispensing, and retrieval (by an independent unblinded study monitor with no other involvement with the study and who did not have access to the eCRFs or other study documents).

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

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

9.6.1.3. Audits and Inspections

An Investigator site audit was conducted as per ICH GCP, applicable regulations, and study procedures for the current study by an independent auditor contracted by the Sponsor at the below site 304:

- Dr. Vikhram Ramasubhramanian, Site 304, Ahana Hospitals LLP, No.7, Subburam Street Gandhinagar, Madurai - 625020, Tamil Nadu, India, from 19th to 20th July 2023.

No critical or major findings were identified at this site. An audit certificate for this site audit is provided in Appendix 16.1.8.

A quality compliance assessment was conducted at the below site 309:

- Dr. V. Radhika Reddy, Site 309, Help Hospital Pvt Ltd, Door No: 27-29-23, Governorpet, MG Road, Vijaywada, Andhra Pradesh - 520002, India, from 26th to 27th May 2022.

No critical observations were made. Effective implementation of corrective and preventive actions were undertaken, verified and closed.

9.7. Statistical Methods

9.7.1. Statistical and Analytical Plan

The Statistical Analysis Plan (SAP) described the statistical methods that were used during the analysis and reporting of data collected under Newron Pharmaceuticals S.p.A. clinical study protocol NW-3509/015/II/2019 *(Amendment 4.2 dated 08th July 2022 for India)*. Complete details of the statistical

methods were outlined separately in the SAP presented in Appendix 16.1.9 of this clinical study report (CSR).

All data collected in this study was documented using summary tables, patient data listings and figures. Efficacy analyses were limited to the overall evenamide group, including all doses of evenamide; however, safety analyses included both dose-wise analyses and overall analyses considering evenamide as a single group.

Week 70 and Week 94 were used as efficacy and safety endpoints for the Study 015 beyond Week 46.

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

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

Decimal places in data presentations

The mean and median were reported to an additional 1 decimal place, and the standard deviation (SD) was reported to an additional 2 decimal places, compared to the original result. Minimum and maximum were reported to the same decimal place as in the original result, unless otherwise specified. Percentages were presented to 1 decimal place; except percentage was not presented when the count was zero, and 100% was presented as an integer. The values were rounded to the specified decimal places as above.

Long Text Handling

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

Data Derivation

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

Baseline

The protocol stated that the final Day 43 safety and efficacy evaluations in Study 014 would serve as the baseline assessments for this extension Study 015. However, from a statistical perspective, the date of first dose of evenamide (i.e., in-clinic administration on Day 1 of Study 014) has been considered as the anchor date, and this is also supported by protocol clarification document dated 23rd November 2023. Therefore, relevant baseline assessments of Study 014 are retained, and Day 43 data have been ignored for the analysis of changes from baseline.

Anchor Date

First Dose Date of Study 014 (i.e., Day 1) was considered as the first dose date for safety and efficacy analysis for Study 015 beyond Week 46.

First Dose Date of Study 015 beyond Week 46

Week 46 drug dispensation date was considered the starting point for determining treatment compliance. For some subjects IP kits were dispensed later at an Unscheduled visit and that visit date was considered as first dose date.

Last Dose Date

Last dose date was available in the Week 70 and Week 94/End of Study form in the eCRF. For "lost to follow-up" or "withdrawal of consent" cases, the last dose date was taken from drug accountability (kit dispensed date) in the eCRF in case it was not available in the Week 70 and Week 94/End of Study form in the eCRF.

Week 70/Early Termination visit: All Week 70 evaluations were to be performed when a subject discontinued from the study prematurely before completing the 70-week treatment period.

Week 94/Early Termination visit: All Week 94 evaluations were to be performed when a subject discontinued from the study prematurely before completing the 94-week treatment period.

Complete details of the statistical methods were outlined separately in the SAP presented in Appendix 16.1.9 of this clinical study report (CSR).

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

Study Completion and Discontinuation

The study completion date of any patient from Study 015 beyond Week 46 was the Week 70 / Week 94 date for Additional Periods I and II, respectively, irrespective of whether the subject attended the Safety Follow-up (SFUP) visits or not.

Date of discontinuation was the date captured in the Week 70 and Week 94/End of Study form, for Additional Periods I and II respectively, documented by the Investigator and documented in source documents, regardless of the date on which the last dose of study medication was taken.

Unscheduled Visits

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

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

Analysis time-points

Post-baseline analysis time-points included Weeks 58, 70, 82 and 94 as per the Study 015 beyond Week 46 visit schedule, i.e., relative to the first dose of study medication in the extension study (i.e., Day 1 of 015), as applicable. Telephonic visits were listed but not analyzed.

9.7.1.1. *Analysis Populations*

Rolled Over Population

The "Rolled Over" population consisted of those subjects randomized in Study 014 who had completed Study 015 Week 46 and signed the ICF for the additional extension periods I and II until Week 70 and Week 94, respectively.

Safety Population

The Safety population consisted of all subjects who signed the ICF of the extension period beyond Week 46 and took at least one dose of study medication in this extension period (Study 015 beyond Week 46).

Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population comprised rolled over patients who received at least one dose of the study medication in this extension Study 015 beyond Week 46, had a valid Study 014 baseline, and had at least one assessment for the primary efficacy measure, the PANSS total score, in this extension Study 015 beyond Week 46.

Modified Intent-to-Treat Population - Completers (mITT-C1)

The mITT-C1 completers population includes subjects in the mITT population who had completed treatment till the Week 70 visit.

Modified Intent-to-Treat Population - Completers (mITT-C2)

The mITT-C2 completers population includes subjects in the mITT population who had completed treatment till the Week 94 visit.

9.7.1.2. *General Considerations*

9.7.1.2.1. Data Processing

Data were extracted from the clinical study database once all subjects in the Study 015 beyond Week 46 completed Week 94 or had discontinued from the study prior to this visit (Week 94/Early Termination visit), and the database was cleaned and locked.

9.7.1.2.2. Missing Safety Data Dates

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

If an AE 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 end 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 rules shown in the table below were used to impute the date. The imputed date was used to determine whether a medication was a prior or concomitant medication.

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

9.7.1.3. *Missing Data Imputation*

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

9.7.1.4. *Adjustments for Multiplicity*

Not applicable, as a dose-wise efficacy analysis was not performed.

9.7.1.5. *Site Effects*

Site effects were not evaluated.

9.7.1.6. *Analysis Visits*

Scheduled visits with efficacy evaluations were designated as analysis visits. ‘Analysis windows’ were defined and considered for unscheduled or early withdrawal visit data for the efficacy analysis in cases where a scheduled visit evaluation was not performed; these are detailed in the SAP document presented in Appendix 16.1.9.

9.7.1.7. *Visit Window*

A window of ± 7 days was allowed on scheduled visits at Weeks 58, 70, 82 and 94, and for the telephone contacts at Weeks 52, 64, 76 and 88. The last day of dosing for the study medication in this open-label extension study was on the morning of the Week 70 (final for Additional Period I) or Week 94 (final for Additional Period II) visit (preferably at the patient’s residence). All final evaluations were performed at Week 70/Week 94 (or at early discontinuation); however, if the patient was delayed by up to 7 days in returning for the final evaluations, he/she was instructed to continue taking the study medication twice daily through the morning of the visit.

9.7.1.8. *Subject Enrollment and Disposition*

A subject enrollment listing with enrollment details (the ICF Date), and the protocol version was provided for the Study 015 additional treatment periods up to Week 70 and Week 94.

The number and percentage of subjects included in each analysis population (Safety population, Modified Intent-to-Treat Population, Modified Intent-to-Treat Population-Completers at Week 70 or Week 94, and Rolled over Population) were presented. Subjects who completed Week 70 or Week 94, or discontinued prematurely, along with a breakdown of the reasons for early discontinuation (e.g., adverse events, lost to follow up, withdrawal of consent), were summarized by each evenamide dose group and total.

A subject listing was presented for disposition, including details of randomization (Randomization number and date) and reason for discontinuation, for all randomized subjects who participated in the additional treatment periods until Week 70 and Week 94.

9.7.1.9. *Protocol Deviations*

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

9.7.1.10. *Demographic and Baseline Characteristics*

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

9.7.1.11. *Disease Characteristics*

The disease characteristics, including duration of illness, duration of current episode, number of psychiatric hospitalizations, family history of schizophrenia, and baseline depressive symptoms assessed by the CDSS, 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 parents, siblings, or children as first-degree relatives and others as second-degree relatives.

The duration of current episode was calculated as:

> Duration of Current Episode (months) = (Date of Randomization - Start Date of Current Episode+1)/30.4167.

The duration of illness for schizophrenia was calculated as:

Duration of Illness (years) = (Date of randomization - Date of First diagnosis + 1)/365.

9.7.1.12. *Medical History*

Medical history was coded using the latest Medical Dictionary for Regulatory Activities (MedDRA v23.0). 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.

9.7.1.13. *Psychiatric History*

The count and percentage of subjects in each of the reported psychiatric history categories were provided for 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.

9.7.1.14. *Prior and Concomitant Medication*

Prior medications were considered as those medications that had a start date and end date before ICF signature (015 Day 1 ICF date), using the Study 015 prior medication CRF field. Concomitant medications were considered those medications taken at any time during Study 015 beyond Week 46 or ongoing from prior extension, irrespective of the start date. Prior and current antipsychotic medications were summarized separately. 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 belong to the same extended ATC4 classification. In case ATC level 4 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.

9.7.1.15. *Prior and Current Antipsychotic Medication*

Prior antipsychotic medications (PAM) are antipsychotic medications that have a start date and end date before 015 Day 1 ICF signature date, using Study 015 PAM CRF field.

Current antipsychotic medications (CAM) are antipsychotic medications taken by subjects during the study, using Study 015 CAM CRF field.

The prior and current antipsychotic medications were 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.

9.7.1.16. *Study Drug Accountability*

Study drug accountability data was presented as an individual data listing at Week 70 and Week 94, as applicable.

9.7.1.17. *Dose Switch-over*

As per protocol amendment 4.1, patients randomized to the 7.5 mg *BID* dose in Study 015 had their dose increased to 15 mg *BID* upon entry into Study 015 beyond Week 46.

Tables and listings included the doses assigned to the patients at the time of randomization (i.e. Study 014 Day 1). The patients who had their dose increased from 7.5 mg *BID* to 15 mg *BID* had the 15 mg *BID* dose displayed in brackets.

9.7.1.18. *Safety and Tolerability Analyses*

9.7.1.18.1. Exposure and Treatment compliance

A drug exposure table summarizes the duration of exposure and treatment compliance in Study 015 beyond Week 46 by evenamide dose group and total for the Safety Population. The duration of exposure was calculated as the number of days from treatment start date (from Week 46 of Study 015) to treatment end date (Week 94 of Study 015).

Dosing compliance (% compliance) was assessed by calculating the number of capsules consumed from Week 46 of Study 015 to Week 94 and comparing that to the number of capsules expected to be consumed as follows:

- % Compliance = 100*[#Capsules consumed/#Capsules expected to be consumed]
  Where, #Capsules consumed = Sum of the (#Capsules consumed per kit).
- #Capsules consumed per kit calculated as #dispensed Capsules in the kit – #returned/lost capsules in the kit.
- #Capsules expected to be consumed = 2 * (Last dose date – First dose date + 1).

The judgement of the PI was considered in case the kit was not returned/not dispensed. If, according to the PI judgement, the patient was considered compliant despite the kit not being returned, all capsules expected to be consumed over the period from IP bottle dispensing to returning visits were counted in the calculation.

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

In some exceptional cases manual coding was to be performed for compliance calculation as per eCRF text data and protocol deviation (PD) list.

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

Compliance was summarized overall at Week 70 and Week 94, as applicable.

Study exposure data were 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, was provided. Note that more than one reason per subject could be provided for dose adjustment, kit replacement, and other actions due to multiple modifications.

Reasons for unscheduled dose adjustment are listed below:

- 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.

9.7.1.18.2. Adverse Events

All adverse Events (AEs) that started or ended after Week 46, or were ongoing from the prior extension Study 015 (before or till Week 46), were included in the analysis.

Treatment-emergent AEs (TEAEs) are adverse events that are newly occurring or worsened in severity during the extension beyond Week 46, i.e. after the first administration of the study medication in Study 015 beyond Week 46. The following criteria were used to define treatment emergence for AEs with missing start or stop dates:

- If both the start and stop dates for a particular event were missing, then that event was considered treatment-emergent,
- If the start date for a particular event was missing and the stop date was after the first dose date, then the event was considered treatment-emergent,
- If the start date was the same as the first dose date, 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 patients who experienced TEAEs for the Safety Population were summarized using the MedDRA v23.0 system organ class (SOC) and preferred term (PT), by evenamide dose group and total of all dose groups.

AE summary tables included the following information, if applicable:

- Overall incidence of SAEs, AEs leading to study drug discontinuation, AEs leading to study discontinuation (ADOs), and AEs leading to deaths
- Summary of TEAEs by SOC by PT
- Summary of TESAEs (treatment-emergent serious AEs) by SOC by PT
- Summary of Treatment-Related TEAEs by SOC by PT
- Summary of AEs leading to study drug discontinuation and AEs leading to study discontinuation (ADOs) by SOC by PT
- Summary of TEAEs by maximum Severity.

Treatment-Related TEAEs were the TEAEs that were 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 changed in severity was counted only once under the highest reported severity or relationship. All AEs, SAEs, and TEAEs were presented in individual subject data listings. A separate listing was also made for any occurrence of death with additional details of autopsy status and brief description of the event.

9.7.1.18.3. Vital Signs

Tables presenting descriptive statistics for all the observed vital signs were provided. Changes from baseline (Study 014) at each post-dose visit/timepoint, as applicable, were presented by evenamide dose groups and overall combined dose group for temperature, respiratory rate, pulse, weight, BMI, waist circumference, systolic blood pressure and diastolic blood pressure.

Counts and percentages of subjects at each visit meeting the clinically notable abnormalities criteria (Appendix 2 of the SAP document presented in Appendix 16.1.9) were provided for evenamide dose group and overall combined dose group. Listing of data containing individual subject's vital signs values was provided in three parts: Individual subject's listing with change from baseline (one subject all parameter), time profile (by parameter; all subjects), and newly emergent clinically notable abnormalities. The analysis of vital signs data was done on the Safety Population.

9.7.1.18.4. Clinical Laboratory Evaluation

The counts and percentages of subjects meeting the newly emergent clinically notable abnormalities criteria (Appendix 2 of the SAP document presented in Appendix 16.1.9) for post-baseline visit hematology and biochemistry parameters were presented for each evenamide dose group and overall combined dose group in the Safety Population.

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

The summary of change from baseline to each post-Week 46 visit was also provided for hematology and biochemistry parameters (Appendix 3 of the SAP document presented in Appendix 16.1.9) by evenamide dose groups and overall combined dose group.

The individual values of hematology and biochemistry parameters collected at the central laboratory was standardized in SI units for each of the parameters mentioned in (Appendix 4 of the SAP document presented in Appendix 16.1.9).

Metropolis Healthcare Ltd, was used as a central laboratory.

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

• Urine drug screen (Baseline [of Study 014] and final visit, i.e. Week 70 and Week 94)

• Serum prolactin (Baseline and final visit, i.e. Week 70 and Week 94)

• Serum pregnancy tests (Baseline, Week 70 and Week 94)

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

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

At some Indian sites (Subjects #304002, 311003, 311006 and 311022), repeat laboratory tests have been performed using local laboratories for certain parameters (e.g., Alanine Aminotransferase, Aspartate Aminotransferase, Chloride, Creatinine, Glucose, Potassium, Sodium and Bilirubin) at unscheduled visits.

Note that alpha-numeric lab values like <X (below X) and >X (higher than X) were treated as X ±0.1 for statistical analysis purposes. Values like ≤X or ≥X were treated simply as X.

9.7.1.18.5. Electrocardiogram (ECG)

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

1) Change from baseline at Week 58 and at endpoint (Week 70 and Week 94 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 PI.
3) The number (%) of patients meeting the following categorical criteria was summarized by each evenamide dose group and overall:
    a. Change from baseline in QTc interval: from > 30 msec to ≤ 60 msec, and > 60 msec
    b. Absolute QTc interval: > 450 msec and ≤ 480 msec; > 480 msec and ≤ 500 msec; > 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.

A treatment-emergent abnormality for the central reader was defined as the change from Normal or Abnormal Not Clinically Significant (NCS) at baseline to Abnormal or Abnormal CS, respectively, at any post-baseline visit. Subjects with multiple abnormal post-baseline findings were counted only once.

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

Unscheduled visit data was considered for analysis in case scheduled data was missing. In case both scheduled and unscheduled data are present, unscheduled data was not considered for analysis but was listed.

9.7.1.18.6. Physical Examinations

Treatment-emergent post-baseline abnormal findings on any body system in the physical examination were listed by evenamide dose group and summarized by evenamide dose group and overall combined dose group for the Safety Population.

A treatment-emergent abnormality was defined as the change from Normal or Abnormal NCS at baseline to Abnormal NCS or Abnormal CS, respectively, at any post baseline visit. Subjects with multiple abnormal post-baseline findings on any body system were counted only once.

9.7.1.18.7. Neurological Examinations

Treatment-emergent post-baseline abnormal findings on any body system in the neurological examination were listed by evenamide dose group and summarized by evenamide dose group and overall combined dose group for the Safety Population.

A treatment-emergent abnormality was defined as the change from Normal or Abnormal NCS at baseline to Abnormal NCS or Abnormal CS, respectively, at any post baseline visit. Subjects with multiple abnormal post-baseline findings on any body system were counted only once.

9.7.1.18.8. Standard Eye Examination

Treatment-emergent post-baseline abnormal findings on the eye examination were listed by evenamide dose group and summarized by evenamide dose group and overall combined dose group for the Safety Population.

A treatment-emergent abnormality was defined as the change from Normal or Abnormal NCS at baseline to Abnormal NCS or Abnormal CS, respectively, at any post baseline visit. Subjects with multiple abnormal post-baseline findings on any body system were counted only once.

9.7.1.18.9. 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 and overall combined dose.

9.7.1.18.10. Calgary Depression Scale for Schizophrenia (CDSS)

The change from baseline to the final assessment in the CDSS total score for the Safety Population was presented by evenamide dose group and overall combined dose. CDSS scores at baseline (of Study 014) and final assessment in the Safety Population were listed.

9.7.1.19. *Analysis of Efficacy Parameters*

9.7.1.19.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS was used as the primary efficacy measure in the trial.

The effect of evenamide treatment on the PANSS Total scores measured at each visit was analyzed descriptively for the overall evenamide 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 presented by mean, median, standard deviation and range (min, max).

Demonstration of a clinically relevant improvement ('Responder analysis') from baseline to endpoint (Week 70/Week 94 or early discontinuation) on the PANSS total score for the overall combined dose of evenamide, would be considered as preliminary evidence of benefit of evenamide used 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 the combined evenamide dose group with improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale (i.e., PANSS Total score change ≥ 20% improvement, as described by Rosenheck et al., 1997 and Meltzer et al., 2008, and ≥ 4 points improvement on PANSS Positive Symptoms sub-scale score).

To date, no prospective trial evaluating the benefit of a new chemical entity as an add-on to an antipsychotic in patients with TRS has been published. Currently, available data suggests that the benefits of an intervention as an add-on in TRS patients would be of low magnitude, i.e., 10% to 20% improvement.

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

9.7.1.19.2. Clinical Global Impression (CGI)

Change from baseline to endpoint on the CGI-S was summarized, and a graph, including mean change from baseline of the CGI-S for each treatment group was presented by visit. In addition, the mean rating of the CGI-C at each post-dose visit was summarized.

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

A line graph of mean change from baseline of the CGI-S by visit for overall combined evenamide dose group was presented. The bar chart of the responder analyses on the CGI-C (any improvement and at

least much improved) was presented. Overall combined efficacy analyses were performed on the modified Intent-to-Treat (mITT), mITT-C1 and mITT-C2 populations, as applicable.

9.7.1.19.3. Strauss-Carpenter Level of Functioning (LOF) scale

Change from baseline to endpoint on the total scores and sub-scale scores on the LOF were summarized at each post-dose time point (i.e., Weeks 58, 70, 82 and 94, as applicable). A graph depicting mean (SD) change from baseline by visit was presented for each dose group.

Overall combined efficacy analyses were performed on the modified Intent-to-Treat (mITT), mITT-C1 and mITT-C2 populations, as applicable.

9.7.1.19.4. Efficacy Estimands

Efficacy estimands were considered for the primary efficacy endpoint (PANSS total score change from baseline at Week 70/Week 94 only).

Estimand: Effect of continuing on the randomized dose of evenamide in the additional periods of the extension Study 015, as it was administered in the core study, regardless of withdrawal from treatment.

Estimator: Estimate of the change from baseline in PANSS total score at Week 70 /Week 94.

Intercurrent Events: Randomized treatment discontinuation due to intake of rescue medication, if applicable.

Cases of dose up-titrations from 7.5 mg *BID* to 15 mg *BID* at Week 46 were not considered as intercurrent events, because they occurred in the prior extension study (015 up to Week 46).

Some patients could not be dosed due to non-availability of IP; this was also not considered as an intercurrent event due to being a logistic issue.

Treatment Policy strategy was considered as a primary efficacy estimand where actual values of the variable were used regardless of whether the intercurrent events have occurred (OC). In other words, all observations, including those made for patients withdrawn from treatment and returning at Week 70/Week 94, regardless of other medication taken, were utilized.

For the long-term add-on therapy efficacy assessment, the treatment policy estimand might be of interest, as it evaluated randomized policy.

Hypothetical estimand was considered as a supportive efficacy estimand where base analysis was based on data observed (OC) prior to the randomized treatment withdrawal or discontinuation. Those discontinued subjects who provided post withdrawal data at Week 70/Week 94 follow-up were removed from the analysis, as applicable.

Combined efficacy analyses were performed on the modified Intent-to-Treat (mITT), mITT-C1 and mITT-C2 populations, as applicable.

Table 9-6 describes the estimand panel.

Table 9-6 Estimand Panel

Estimand	Estimand Attributes				Analysis
	Population (s)	Variable	Intercurrent events	Summary	
Primary efficacy estimand	mITT, mITT-C1 and mITT-C2	Change from baseline to Week 70 and Week 94 in PANSS total score	Treatment estimand policy: What is the effect if patients continue treatment until completion as observed cases (OC).	Mean change at Week 70/94	Descriptive statistics
Supportive efficacy endpoint	mITT, mITT-C1 and mITT-C2	Change from baseline to Week 70 and Week 94 in PANSS total score	Hypothetical estimand: What is the effect if patients start treatment with a rescue medication.	Mean change at Week 70/94	Descriptive statistics

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

Detailed descriptions of changes implemented with Protocol Amendments are provided in Study 015 CSR. The two amendments that introduced the possibility of continuing treatment with evenamide beyond Week 46 are the following:

Amendment 4.1 (India), dated 30 November 2021:

The primary purpose of this amendment to the protocol for Study NW-3509/015/II/2019 (Study 015) was to discontinue the evenamide 7.5 mg *BID* dose from the study (This is described in detail in the prior CSR for the initial 46-week treatment period in Study 015). Additionally, this amendment extended open-label treatment with evenamide in Study 015 for an additional 24 weeks at sites in India. This allowed patients who were doing well on evenamide and completed the full 46 weeks of treatment the option of continuing treatment for another 24 weeks, for a total treatment period of 70 weeks.

Amendment 4.2 (India), dated 08 July 2022:

This amendment extended open-label treatment with evenamide in Study 015 for an additional 24 weeks at sites in India., This allowed patients who were doing well on evenamide and completed Week 70 the option of continuing treatment for an additional 24 weeks in a second additional treatment period, for a total treatment duration of 94 weeks.

The Sponsor had submitted to the DCGI the protocol Amendment 4.2 on 30th December 2022 to provide the opportunity to roll over into an additional treatment period (Additional Period II) from Week 70 to Week 94. This amendment was approved by the DCGI on 23rd November 2023, when most of the patients had already completed the Additional Period I (until Week 70).

9.8.2. Changes in the Planned Analyses for the Study

Changes from the planned analysis described in the protocol that were made in the final SAP (Appendix 16.1.9) are summarized in Table 9-7.

Table 9-7 Changes from Planned Analysis

Sl No	New Changes	Protocol Text	Comments
1	Week 46 as an endpoint not required.	Week 46 as an Endpoint	Already covered in the prior analysis.
2	Paired t-test is not required. Only descriptive statistics will be presented.	Paired t-test	Combined dose group, and unbalanced.
3	Efficacy estimands	Not mentioned	As per ICH E9 R1, good statistical practice.
4	Revised Schedule of Evaluations	Schedule of Evaluations	Adapted from statistical programming.
5	Revised Study Design	Study Design	Adapted from protocol for statistical analysis.
6	Baseline and First dose of Core Study 014 to be used as Baseline of Study 015	Day 43 of Study 014	Adapted from protocol clarification document of prior extension study.
7	Responder Analysis for PANSS and CGI-C/S.	Not mentioned	Adapted from protocol clarification document of prior extension study.
8	mITT-C1 and mITT-C2 populations for PANSS, CGI-C/S and LOF.	Not mentioned	Adapted from protocol clarification document of prior extension study.

10. STUDY SUBJECTS

10.1. Disposition of Subjects

A total of 153 subjects completed Study 014. Of these subjects, 144 consented to enter and rolled over into Study 015 extension up to and including Week 46. Patients enrolled in India who completed the 46 weeks of treatment were eligible to further rollover into two extension periods – Additional Period I up to Week 70 (24 Weeks) and Additional Period II up to Week 94 (24 Weeks). Ninety-six (96) subjects who completed Week 46 rolled over in Additional Period I, and among these, 92 subjects completed the Additional Period I at Week 70. Eleven (11) of these 92 subjects participated in the Additional Period II, and 9 subjects completed the Additional Period II at Week 94. Subject enrollment details are presented in Listing 16.2.1.1.

The Sponsor submitted to the DCGI on 30th December 2022 the protocol amendment 4.2 dated 08 July 2022, to provide the opportunity to continue the treatment with evenamide for the patients who completed the Additional Period I (Week 70). The DCGI approved the protocol amendment on 23rd November 2023 when most of the patients had already completed the previous treatment period, and therefore, only 19 patients were eligible, of which 11 patients signed the ICF and rolled over beyond Week 70.

The subject disposition in Study 015 Beyond Week 46 until the end of the study (Week 94), including details of the number of subjects rolled over into the study and dosed, completed, and discontinued, along with the reason for discontinuation, is summarized in Table 10-1 and presented in Listing 16.2.1.2.

Of the 96 subjects who participated in the Additional Period I, 31, 34 and 31 subjects were in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), evenamide 15 mg *BID* and evenamide 30 mg *BID* treated groups, respectively. During this period, four subjects including three from the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and one from the evenamide 15 mg *BID* withdrew their consent and discontinued prematurely from the study. Of the 11 subjects who participated in the Additional Period II,

none, four and seven subjects were in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), evenamide 15 mg *BID* and evenamide 30 mg *BID* treated groups respectively. During this period, one subject each from the evenamide 15 mg *BID* and evenamide 30 mg *BID* withdrew their consent and discontinued prematurely from the study. No subjects discontinued during the additional treatment periods for any other reason.

Table 10-1 Subject Disposition – Safety Population

Status	**Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)**	**Evenamide 15 mg *BID* (N=34) n (%)**	**Evenamide 30 mg *BID* (N=31) n (%)**	**Total (N=96) n (%)**
Rolled Over from Week 46 to Week 70	31 (100.0)	34 (100.0)	31 (100.0)	96 (100.0)
Rolled Over from Week 70 to Week 94	0 (0.0)	4 (11.8)	7 (22.6)	11 (11.5)
Not entered in the second additional period	31 (100.0)	30 (88.2)	24 (77.4)	85 (88.5)
Safety Population [a]	31 (100.0)	34 (100.0)	31 (100.0)	96 (100.0)
Modified Intent-to-Treat Population [b]	28 (90.3)	34 (100.0)	31 (100.0)	93 (96.9)
Modified Intent-to-Treat Population-C1	27 (87.1)	33 (97.1)	31 (100.0)	91 (94.8)
Modified Intent-to-Treat Population-C2	0 (0.0)	3 (8.8)	6 (19.4)	9 (9.4)
Completed Week 70	28 (90.3)	33 (97.1)	31 (100.0)	92 (95.8)
Discontinuation reasons from Week 46 to Week 70				
Withdrawal Of Consent	3 (9.7)	1 (2.9)	0 (0.0)	4 (4.2)
Completed Week 94	0 (0.0)	3 (75.0)	6 (85.7)	9 (81.8)
Discontinuation reasons from Week 70 to Week 94				
Withdrawal Of Consent	0 (0.0)	1 (25.0)	1 (14.3)	2 (18.2)
Total Discontinuation reasons from Week 46 to Week 94				
Withdrawal Of Consent	3 (9.7)	2 (5.9)	1 (3.2)	6 (6.3)

Source: *Listing 16.2.1.2*; Adapted from *Table 14.1.1.*
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
[a] Safety Population: all subjects who signed the ICF of the extension period beyond week 46 and took at least one dose of study medication in this extension period (study 015 beyond week 46).
[b] Modified Intent-to-Treat Population (mITT): rolled over patients who received at least one dose of the study medication in this extension study (015 beyond Week 46), who had a valid 014 baseline, and had at least one post-baseline assessment for the primary efficacy measure, the PANSS total score, in the extension Study 015 beyond Week 46.
mITT-C1: Those mITT subjects who have completed treatment till Week 70 visit.
mITT-C2: Those mITT subjects who have completed treatment till Week 94 visit.
Percentages for Second additional period (Week 70 to Week 94) are based on the total number of subjects in each group (N) under Rolled Over from Week 70 to Week 94.

10.2. Protocol Deviations

Protocol deviations were reviewed on a case-by-case basis and classified as minor, major, or critical prior to database lock. Critical and major protocol deviations are presented in Table 14.1.2 and summarized in Table 10-2, and all critical and major protocol deviations by subjects are presented in Listing 16.2.2.

No critical protocol deviation was reported in this study. A total of 72 (75%) subjects had a major protocol deviation, of which 31 (100%) were from evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 28 (82.4%) were from evenamide 15 mg *BID*, and 13 (41.9%) were from evenamide 30 mg *BID* groups.

All the major protocol deviations were classified as pertaining to study drug, and none to safety, eligibility, or procedural issues. The majority of these protocol deviations are pertaining to the non-availability of study medication for a period of time.

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

Category	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Subjects with Major Protocol Deviation	31 (100.0)	28 (82.4)	13 (41.9)	72 (75.0)
Subjects with Critical Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: *Listing 16.2.2*; Adapted from *Table 14.1.2.*
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.

11. SAFETY EVALUATION

11.1. Data Sets Analyzed

Of the 96 subjects who rolled over from Study 015 after completing Week 46 to the Study 015 additional treatment period beyond Week 46, all subjects (100%) received at least one dose of study drug and thus were included in the Safety Population. Among these 96 rolled-over subjects, 93 (96.9%) subjects were included in the mITT Population, 91 (94.8%) subjects were included in the mITT Population-C1 and 9 (9.4%) subjects were included in the mITT Population-C2 for the 'Study 015 Beyond Week 46' analysis.

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. Demographic and Baseline Characteristics

Demographic and baseline characteristics data of the Safety Population are presented in Table 14.1.3.1.1 and by subject details in Listing 16.2.4.1. A summary of the demographic and baseline characteristics of the Safety Population is shown in Table 11-1. Subjects were predominantly male (75.0%), Asian (100%), single (47.9%), not employed (79.2%), living with family (100%) and had education of 9-16 years (69.8%).

The mean (SD) age of the subjects was 38.2 (10.44) years, ranging from 20 to 64 years. The mean (SD) weight, height and body mass index were 67.1 (13.05) kg, 163.5 (8.34) cm, and 25.1 (4.63) kg/m^2, respectively. No demographic or baseline characteristics differed notably between the treatment groups.

Table 11-1 Demographics and Baseline Characteristics – Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)	Evenamide 15 mg *BID* (N=34)	Evenamide 30 mg *BID* (N=31)	Total (N=96)
Age (years)	n	31	34	31	96
	Mean (SD)	38.5 (9.07)	36.3 (11.49)	39.8 (10.52)	38.2 (10.44)
	Median	38.0	33.0	40.0	37.0
	Min, Max	23, 58	21, 62	20, 64	20, 64
Weight (kg)	n	31	34	31	96
	Mean (SD)	66.3 (12.92)	67.0 (13.24)	68.0 (13.34)	67.1 (13.05)
	Median	67.3	66.6	65.0	66.3
	Min, Max	42.6, 102.7	44.7, 91.0	42.0, 89.4	42.0, 102.7
Height (cm)	n	31	34	31	96
	Mean (SD)	163.6 (10.28)	164.1 (8.48)	162.7 (5.85)	163.5 (8.34)
	Median	163.0	165.1	164.0	164.0
	Min, Max	136.5, 183.0	145.0, 182.6	149.4, 172.4	136.5, 183.0
BMI (kg/m2)	n	31	34	31	96
	Mean (SD)	24.8 (4.28)	24.9 (4.61)	25.7 (5.08)	25.1 (4.63)
	Median	24.3	24.4	24.5	24.4
	Min, Max	17.28, 36.23	17.70, 34.67	15.62, 37.70	15.62, 37.70
Sex					
Male	n (%)	23 (74.2)	25 (73.5)	24 (77.4)	72 (75.0)
Female	n (%)	8 (25.8)	9 (26.5)	7 (22.6)	24 (25.0)
Childbearing Potential [a]					
Yes	n (%)	6 (75.0)	5 (55.6)	4 (57.1)	15 (62.5)
No	n (%)	2 (25.0)	4 (44.4)	3 (42.9)	9 (37.5)
Race					
Asian	n (%)	31 (100.0)	34 (100.0)	31 (100.0)	96 (100.0)
American Indian or Alaska Native	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
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)
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					
Not Hispanic Or Latino	n (%)	31 (100.0)	34 (100.0)	31 (100.0)	96 (100.0)
Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Education					
1-8 years	n (%)	10 (32.3)	7 (20.6)	8 (25.8)	25 (26.0)
9-16 years	n (%)	20 (64.5)	26 (76.5)	21 (67.7)	67 (69.8)
>16 years	n (%)	1 (3.2)	1 (2.9)	2 (6.5)	4 (4.2)
Marital Status					
Married	n (%)	13 (41.9)	13 (38.2)	17 (54.8)	43 (44.8)
Single	n (%)	15 (48.4)	18 (52.9)	13 (41.9)	46 (47.9)
Stable union	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Widowed	n (%)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Divorced	n (%)	3 (9.7)	2 (5.9)	1 (3.2)	6 (6.3)

Characteristics	Statistic	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)	Evenamide 15 mg *BID* (N=34)	Evenamide 30 mg *BID* (N=31)	Total (N=96)
Employment					
Full-Time Employment	n (%)	3 (9.7)	1 (2.9)	3 (9.7)	7 (7.3)
Not employed	n (%)	24 (77.4)	29 (85.3)	23 (74.2)	76 (79.2)
Part-Time Employment	n (%)	4 (12.9)	4 (11.8)	5 (16.1)	13 (13.5)
Housing Status					
Living with family	n (%)	31 (100.0)	34 (100.0)	31 (100.0)	96 (100.0)
Living alone	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living with companion	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living in residential care	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living in institution	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living alone, with a caregiver	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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

11.2.2. Disease Characteristics

The study subjects enrolled in the current study met the DSM-5 criteria for schizophrenia and had an operational diagnosis of treatment-resistant schizophrenia (TRS) as per Study 014 inclusion criteria. In the Safety Population, the mean (SD) duration of schizophrenia was shorter in evenamide 15 mg *BID* treated group [5.5 (2.96) years] compared to evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 30 mg *BID* treated groups [7.0 (2.20) and 7.2 (3.09) years, respectively], with an overall mean (SD) duration of 6.5 (2.86) years. The mean (SD) duration of the current episode of schizophrenia was 8.1 (5.22) months. The mean (SD) duration of the current episode in evenamide 30 mg *BID* treated subjects was shorter [6.5 (3.27) months] compared to evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated subjects [8.9 (6.29) months] and evenamide 15 mg *BID* treated subjects [8.8 (5.41) months]. The mean (SD) number of psychiatric hospitalizations was 0.2 (0.44) with a range of 0-2. Most of the subjects [75 (78.1%)] did not have a family history of schizophrenia. Among those who had a family history of schizophrenia, 10 (10.4%) subjects had 1st degree relatives and 4 (4.2%) had 2nd degree relatives with schizophrenia.

The number of subjects with other psychiatric disorders was 15 (15.6%). The mean (SD) CDSS total score at baseline (Study 014) was 0.2 (0.56), 0.4 (0.78) and 0.3 (0.68) for subjects in the 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* treated groups, respectively. No disease characteristics differed notably between the treatment groups (Table 11-2).

Disease characteristics data are presented by subject in Listing 16.2.4.3.1, Listing 16.2.4.3.2, and Listing 16.2.15, and summarized in Table 14.1.3.2.1.

Table 11-2 Disease Characteristics - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)	Evenamide 15 mg *BID* (N=34)	Evenamide 30 mg *BID* (N=31)	Total (N=96)
Duration of Illness - Schizophrenia (Years)[a]	n	31	34	31	96
	Mean (SD)	7.0 (2.20)	5.5 (2.96)	7.2 (3.09)	6.5 (2.86)
	Median	7.3	5.4	7.3	6.6
	Min, Max	3, 13	1, 15	1, 15	1, 15
Duration of Current Episode of Schizophrenia (Months)[b]	n	31	34	31	96
	Mean (SD)	8.9 (6.29)	8.8 (5.41)	6.5 (3.27)	8.1 (5.22)
	Median	6.3	8.3	5.8	6.4
	Min, Max	3, 25	2, 23	2, 15	2, 25
Number of Psychiatric Hospitalization	n	31	34	31	96
	Mean (SD)	0.2 (0.56)	0.2 (0.46)	0.1 (0.25)	0.2 (0.44)
	Median	0.0	0.0	0.0	0.0
	Min, Max	0, 2	0, 2	0, 1	0, 2
Family History of Schizophrenia					
None	n (%)	24 (77.4)	26 (76.5)	25 (80.6)	75 (78.1)
1st Degree Relatives [c]	n (%)	2 (6.5)	3 (8.8)	5 (16.1)	10 (10.4)
Father	n (%)	1 (3.2)	0 (0.0)	1 (3.2)	2 (2.1)
Mother	n (%)	0 (0.0)	2 (5.9)	1 (3.2)	3 (3.1)
Brother	n (%)	1 (3.2)	1 (2.9)	2 (6.5)	4 (4.2)
Sister	n (%)	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.0)
2nd Degree Relatives [d]	n (%)	2 (6.5)	2 (5.9)	0 (0.0)	4 (4.2)
Paternal Grandfather	n (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Paternal Grandmother	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal Grandfather	n (%)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Maternal Grandmother	n (%)	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)
Other	n (%)	4 (12.9)	4 (11.8)	2 (6.5)	10 (10.4)
Number of subjects with other psychiatric disorders	n (%)	2 (6.5)	3 (8.8)	10 (32.3)	15 (15.6)
Calgary Depression Scale for Schizophrenia (CDSS)					
CDSS Total Score	n	31	34	31	96
	Mean (SD)	0.2 (0.56)	0.4 (0.78)	0.3 (0.68)	0.3 (0.68)
	Median	0.0	0.0	0.0	0.0
	Min, Max	0, 2	0, 2	0, 2	0, 2

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

11.2.3. Medical History and Psychiatric History

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

Overall, 21 subjects (21.9%), including 6 (19.4%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 9 (26.5%) subjects in the evenamide 15 mg *BID* treated group and 6 (19.4%) subjects in the evenamide 30 mg *BID* treated group, reported having medical history. Diabetes Mellitus was the most commonly reported medical history term by 7 (7.3%) subjects overall, including 3 (9.7%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 3 (8.8%) subjects in the evenamide 15 mg *BID* treated group and 1 (3.2%) subject in the 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, 15 (15.6%) subjects, including 2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 3 (8.8%) subjects in the evenamide 15 mg *BID* treated group and 10 (32.3%) subjects in the evenamide 30 mg *BID* treated group, reported any other psychiatric history. The most common finding in the psychiatric records was, by preferred term (PT): mental disorder (verbatim term, psychiatric illness) in 10 (10.4%) subjects overall [1 subject (3.2%) in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 1 subject (2.9%) in the evenamide 15 mg *BID* treated group and 8 subjects (25.8%) in the evenamide 30 mg *BID* treated group], followed by depression (PT) in 3 (3.1%) subjects overall [none in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 1 (2.9%) subject in the evenamide 15 mg *BID* treated group and 2 (6.5%) subjects in the evenamide 30 mg *BID* treated group].

Other psychiatric history terms include insomnia in 2 (2.1%) subjects overall, and anxiety and sleep disorder each in one (1.0%) subject overall.

11.3. 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, respectively, and by subject details in Listing 16.2.4.4.1.1 and Listing 16.2.4.4.1.2, respectively.

Overall, use of any prior medication was reported in 29 (30.2%) subjects, including 6 (19.4%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 12 (35.3%) subjects in the evenamide 15 mg *BID* treated group and 11 (35.5%) subjects in the evenamide 30 mg *BID* treated group. Overall, Tertiary amines were the most commonly used prior medications, reported for 18 (18.8%) subjects, followed by Benzodiazepine derivatives in 11 (11.5 %) subjects, Diazepines, Oxazepines, Thiazepines and Oxepines in 4 (4.2%) subjects, Vitamin, Other Combinations in 4 (4.2%) subjects, Phenothiazines with Piperazine Structure in 3 (3.1%) subjects, Vitamin B-Complex, Plain in 3 (3.1%) subjects, Other Antipsychotics in 2 (2.1%) subjects, and other medications in one subject each.

Overall, 83 (86.5%) subjects, including 28 (90.3%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 30 (88.2%) subjects in the evenamide 15 mg *BID* treated group and 25 (80.6%) subjects in the evenamide 30 mg *BID* treated group, had a record of concomitant medications [i.e., those medications taken at any time during the Study 015 beyond Week 46, or ongoing from prior extension irrespective of the start date] other than antipsychotics. The most commonly used concomitant medications were Trihexyphenidyl (ATC class: Tertiary amines) [66 subjects (68.8%) overall] and Lorazepam (ATC class: Benzodiazepine derivatives) [25 subjects (26.0%) overall].

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 96 subjects in the Safety Population (100%), including 31 subjects (100%) in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 34 subjects (100%) in the evenamide 15 mg *BID* treated group and 31 subjects (100%) in the evenamide 30 mg *BID* treated group, had a record of PAM [i.e., those prior medications that were reported by sites in the PAM form within the eCRF]. The most commonly used PAMs were Risperidone [85 subjects (88.5%) overall] and Olanzapine [73 subjects (76%) overall].

Current antipsychotic medications taken by the subjects in the Safety Population are summarized in Table 14.1.4.2.2. As required by the protocol, all subjects were receiving a stable dose of a single antipsychotic, other than clozapine, at the time of enrolment in the study. Out of the 96 subjects who were currently on antipsychotics during the study treatment, 60 (62.5%) subjects were taking Risperidone, and 25 (26.0%) subjects were taking Olanzapine (Table 11-3).

Three subjects were taking other atypical (second-generation) antipsychotics (Aripiprazole - 2, Paliperidone - 1) and only 8 (8.3%) subjects were receiving other types of antipsychotics, including first-generation antipsychotics (e.g., Haloperidol, Trifluoperazine, Amisulpride, and Blonanserin).

Details of current antipsychotic medication by subject during the study treatment are presented in Listing 16.2.4.4.3.2.

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

Drug Name	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Current Antipsychotic Medication				
Risperidone	21 (67.7)	22 (64.7)	17 (54.8)	60 (62.5)
Olanzapine	7 (22.6)	8 (23.5)	10 (32.3)	25 (26.0)
Aripiprazole	0 (0.0)	1 (2.9)	1 (3.2)	2 (2.1)
Paliperidone	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.0)
Other	3 (9.7)	3 (8.8)	2 (6.5)	8 (8.3)
Other Specify				
Haloperidol	2 (6.5)	0 (0.0)	1 (3.2)	3 (3.1)

Drug Name	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Trifluoperazine	1 (3.2)	2 (5.9)	0 (0.0)	3 (3.1)
Amisulpride	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Blonanserin	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.0)

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

11.3.1. Prior and Concomitant Procedures

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

11.3.2. Rescue Medications

A summary of the rescue medications taken by patients in the Safety Population during the study is presented in Table 11-4. The number of subjects who received at least one rescue medication was 3 (3.1%) subjects, with 2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group and 1 (2.9%) subject in the evenamide 15 mg *BID* treated group. Risperidone was used by 1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and by 1 (2.9%) subject in the evenamide 15 mg *BID* treated groups. Lorazepam was used by 1 (2.9%) subject in the evenamide 15 mg *BID* treated group, and Trifluoperazine was used by 1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group.

A 23-year-old female subject (303021) required Risperidone, and a 41-year-old female subject (311010) required Trifluoperazine as rescue medication, for exacerbation of schizophrenia. Both the subjects were from the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group. A 30-year-old male subject (303011) required Lorazepam and Risperidone as rescue medications in the evenamide 15 mg *BID* treated group.

Rescue medication details of the Safety Population are presented by subject in Listing 16.2.4.4.3.3 and in Table 14.1.4.3.

Table 11-4 Summary of Rescue Medications - Safety Population

Rescue Medication Name	Statistic	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)	Evenamide 15 mg *BID* (N=34)	Evenamide 30 mg *BID* (N=31)	Total (N=96)
No. Of Subjects Who Received At Least One Rescue Medication	n (%)	2 (6.5)	1 (2.9)	0 (0.0)	3 (3.1)
Lorazepam	n (%)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Risperidone	n (%)	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)

Trifluoperazine	n (%)	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)

Source: *Listing 16.2.4.4.3.3*; Adapted from *Table 14.1.4.3*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Dose adjustments for atypical antipsychotics of 25% or more, upwards, or downwards or any antipsychotic administered for Exacerbation of Schizophrenia not temporarily (more than 5 days) in the treatment period due to significant worsening are considered rescue medications.
Refer to study protocol or statistical analysis plan for the full definition of rescue medication.

11.4. Measurements of Treatment Compliance

Compliance with the study medication was monitored as described in Section 9.4.8 and analyzed as detailed in Section 9.7.1.18.1.

The mean (SD) overall treatment compliance in the Additional Period I (Week 46 to Week 70) was 99.3% (2.08), with a median of 99.9% (range: 89 to 112%). The mean (SD) treatment compliance during this period for subjects in the evenamide 7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID* treated groups was 99.6% (3.03), 99.6% (0.71) and 98.8% (1.89), respectively. The maximum treatment compliance of 112% was reported for a subject on evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), and the minimum of 89% was also reported for a subject in the same group (Table 11-5).

The mean (SD) overall treatment compliance in the Additional Period II (Week 70 to Week 94) was 110.6% (6.58), with a median of 109.2% (range: 104 to 123%). No patients in the evenamide 7.5 mg (up-titrated to 15 mg *BID*) group were treated in Additional Period II. The mean (SD) treatment compliance during this period for subjects in the evenamide 15 mg and 30 mg *BID* treated groups was 107.2% (2.58) and 112.6% (7.49), respectively. The maximum treatment compliance of 123% was reported for a subject on evenamide 30 mg and the minimum of 104% was reported in 2 subjects in the evenamide 15 mg *BID* and 30 mg *BID* treated groups (Table 11-5).

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.

11.5. Extent of Exposure

During the Additional Period I, the mean (SD) overall study drug exposure was 132.5 (41.37) days, with a median of 149.5 (range: 32 to 194) days. The mean (SD) study drug exposure for subjects in evenamide 7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID* treated groups were 111.4 (39.30), 125.6 (44.55) and 161.0 (18.42) days, respectively. The maximum study drug exposure of 194 days was reported for a subject in the evenamide 30 mg *BID* treated group, and the minimum of 32 days was reported for a subject in the evenamide 15 mg *BID* treated group (Table 11-5).

During the Additional Period II, the mean (SD) overall study drug exposure was 148.5 (36.19) days, with a median of 163.0 (range: 70 to 175) days. The mean (SD) study drug exposure for subjects in evenamide 15 mg and 30 mg *BID* treated groups were 150.8 (42.65) and 147.1 (35.60) days, respectively. No patients in the 7.5 mg *BID* (up-titrated to 15 mg *BID*) group were enrolled in this period. The maximum study drug exposure of 175 days was reported for a subject in the evenamide 15 mg *BID* treated group, and the minimum of 70 days was reported for a subject in the evenamide 30 mg *BID* treated group (Table 11-5).

Study drug exposure is presented in Table 14.3.0.1 and by subject details in Listing 16.2.5.2.

Table 11-5 Study Drug Exposure - Safety Population

Characteristics	Statistic	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)	Evenamide 15 mg *BID* (N=34)	Evenamide 30 mg *BID* (N=31)	Total (N=96)
Duration of Exposure (days) from Week 46 to Week 70 [a]	n	31	34	31	96
	Mean (SD)	111.4 (39.30)	125.6 (44.55)	161.0 (18.42)	132.5 (41.37)
	Median	99.0	130.0	167.0	149.5
	Min, Max	33, 171	32, 177	113, 194	32, 194
Treatment Compliance (%) from Week 46 to Week 70 [b]	n	31	34	31	96
	Mean (SD)	99.6 (3.03)	99.6 (0.71)	98.8 (1.89)	99.3 (2.08)
	Median	100.0	100.0	99.5	99.9
	Min, Max	89, 112	97, 100	92, 100	89, 112
Duration of Exposure (days) from Week 70 to Week 94 [a]	n	0	4	7	11
	Mean (SD)	0 (0)	150.8 (42.65)	147.1 (35.60)	148.5 (36.19)
	Median	0.0	170.5	163	163
	Min, Max	0.0	87, 175	70, 173	70, 175
Treatment Compliance (%) from Week 70 to Week 94 [b]	n	0	4	7	11
	Mean (SD)	NA	99.3 (0.35)	99.4 (0.35)	99.3 (0.34)
	Median	NA	99.3	99.4	99.4
	Min, Max	NA	99, 100	99, 100	99, 100

Source: *Listing 16.2.5.2*; Adapted from *Table 14.3.0.1*.
N - Total number of subjects in the Safety Population, n = number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum, NA=Not Applicable.
[a] Duration of exposure (days) = (Treatment end date - Treatment start date + 1).
[b] Treatment compliance is computed as 100*[#Capsules consumed / #Capsules expected to be consumed].

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

A total of 62 (64.6%) subjects had a kit replacement or dose adjustment, which includes 22 (71.0%), 23 (67.6%), 17 (54.8%) subjects in the evenamide 7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID* treated groups, respectively. None of the subjects in any group had a dose adjustment. The maximum number of subjects with kit replacements was seen in the evenamide 15 mg *BID* group [23 subjects (67.6%)].

11.6. Adverse Events

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

11.6.1. Brief Summary of Adverse Events

An overall summary of the TEAEs in the Safety Population is presented in Table 14.3.1.1 and summarized in Table 11-6, and by subject details are presented in Listing 16.2.7.1, Listing 16.2.7.2, and Listing 16.2.7.3.

During the study duration (from Week 46 to Week 94), 6 (6.3%) subjects reported at least one TEAE, which included 3 (9.7%), 3 (8.8%) and 0 (0.0%) subjects in the evenamide 7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID* treated groups, respectively. A Serious TEAE was reported in only 1 (1.0%) subject overall, and that subject was in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group [1 (3.2%) subject]. Of the 6 overall TEAEs reported, 4 (4.2%) were of mild severity, 2 (2.1%) were of moderate severity, and none were of severe intensity.

Overall, the number of subjects with at least one Treatment-Related TEAE was 1 (1.0%), with that subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group [1 (3.2%) subject]; this event was of mild severity. None of the subjects in any group had Any Serious and Treatment-Related TEAE. In addition, none of the subjects in any group had Any TEAE leading to study drug discontinuation.

Table 11-6 Overall Summary of Treatment-Emergent Adverse Events - Safety Population

Category	**Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)**	**Evenamide 15 mg *BID* (N=34) n (%)**	**Evenamide 30 mg *BID* (N=31) n (%)**	**Total (N=96) n (%)**
No. of Subjects with at least one TEAE	3 (9.7)	3 (8.8)	0 (0.0)	6 (6.3)
No. of Subjects with at least one Serious TEAE	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
No. of Subjects with at least one Treatment-Related TEAE [a]	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
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	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of Subjects with Any TEAE Resulting in Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of Subjects with Any TEAE by Severity				
Mild	2 (6.5)	2 (5.9)	0 (0.0)	4 (4.2)
Moderate	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of Subjects with Any Treatment-Related TEAE by Severity				
Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
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*; Adapted from *Table 14.3.1.1*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication in the additional treatment period of Study 015 (beyond Week 46). Subject are counted only under the maximum severity observed for TEAEs.
[a] Treatment-Related TEAEs are the TEAEs which are possibly or probably related to study drug, or not reported.

11.6.2. Display of Adverse Events

A summary of TEAEs by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.2 and by subject details in Listing 16.2.7.1.

Overall, 1 (1.0%) subject, in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, reported one Serious TEAE. The details are presented in Table 14.3.1.3 and by subject details in Listing 16.2.7.2.

A summary of Treatment-Related TEAEs by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1. Overall, 1 (1.0%) subject, in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, reported a Treatment-Related TEAE. The details are presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1.

A summary of TEAEs leading to study drug discontinuation by System Organ Class (SOC) and Preferred Term (PT) for the Safety Population is presented in Table 14.3.1.5.

11.6.3. Analysis of Adverse Events

11.6.3.1. Overall Incidence of Treatment-Emergent Adverse Events

A summary of TEAEs that occurred in the evenamide treated groups is presented by SOC and PT in Table 11-7, and by subject details in Listing 16.2.7.1.

Overall, 6 (6.3%) of subjects experienced at least one TEAE. The maximum number of subjects with any TEAEs was reported in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and in the evenamide 15 mg *BID* treated groups, with 3 (9.7%) and 3 (8.8%) subjects, respectively.

The most frequently reported TEAEs by SOC were found in 'Investigations' with 2 subjects overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 1 (2.9%) subject in the evenamide 15 mg *BID* treated groups], 'Metabolism and Nutrition Disorders' with 2 subjects overall [2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group] and in 'Psychiatric Disorders' with 2 subjects overall [2 (5.9%) subjects in the evenamide 15 mg *BID* treated group]. The other reported TEAEs by SOC were found in 'Blood and lymphatic system disorders' with 1 subject overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*)] and in 'Nervous system disorders' with 1 subject overall [1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*)] treated group].

For the two reported TEAEs under the SOC 'Metabolism and Nutrition Disorders', the preferred term 'Hyponatraemia' was reported in two subjects. For the two reported TEAEs under the SOC 'Investigations' the preferred terms 'Body temperature increased' and 'Liver function test increased' were reported in one subject each . For the two reported TEAEs under the SOC 'Psychiatric disorders' the preferred terms 'Restlessness' and 'Schizophrenia' were reported in one subject each. The preferred term of the only reported TEAE under the SOC 'Blood and lymphatic system disorders' was 'Anaemia' and the preferred term of the only reported TEAE under the SOC 'Nervous system disorders' was 'Seizure'.

All TEAEs are presented by SOC and Preferred Term in Table 14.3.1.2.

Table 11-7 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* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Number of subjects with any TEAE	3 (9.7)	3 (8.8)	0 (0.0)	6 (6.3)
Investigations	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)
Body temperature increased @	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Liver function test increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Metabolism and nutrition disorders	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.1)
Hyponatraemia	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.1)
Psychiatric disorders	0 (0.0)	2 (5.9)	0 (0.0)	2 (2.1)
Restlessness	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Schizophrenia	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
Blood and lymphatic system disorders	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Anaemia	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Nervous system disorders	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Seizure	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)

Source: *Listing 16.2.7.1*; Adapted from *Table 14.3.1.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
@ = The event occurred after week 46 of study 015, all the other adverse events were already reported in the previous CSR up to 1-year of treatment.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication in Study 015 (i.e. day 1 of study 015).
Adverse events are coded with MedDRA Version 23.0. Subjects are counted only once per SOC and per PT.

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

A summary of Treatment-Related TEAEs is presented by SOC and PT for the Safety Population in Table 11-8. Other details are presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1.

Overall, only one (1.0%) subject reported at least one Treatment-Related TEAE, which was in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, and it was reported under the preferred term ‘Anaemia’ in the SOC ‘Blood and lymphatic system disorders’.

Relatedness of TEAEs presented by subject is included in Listing 16.2.7.1.

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* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Number of subjects with any Treatment-Related TEAE	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Blood and lymphatic system disorders	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)

Anaemia	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)

Source: *Listing 16.2.7.1*; Adapted from *Table 14.3.1.4*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication in Study 015 (i.e. day 1 of study 015).
Treatment-Related TEAE are the TEAE which are possibly or probably related to study drug, or not reported.
Adverse events are coded with MedDRA Version 23.0.
Subjects are counted only once per system organ class and per preferred term.

11.6.3.3. 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. A summary of TEAEs by severity is provided in Table 11-9.

A total of six subjects reported any TEAE, of which 4 (4.2%) subjects reported TEAEs of mild severity [2 (6.5%) subjects in evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 2 (5.9%) subjects in evenamide 15 mg *BID* treated groups] and 2 (2.1%) subjects reported TEAEs of moderate severity [1 (3.2%) subject in evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 1 (2.9%) subject in the evenamide 15 mg *BID* treated groups]. No severe TEAEs were reported.

Table 11-9 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* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Number of subjects with any TEAE	Mild	2 (6.5)	2 (5.9)	0 (0.0)	4 (4.2)
	Moderate	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	Mild	1 (3.2)	1 (2.9)	0 (0.0)	2 (2.1)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body temperature increased	Mild	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver function test increased	Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Moderate	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Severity	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Hyponatraemia	Mild	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Moderate	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Seizure	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	Mild	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Restlessness	Mild	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Schizophrenia	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.0)
	Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: *Listing 16.2.7.1*; Adapted from *Table 14.3.1.6*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication in Study 015 (i.e. day 1 of study 015).
Adverse events are coded with MedDRA Version 23.0.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity.

11.6.4. Listing of Adverse Events by Subject

All AEs for each subject are listed in Listing 16.2.7.1.

11.7. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.7.1. Listing of Deaths, Other SAEs, and Other Significant Adverse Events

No death was reported in Study 015 beyond Week 46.

Overall, 1 (1.0%) subject, in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, reported one Serious TEAE in Study 015 beyond Week 46 (Table 11-10). The details are presented in Table 14.3.1.3 and by subject details in Listing 16.2.7.2.

There were no adverse events leading to study drug discontinuation in Study 015 beyond Week 46.

There were no overdose/ medication errors reported in this Study 015 beyond Week 46.

The brief narrative of the SAE is presented in Section 11.7.2. The Expanded Narrative of the SAE is provided in Section 14.

11.7.2. Narrative of Serious Adverse Event

The narrative of the serious adverse events (experienced by a single patient) is presented in the CSR main body in Section 14. The short narrative is reported below.

11.7.2.1. Short Narrative of Serious Adverse Event

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

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

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

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

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

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

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

11.7.3. Analysis and Discussion of Serious Adverse Events

11.7.3.1. *Serious Adverse Events*

A summary of treatment-emergent SAEs is presented by SOC and PT for the Safety Population in Table 14.3.1.3 and Table 11-10, and by subject details in Listing 16.2.7.2.

A short narrative of SAE is provided in Section 11.7.2.

Table 11-10 Summary of Treatment-Emergent Serious Adverse Events by SOC and Preferred Term - Safety Population

System Organ Class Preferred Term	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Number of subjects with any Serious TEAE	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Metabolism and nutrition disorders	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Hyponatraemia	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Nervous system disorders	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)
Seizure	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.0)

Source: *Listing 16.2.7.2*; Adapted from *Table 14.3.1.3*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are based on the total number of subjects in each group (N) under Safety Population.
TEAE = Treatment Emergent Adverse Events are adverse events that are newly occurring or worsened in severity after the first administration of the study medication in Study 015 (i.e. day 1 of study 015). Both SAEs were already reported in the previous 015 CSR up to 1-year of treatment.
Adverse events are coded with MedDRA Version 23.0. Subjects are counted only once per SOC and per PT.

11.8. Clinical Laboratory Evaluation

11.8.1. Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

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

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

11.8.2. Evaluation of Each Laboratory Parameter

11.8.2.1. Hematology

11.8.2.1.1. Laboratory Values over Time

Summary statistics for change from baseline in hematology parameters of the Safety Population are presented in Table 14.3.2.1 (observed values and change from baseline). There were no clinically meaningful changes in mean values from baseline for hematology parameters in any of the three treatment groups.

11.8.2.1.2. Individual Subject Changes

A summary of newly emergent clinically notable abnormal findings in laboratory hematology parameters at any post-baseline timepoint 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 among 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 hemoglobin, for which notable low levels (≤ 0.85 x lower limit of normal (LLN) g/L) were reported in 5 subjects overall at Week 58 [4 (12.9%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group and 1 (2.9%) subject in the evenamide 15 mg *BID* treated group] and at Week 70 [2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 1 (2.9%) subject in the evenamide 15 mg *BID* treated group and 2 (6.5%) subjects in the evenamide 30 mg *BID* treated group] (Table 11-11).

Table 11-11 Laboratory Hematology: Newly Emergent Clinically Notable Abnormal Findings - Safety Population

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n(%)	Evenamide 15 mg *BID* (N=34) n(%)	Evenamide 30 mg *BID* (N=31) n(%)
Hematocrit (fraction of 1)	Week 58	≤ 0.85 x LLN	1 (3.2)	1 (2.9)	1 (3.2)
	Week 70/End of Study	≤ 0.85 x LLN	2 (6.5)	0 (0.0)	2 (6.5)
Hemoglobin (g/L)	Week 58	≤ 0.85 x LLN	4 (12.9)	1 (2.9)	0 (0.0)
	Week 70/End of Study	≤ 0.85 x LLN	2 (6.5)	1 (2.9)	2 (6.5)
	Week 94/End of Study	≤ 0.85 x LLN	0 (0.0)	0 (0.0)	1 (3.2)

Source: *Listing 16.2.8.1*; Adapted from *Table 14.3.2.3*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are calculated by considering Male/Female count in each treatment group (Evenamide 7.5 mg *BID*: 23/8, Evenamide 15 mg *BID*: 25/9 and Evenamide 30 mg *BID*: 24/7) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

11.8.2.2. Blood Chemistry

11.8.2.2.1. Laboratory Values over Time

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

11.8.2.2.2. Individual Subject Changes

A summary of newly emergent clinically notable abnormal findings in laboratory blood chemistry parameters at any post-baseline in the Safety Population is presented in Table 14.3.2.4. There were no clinically meaningful trends observed in the newly emergent clinically notable abnormalities in any of

the three treatment groups. The number of newly emergent clinically notable abnormalities was low across all the treatment groups, with no meaningful differences.

At Week 58, the maximum number of newly emergent clinically notable abnormal findings in blood chemistry parameters were observed in high density lipoprotein (HDL) cholesterol level (≤ 0.8 mmol/L) with 5 (16.1%) and 5 (14.7%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 15 mg *BID* treated groups, respectively, and 2 (6.5%) subjects in the evenamide 30 mg *BID* treated group (Table 11-12).

Table 11-12 Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings - Safety Population

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)
Bicarbonate (mmol/L)	Week 58	≤ 18	1 (3.2)	3 (8.8)	0 (0.0)
	Week 70/End of Study	≤ 18	0 (0.0)	1 (2.9)	0 (0.0)
	Week 58	≥33	0 (0.0)	0 (0.0)	1 (3.2)
Bilirubin (umol/L)	Week 70/End of Study	≥ 34	0 (0.0)	0 (0.0)	1 (3.2)
Calcium (mmol/L)	Week 70/End of Study	≤ 1.9	0 (0.0)	1 (2.9)	1 (3.2)
Potassium (mmol/L)	Week 58	≥ 6.0	0 (0.0)	1 (2.9)	0 (0.0)
Creatine Kinase (U/L)	Week 58	≥400	1 (3.2)	3 (8.8)	3 (9.7)
	Week 70/End of Study	≥400	0 (0.0)	1 (2.9)	2 (6.5)
Creatinine (umol/L)	Week 58	≥ 177	1 (3.2)	1 (2.9)	1 (3.2)
	Week 70/End of Study	≥ 177	1 (3.2)	0 (0.0)	0 (0.0)
Glucose (mmol/L)	Week 58	≥ 11.1	0 (0.0)	0 (0.0)	1 (3.2)
	Week 70/End of Study	≥ 11.1	0 (0.0)	0 (0.0)	1 (3.2)
HDL Cholesterol (mmol/L)	Week 58	≤ 0.8	5 (16.1)	5 (14.7)	2 (6.5)
	Week 70/End of Study	≤ 0.8	1 (3.2)	2 (5.9)	3 (9.7)
	Week 94/End of Study	≤ 0.8	0 (0.0)	2 (5.9)	1 (3.2)
LDL Cholesterol (mmol/L)	Week 58	≥ 4.1	0 (0.0)	0 (0.0)	1 (3.2)
	Week 70/End of Study	≥ 4.1	2 (6.5)	0 (0.0)	0 (0.0)
Sodium (mmol/L)	Week 58	≤ 127	0 (0.0)	1 (2.9)	0 (0.0)
Sodium (mmol/L)	Week 58	≥ 152	1 (3.2)	0 (0.0)	0 (0.0)
Triglycerides (mmol/L)	Week 58	≥ 4.5	1 (3.2)	0 (0.0)	1 (3.2)

Test (Unit)	Visit	Notable Criteria	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)
	Week 70/End of Study	≥ 4.5	0 (0.0)	0 (0.0)	1 (3.2)

Source: *Listing 16.2.8.2*; Adapted from *Table 14.3.2.4*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are calculated by considering Male/Female count in each treatment group (Evenamide 7.5 mg *BID*: 23/8,
Evenamide 15 mg *BID*: 25/9 and Evenamide 30 mg *BID*: 24/7) whenever the criterion is specific for Male/Female.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

11.8.2.3. Urinalysis

Urinalysis data are 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 pattern of abnormalities were detected for any parameter.

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

11.9. Vital Signs, Physical Findings and Other Observations Related to Safety

11.9.1. Vital Signs

Vital sign measurements are listed by subject in Listing 16.2.9.1, Listing 16.2.9.2 and Listing 16.2.9.3 and at each of the scheduled timepoints in Listing 16.2.9a.

11.9.1.1. 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 in mean values from baseline for vital signs in any of the three treatment groups.

11.9.1.2. Individual Clinically Notable Abnormalities – Vital Signs

A summary of incidence of clinically notable abnormalities in vital signs parameters is presented in Table 14.3.3.2, and by subject details are presented in Listing 16.2.9b. The criteria for clinically notable vital signs abnormalities are displayed in Appendix 2 of the Study Protocol presented in Appendix 16.1.1. No clinically meaningful trends were observed in the clinically notable abnormalities in the vital sign parameters in any of the three treatment groups. The numbers of clinically notable abnormalities were low across all the treatment groups, with no meaningful differences (Table 11-13).

Table 11-13 Incidence of Clinically Notable Abnormalities for Vital Signs - Safety Population

Vital Signs	Visit	Criteria	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)
Weight (kg)	Week 58	≥ 7% decrease from Baseline	1 (3)	1 (3)	0 (0)
	Week 58	≥ 7% increase from Baseline	1 (3)	3 (9)	1 (3)
	Week 70/ End of Study	≥ 7% decrease from Baseline	1 (3)	1 (3)	0 (0)
	Week 70/ End of Study	≥ 7% increase from Baseline	2 (6)	3 (9)	1 (3)
	Week 94/ End of Study	≥ 7% increase from Baseline	0 (0)	1 (3)	1 (3)
Weight (kg)	Safety follow-up-015 - Day 7	≥ 7% increase from Baseline	0 (0)	2 (6)	0 (0)

Source: *Listing 16.2.9b*; Adapted from *Table 14.3.3.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

11.9.2. Electrocardiogram Findings

11.9.2.1. Individual Subject Changes

The change from baseline at each visit and at endpoint (Week 70 or Week 94 or early discontinuation) for ECG parameters (Mean heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval) is presented in Table 14.3.5.1, and by subject details in Listing 16.2.11.1. There were no clinically meaningful changes from baseline in mean values for any ECG parameters in any of the three treatment groups.

11.9.2.2. 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 Table 11-14, and by subject details in Listing 16.2.11.2. The number of post-baseline ECGs that were assessed as abnormal was low. The Central Reviewer assessed that 1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 4 (11.8%) subjects in evenamide 15 mg *BID* and 3 (9.7%) subjects in evenamide 30 mg *BID* treated groups had treatment-emergent abnormalities in the ECG recordings.

Table 11-14 Electrocardiogram (ECG): Treatment Emergent Abnormalities as Assessed by Central Reader - Safety Population

Result	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Abnormal	1 (3.2)	4 (11.8)	3 (9.7)	8 (8.3)

Source: *Listing 16.2.11.2*; Adapted from *Table 14.3.5.2*.
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 have been counted only once. Percentages are based on the total number of subjects in each group (N) under Safety population.

Summary of Treatment-Emergent Abnormalities in ECG as Assessed by Investigator in the Safety Population is presented in Table 14.3.5.3 and Table 11-15, and by subject details in Listing 16.2.11.1. The Investigators assessed that 2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group, 6 (17.6%) in the 15 mg *BID* treated group and 7 (22.6%) subjects in the 30 mg *BID* treated group had treatment-emergent abnormalities in the ECG recordings. None of these abnormalities were considered as clinically significant by the Investigators in any of the three treatment groups.

Table 11-15 Electrocardiogram (ECG): Treatment Emergent Abnormalities as Assessed by Investigator - Safety Population

Result	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Abnormal NCS	2 (6.5)	6 (17.6)	7 (22.6)	15 (15.6)
Abnormal CS	0	0	0	0

Source: *Listing 16.2.11.1*; Adapted from *Table 14.3.5.3*.
N - Total number of subjects in the Safety population, n - number of subjects in the specified category. Percentages are based on the total number of subjects in each group (N) under Safety population.
CS = Clinically Significant, NCS = Not Clinically Significant.
Subjects with abnormal post-baseline findings at more than one assessment have been counted only once.

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 and overall:

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

A PR Interval, Aggregate (ms) absolute value >200 msec (Table 11-16) was observed at Week 70/End of Study in 1 (2.9%) subject in the evenamide 15 mg *BID* and 1 (3.2%) subject in the evenamide 30 mg *BID* treated groups. More than 25% change from baseline in the PR interval was observed at Week 58 in 1 (2.9%) subject in the evenamide 15 mg *BID* treated group and at Week 70/End of Study in 3 (8.8%) subjects and 1 (3.2%) subject in the evenamide 15 mg *BID* and 30 mg *BID* treated groups, respectively.

A QRS Duration, Aggregate (ms) absolute value >110 msec (Table 11-16) was observed at Week 58 in 1 (2.9%) subject in the evenamide 15 mg *BID* treated group and at Week 70/End of Study in 1 (3.2%) subject and 1 (2.9%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 15 mg *BID* treated groups, respectively. More than 25% change from baseline in the QRS Duration was observed at

Week 58 in 1 (2.9%) subject in the evenamide 15 mg *BID* treated group and at Week 70/End of Study in 1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group.

A QTcB Interval, Aggregate (ms) absolute value >450 msec AND ≤ 480 msec (Table 11-16) was observed at Week 58 in 1 (3.2%) subject and 2 (5.9%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 15 mg *BID* treated groups, respectively and at Week 70/End of Study in 2 (6.5%) subjects and 2 (5.9%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and evenamide 15 mg *BID* treated groups, respectively. A change from baseline > 30 msec AND ≤ 60 msec in the QTcB interval was observed at Week 58 in 4 (12.9%) subjects, 4 (11.8%) subjects, and 1 (3.2%) subject in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* treated groups, respectively and at Week 70/End of Study in 2 (6.5%) subjects and 3 (8.8%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 15 mg *BID* treated groups, respectively.

A QTcF Interval, Aggregate (ms) absolute value >450 msec AND ≤ 480 msec (Table 11-16) was observed in 1 (2.9%) subject of the evenamide 15 mg *BID* treated group at Week 58. No values greater than 480 msec were observed. A change from baseline > 30 msec AND ≤ 60 msec in the QTcF interval was observed at Week 58 in 2 (6.5%) subjects, 2 (5.9%) subjects, and 1 (3.2%) in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* treated groups, respectively and at Week 70/End of Study in 1 (3.2%) subject in the evenamide 30 mg *BID* treated group. A change from baseline > 60 msec in the QTcF interval was observed at Week 70/End of Study in 1 (3.2%) subject of the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) treated group.

Table 11-16 Electrocardiogram (ECG) Parameters Categorical Analysis - Safety Population

Parameter	**Visit**	**Criteria**	**Category**	**Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)**	**Evenamide 15 mg *BID* (N=34) n (%)**	**Evenamide 30 mg *BID* (N=31) n (%)**
PR Interval, Aggregate (ms)	Week 58	Change From Baseline value	More than 25% change from baseline	0 (0)	1 (2.9)	0 (0)
	Week 70/End of Study	Absolute Value	> 200 msec	0 (0)	1 (2.9)	1 (3.2)
		Change From Baseline value	More than 25% change from baseline	0 (0)	3 (8.8)	1 (3.2)
QRS Duration, Aggregate (ms)	Week 58	Absolute Value	> 110 msec	0 (0)	1 (2.9)	0 (0)
		Change From Baseline value	More than 25% change from baseline	0 (0)	1 (2.9)	0 (0)
	Week 70/End of Study	Absolute Value	> 110 msec	1 (3.2)	1 (2.9)	0 (0)
		Change From Baseline value	More than 25% change from baseline	1 (3.2)	0 (0)	0 (0)
QTcB Interval,	Week 58	Change From Baseline value	> 30 msec AND ≤ 60 msec	4 (12.9)	4 (11.8)	1 (3.2)

Parameter	Visit	Criteria	Category	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)
Aggregate (ms)		Absolute Value	> 450 msec AND ≤ 480 msec	1 (3.2)	2 (5.9)	0 (0)
	Week 70/End of Study	Change From Baseline value	> 30 msec AND ≤ 60 msec	2 (6.5)	3 (8.8)	0 (0)
	Week 70/End of Study	Absolute Value	> 450 msec AND ≤ 480 msec	2 (6.5)	2 (5.9)	0 (0)
QTcF Interval, Aggregate (ms)	Week 58	Change From Baseline value	> 30 msec AND ≤ 60 msec	2 (6.5)	2 (5.9)	1 (3.2)
		Absolute Value	> 450 msec AND ≤ 480 msec	0 (0)	1 (2.9)	0 (0)
	Week 70/End of Study	Change From Baseline value	> 30 msec AND ≤ 60 msec	0 (0)	0 (0)	1 (3.2)
		Change From Baseline value	> 60 msec	1 (3.2)	0 (0)	0 (0)

Source: *Listing 16.2.11.3*; Adapted from *Table 14.3.5.4*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

11.9.3. 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.

11.9.3.1. *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).

11.9.3.2. *Neurological Examination Individual Subject Changes*

As shown in Table 11-17, one (3.2%) subject from evenamide 30 mg *BID* treated group was found to have a clinically non-significant treatment-emergent abnormality (Delusions and Hallucinations) on the neurological examination conducted at Week 70, while no treatment-emergent abnormalities were reported in either of the other treatment groups (Table 14.3.6).

Table 11-17 Neurological Examination: Treatment Emergent Abnormalities - Safety Population

Result	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Abnormal, NCS	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.0)

Abnormal, CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: *Listing 16.2.12*; Adapted from *Table 14.3.6*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are based on the total number of subjects in each group (N) under Safety Population. CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal NCS or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any neurological system are counted only once.

11.9.4. 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.

As shown in Table 11-18, overall, 3 (3.1%) subjects were found to have clinically non-significant (NCS) treatment-emergent post-baseline abnormal findings in the standard eye examination with 1 (3.2%) subject and 2 (6.5%) subjects in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) and 30 mg *BID* treated groups, respectively.

Table 11-18 Standard Eye Examination: Treatment Emergent Abnormalities - Safety Population

Result	Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31) n (%)	Evenamide 15 mg *BID* (N=34) n (%)	Evenamide 30 mg *BID* (N=31) n (%)	Total (N=96) n (%)
Abnormal, NCS	1 (3.2)	0 (0.0)	2 (6.5)	3 (3.1)
Abnormal, CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: *Listing 16.2.13*; Adapted from *Table 14.3.7*.
N - Total number of subjects in the Safety 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 NCS or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any body system is counted only once

11.9.5. Extrapyramidal Symptom Rating Scale

A summary of results for the Extrapyramidal Symptoms Rating Scale - Abbreviated Version (ESRS-A) for the Safety Population for each parameter at Baseline and Weeks 58, 70/End of Study, Week 82, and Week 94/End of Study is presented in Table 14.3.8.1. The mean change from baseline score and observed score for the four subscales (parkinsonism, dystonia, dyskinesia, and akathisia) and Total Score of the ESRS-A for the Safety Population are presented in Table 14.3.8.2. The clinical global impression of movement severity (CGI-S) ratings for each of the four subscales, summarized by visit for the Safety Population, are presented in Table 14.3.8.3. ESRS-A results are presented by subject in Listing 16.2.14.

The incidence of extrapyramidal symptoms reported was very low (minimal or absent), and there were no meaningful differences between the treatment groups. None of the symptoms worsened at Week 70 or Week 94 or End of Study compared to Baseline.

11.9.6. Calgary Depression Scale for Schizophrenia

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

The mean (SD) CDSS total score values recorded at Week 70/End of Study were 0.2 (0.54), 0.5 (0.93) and 0.2 (0.60) in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* treated groups, respectively. The mean (SD) changes from baseline in CDSS scores observed at Week 70/End of Study were -0.07 (0.26), -0.15 (0.70) and -0.06 (0.63) in the evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* treated groups, respectively, indicating no overall worsening of depression at the end of the first additional period (Table 11-19).

The mean (SD) CDSS total score values recorded at Week 94/End of Study were 0.5 (1.00) and 0.0 (0.00) in the evenamide 15 mg *BID* and 30 mg *BID* treated groups, respectively. The mean (SD) changes from baseline observed at Week 94/End of Study were 0.50 (1.00) and 0.00 (0.00) in the evenamide 15 mg *BID* and 30 mg *BID* treated groups, respectively, indicating no overall worsening of depression at the end of the second additional period (Table 11-19).

Table 11-19 Change from Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Total Scores - Safety Population

		Evenamide 7.5 mg *BID* (up-titrated to 15 mg *BID*) (N=31)		**Evenamide 15 mg *BID* (N=34)**		**Evenamide 30 mg *BID* (N=31)**	
Visit	Statistic	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
Screening	n	31		34		31	
	Mean (SD)	0.4 (0.75)		0.6 (0.93)		0.3 (0.69)	
	Median	0.0		0.0		0.0	
	Min, Max	0, 3		0, 3		0, 2	
Baseline	n	31		34		31	
	Mean (SD)	0.2 (0.56)		0.4 (0.78)		0.3 (0.68)	
	Median	0.0		0.0		0.0	
	Min, Max	0, 2		0, 2		0, 2	
Week 70/ End of Study	n	29	29	34	34	31	31
	Mean (SD)	0.2 (0.54)	-0.07 (0.26)	0.5 (0.93)	0.15 (0.70)	0.2 (0.60)	-0.06 (0.63)
	Median	0.0	0.00	0.0	0.00	0.0	0.00
	Min, Max	0, 2	-1, 0	0, 3	-2, 2	0, 2	-2, 2
Week 94/End of Study	n			4	4	7	7
	Mean (SD)			0.5 (1.00)	0.50 (1.00)	0.0 (0.00)	0.00 (0.00)
	Median			0.0	0.00	0.0	0.00
	Min, Max			0, 2	0, 2	0, 0	0, 0

Source: *Listing 16.2.15*; Adapted from *Table 14.3.9*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

11.9.7. Safety Conclusions

The primary objective of the study was to evaluate the long-term safety and tolerability of evenamide given orally as add-on at doses up to 30 mg *BID*, in patients with treatment-resistant schizophrenia not responding adequately to a stable, therapeutic dose of their current antipsychotic medication.

The treatment with evenamide beyond 1-year and up to 100 weeks, considering the initial treatment period of 6 weeks in Study 014, continued to be associated with an innocuous safety profile, based on the absence of any pattern of safety abnormality detected on any of the safety measures, including vital signs, laboratory tests, ECGs, physical, neurological, and standard eye examinations, extrapyramidal symptoms (assessed by the ESRS-A), changes in depressive symptoms (assessed by the CDSS), and the review of treatment-emergent adverse events.

No death was reported in this additional treatment period of Study 015 beyond Week 46. None of the subjects treated with evenamide had Any Serious and Treatment-Related TEAE, nor any TEAE leading to study drug discontinuation. Only one subject experienced a Serious AE, which was a seizure related to dilutional hyponatremia induced by excess water consumption in a patient who had discontinued treatment 26 days prior to the event.

Overall, the results for the safety parameters assessed in the study indicated that evenamide given orally at all doses [7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID*] as add-on treatment to first and second generation antipsychotics (excluding clozapine) in patients with treatment-resistant schizophrenia was well tolerated, without any major safety concern.

12. EFFICACY EVALUATION

12.1. Analysis of Efficacy

12.1.1. Positive and Negative Syndrome Scale Results

12.1.1.1. PANSS Total Score

Primary Efficacy Estimand Analysis in mITT Population

The mean change from baseline to Week 70/Week 94/End of Study on the PANSS total score using within group comparisons (*Primary Estimand: Effect of being randomized to an evenamide dose, regardless of withdrawal from treatment; Estimator: Estimate of the change from baseline in PANSS total score at Week 70/Week 94*) was analyzed in the mITT Population for the overall combined evenamide dose group. Results are presented in Table 14.2.1.1c, with by subject details in Listing 16.2.6.1.2.

A summary of mean values and changes from baseline on the PANSS total score (Primary Estimand Treatment Policy) by visit for the mITT Population in the overall combined evenamide dose group is shown in Table 12-1.

A steady decrease (improvement) on the PANSS total score for the mITT Population was recorded at all study visits (Week 58, 70/End of Study, 82 and 94/End of Study) compared to baseline in the overall combined evenamide dose group, reflecting a continuation of improvement in the symptoms of schizophrenia (Figure 12-1). In the overall combined evenamide dose group, the mean (SD) of PANSS total score recorded was 78.8 (5.05), 65.1 (10.02), 64.2 (10.16), 53.0 (7.14) and 53.3 (5.69) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline in the PANSS Total score recorded was -13.7 (9.00), -14.5 (9.32), -23.8 (7.97) and -23.7 (6.53) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-1).

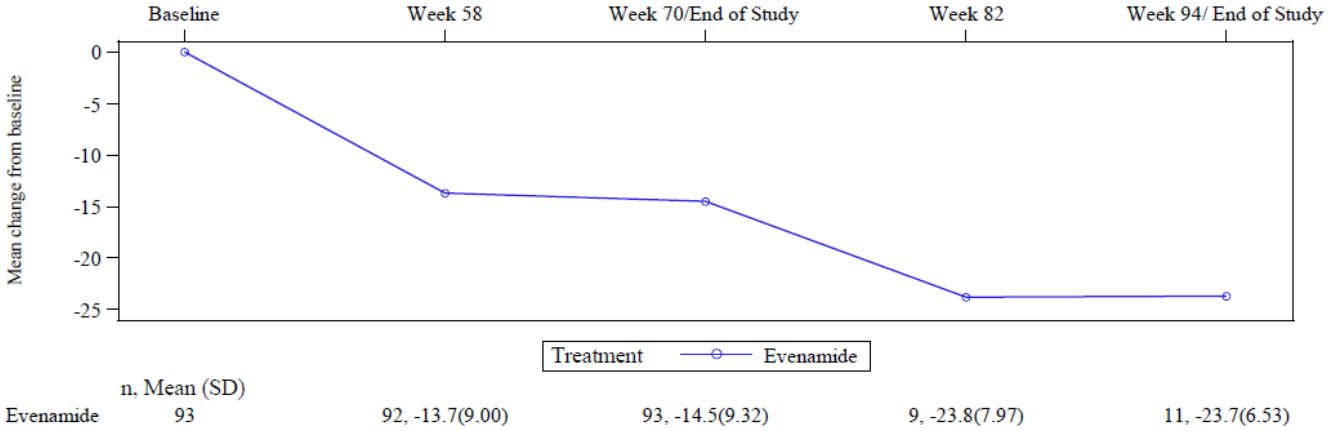
Table 12-1 Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score (Primary Estimand Treatment Policy) mITT Population – Overall

		Evenamide (N=93)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	N	93		
	Mean (SD)	78.8 (5.05)		
	Median	79.0		
	Min, Max	70, 89		
Week 58	N	92	92	92
	Mean (SD)	65.1 (10.02)	-13.7 (9.00)	-17.4 (11.13)
	Median	63.5	-12.5	-16.2
	Min, Max	47, 95	-37, 11	-44, 13
Week 70/ End of Study	N	93	93	93
	Mean (SD)	64.2 (10.16)	-14.5 (9.32)	-18.4 (11.53)
	Median	62.0	-14.0	-17.8
	Min, Max	47, 95	-34, 11	-41, 13
Week 82	N	9	9	9
	Mean (SD)	53.0 (7.14)	-23.8 (7.97)	-30.8 (9.71)
	Median	54.0	-22.0	-29.3
	Min, Max	43, 67	-37, -14	-46, -17
Week 94/ End of Study	N	11	11	11
	Mean (SD)	53.3 (5.69)	-23.7 (6.53)	-30.7 (7.89)
	Median	54.0	-24.0	-31.6
	Min, Max	43, 65	-37, -14	-46, -20

Source: *Listing 16.2.6.1.2*; Adapted from *Table 14.2.1.1c*
N - Total number of subjects in the mITT Population, n = number of patients, SD = Standard Deviation,
mITT = Modified Intent-to-treat, Min = Minimum, Max = Maximum,
Change from Baseline = Post Dose – Baseline, % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

A decreasing trend in the mean change from baseline in PANSS Total score was observed at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study and is depicted in Figure 12-1.

Figure 12-1 Mean Change from Baseline by Visit in PANSS Total Score - mITT Population Overall



Source: *Listing 16.2.6.1.1*, *Table 14.2.1.1c*, *Table 14.2.1.3c*, *Figure 14.2.1.1*

A similar decreasing trend on the PANSS total score in the overall combined evenamide dose group was observed in the mITT-C1 population (Table 14.2.1.1.cd1) and in the mITT-C2 population (Table 14.2.1.1.cd2).

Supportive Efficacy Estimand Hypothetical in mITT Population

A summary of mean values and changes from baseline on the PANSS total score (Supportive Efficacy Estimand Hypothetical) by visit for the mITT Population in the overall combined evenamide dose group is shown in Table 14.2.1.2c.

A steady decrease on the PANSS total score for the mITT Population was recorded at all study visits (Week 58, 70/End of Study, 82 and 94/End of Study) compared to baseline in the overall combined evenamide dose group, confirming the results of the primary efficacy estimand analysis. In the overall combined evenamide dose group, the mean (SD) of PANSS total score recorded was 78.8 (5.05), 64.7 (9.57), 63.7 (9.30), 53.0 (7.14) and 52.9 (6.27) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline on the PANSS Total score recorded in the overall combined evenamide dose group was -13.9 (8.81), -14.9 (8.79), -23.8 (7.97) and -23.9 (7.22) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. A similar decreasing trend on the PANSS total score in the overall combined evenamide dose group was observed in the mITT-C1 population (Table 14.2.1.2.cd1) and in the mITT-C2 population (Table 14.2.1.2.cd2).

12.1.1.1.1. PANSS 'Responder' analyses

The results of a responder analysis by visit for the PANSS total and Positive Syndrome subscale scores in the overall combined evenamide dose group for the mITT population are presented in Table 14.2.1.5 and by subject details in Listing 16.2.6.1.2. 'Responders' were defined as patients who improved by at

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

The proportion of responders, based on a ≥ 20% reduction in the PANSS total score from baseline, increased over time in each additional treatment period. In Additional Period I, the number (%) of responders in the overall combined evenamide dose group were 37 (39.8%) and 38 (40.9%) at Week 58 and Week 70/End of Study, respectively. In Additional Period II, the number (%) of responders in the overall combined evenamide dose group were 7 (63.6%) and 9 (81.8%) at Week 82 and Week 94/End of Study, respectively (Table 12-2).

Table 12-2 Responder Analysis by Visit- Positive and Negative Syndrome Scale (PANSS) - mITT Population Overall

Visit	PANSS	Improvement Category	Statistic	Evenamide*(N=93)
Additional Period I				
Week 58	Total Score	Change ≥ 20%	n (%)	37 (39.8)
	Total Positive Score	≥ 4-Point Improvement	n (%)	68 (73.1)
Week 70/ End of Study	Total Score	Change ≥ 20%	n (%)	38 (40.9)
	Total Positive Score	≥ 4-Point Improvement	n (%)	71 (76.3)
Visit	**PANSS**	**Improvement Category**	**Statistic**	**Evenamide* (N=11)**
Additional Period II				
Week 82	Total Score	Change ≥ 20%	n (%)	7 (63.6)
	Total Positive Score	≥ 4-Point Improvement	n (%)	8 (72.7)
Week 94/ End of Study	Total Score	Change ≥ 20%	n (%)	9 (81.8)
	Total Positive Score	≥ 4-Point Improvement	n (%)	10 (90.9)

Source: *Listing 16.2.6.1.2*; Adapted from *Table 14.2.1.5*.
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat.
Responder analyses have been performed by summarizing the proportion of patients in the overall evenamide group with different categories of improvement from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale.
Additional Period I: Additional 24-Week treatment period after Week 46 to Week 70; Additional Period II: Second additional 24-Week treatment period after Week 70 to Week 94.
*Percentages in Additional Period I are calculated using the N of patients in mITT population as denominator (N=93), while percentages in Additional Period II are calculated using the N of patients in the 'Rolled Over' population (N=11)

A similar responder analysis was conducted using the mITT (N=93) as denominator throughout the study duration till Week-94, see Table 14.2.1.5.

12.1.1.2. PANSS Subscales

PANSS Positive Syndrome subscale scores

The mean scores and changes from baseline on the PANSS Positive Syndrome subscale scores in the overall combined evenamide dose group for the mITT Population are depicted in Table 14.2.1.3c, and the results of the PANSS Positive Syndrome subscale score by subject details are presented in Listing 16.2.6.1.1. At baseline, the mean (SD) of PANSS Positive Syndrome subscale score recorded was 23.6 (3.62), which decreased to 17.5 (5.17), 17.4 (5.04), 14.2 (2.17) and 13.8 (2.14) at Week 58, Week 70/End

of Study, Week 82 and Week 94/End of Study, respectively. The mean (SD) change from baseline in the PANSS Positive Syndrome subscale score calculated in the overall combined evenamide dose group was -6.1 (4.46), -6.2 (4.45), -9.8 (3.60) and -9.6 (3.44) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-3).

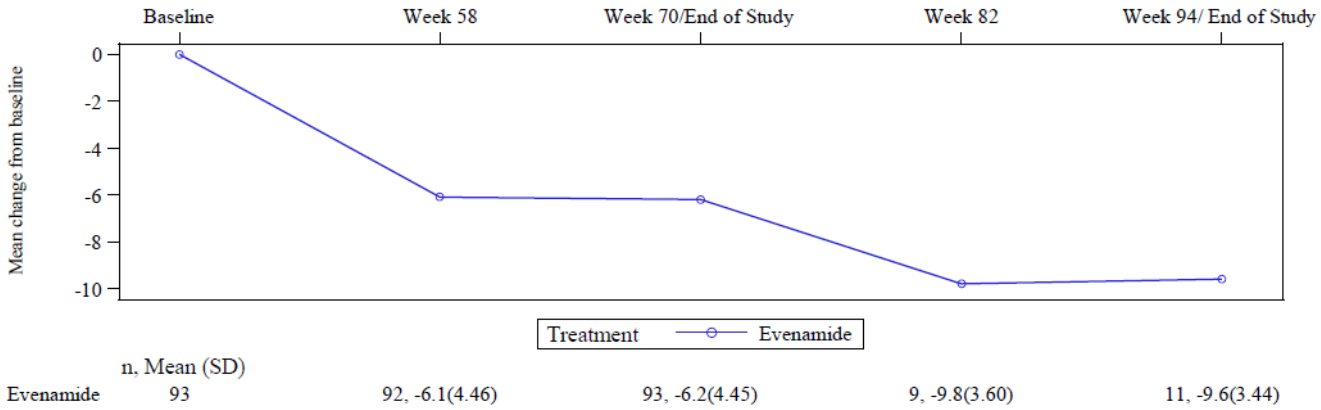
Table 12-3 Change from Baseline in the PANSS Positive Syndrome Subscale Scores - mITT Population Overall

		Evenamide (N=93)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	N	93		
	Mean (SD)	23.6 (3.62)		
	Median	24.0		
	Min, Max	17, 36		
Week 58	N	92	92	92
	Mean (SD)	17.5 (5.17)	-6.1 (4.46)	-25.7 (17.65)
	Median	17.0	-6.0	-25.0
	Min, Max	9, 40	-16, 7	-56, 30
Week 70/ End of Study	n	93	93	93
	Mean (SD)	17.4 (5.04)	-6.2 (4.45)	-26.1 (17.33)
	Median	16.0	-6.0	-25.0
	Min, Max	10, 40	-16, 7	-54, 30
Week 82	n	9	9	9
	Mean (SD)	14.2 (2.17)	-9.8 (3.60)	-40.0 (12.98)
	Median	14.0	-11.0	-42.3
	Min, Max	12, 18	-14, -3	-54, -14
Week 94/ End of Study	n	11	11	11
	Mean (SD)	13.8 (2.14)	-9.6 (3.44)	-40.4 (12.28)
	Median	13.0	-11.0	-45.5
	Min, Max	12, 18	-14, -3	-54, -14

Source: *Listing 16.2.6.1.1*; Adapted from *Table 14.2.1.3c*.
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat,
SD = Standard Deviation, Min = Minimum, Max = Maximum,
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

A decreasing trend in the mean change from baseline on the PANSS Positive Syndrome subscale score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study was observed and is depicted in Figure 12-2.

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



Source: *Listing 16.2.6.1.1, Table 14.2.1.1c, Table 14.2.1.3c, Figure 14.2.1.1*

PANSS Negative Syndrome subscale scores

The mean scores and changes from baseline on the PANSS Negative Syndrome subscale scores in the overall combined evenamide dose group for the mITT Population are depicted in Table 14.2.1.3c, and the results of the PANSS Negative Syndrome subscale score by subject details are presented in Listing 16.2.6.1.1. At baseline, the mean (SD) of PANSS Negative Syndrome subscale score recorded was 19.6 (3.24), which was reduced to 17.1 (3.27), 16.8 (3.37), 14.3 (1.66) and 14.5 (1.92) at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study, respectively. The mean (SD) change from baseline on the PANSS Negative Syndrome subscale score calculated in the overall combined evenamide dose group was -2.5 (2.95), -2.8 (3.21), -6.3 (2.92) and -6.2 (2.68) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-4).

Table 12-4 Change from Baseline in the PANSS Negative Syndrome Subscale Score - mITT Population Overall

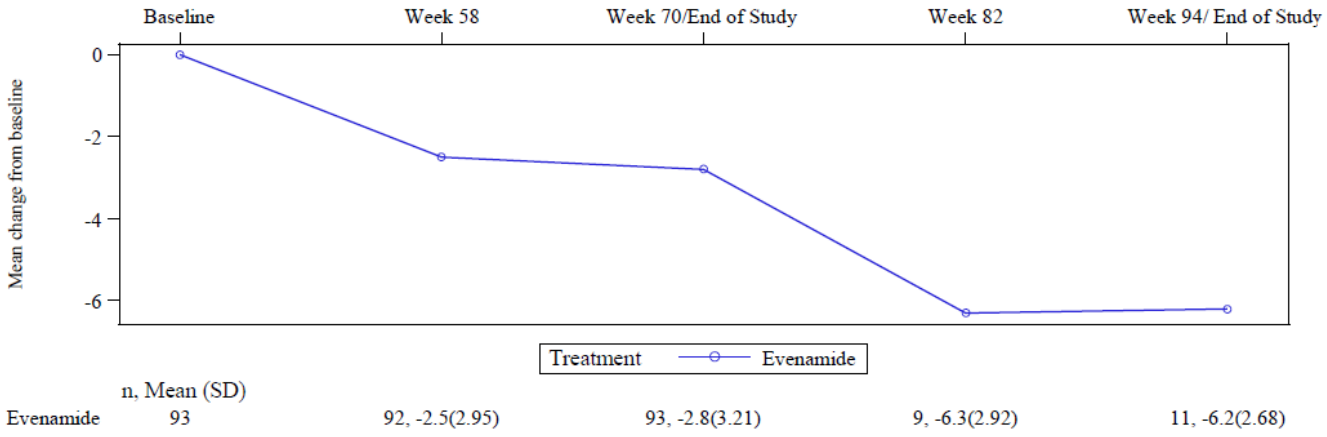
		Evenamide (N=93)		
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Baseline	n	93		
	Mean (SD)	19.6 (3.24)		
	Median	20.0		
	Min, Max	12, 29		
Week 58	n	92	92	92
	Mean (SD)	17.1 (3.27)	-2.5 (2.95)	-11.7 (14.60)
	Median	17.0	-2.0	-10.8
	Min, Max	9, 28	-11, 4	-44, 31
Week 70/ End of Study	n	93	93	93
	Mean (SD)	16.8 (3.37)	-2.8 (3.21)	-13.4 (15.93)
	Median	17.0	-3.0	-14.3
	Min, Max	9, 28	-11, 4	-48, 33

		Evenamide (N=93)		
Visit	**Statistic**	**Observed**	**Change from Baseline**	**% Change from Baseline**
Week 82	n	9	9	9
	Mean (SD)	14.3 (1.66)	-6.3 (2.92)	-29.9 (11.94)
	Median	15.0	-6.0	-28.6
	Min, Max	11, 16	-11, -3	-50, -16
Week 94/ End of Study	n	11	11	11
	Mean (SD)	14.5 (1.92)	-6.2 (2.68)	-29.5 (11.20)
	Median	15.0	-6.0	-30.0
	Min, Max	11, 18	-11, -3	-50, -16

Source: *Listing 16.2.6.1.1*; Adapted from *Table 14.2.1.3c*.
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat,
SD = Standard Deviation, Min = Minimum, Max = Maximum,
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

A decreasing trend in the mean change from baseline on the PANSS Negative Syndrome subscale score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study was observed and is depicted in Figure 12-3.

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



Source: *Listing 16.2.6.1.1, Table 14.2.1.1c, Table 14.2.1.3c, Figure 14.2.1.1*

PANSS General Psychopathology subscale scores

The mean scores and changes from baseline on the PANSS General Psychopathology subscale scores in the overall combined evenamide dose group for the mITT Population are depicted in Table 14.2.1.3c, and the results of the PANSS General Psychopathology subscale score by subject details are presented in Listing 16.2.6.1.1. At baseline, the mean (SD) of PANSS General Psychopathology subscale score recorded was 35.5 (3.48), which decreased to 30.4 (5.30), 30.1 (5.32), 24.4 (4.25) and 25.0 (3.46) at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study, respectively. The mean (SD) change from baseline on the PANSS General Psychopathology subscale score calculated in the overall combined evenamide dose group was -5.2 (4.09), -5.5 (4.19), -7.7 (3.28) and -7.9 (2.66) at Week 58,

Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-5).

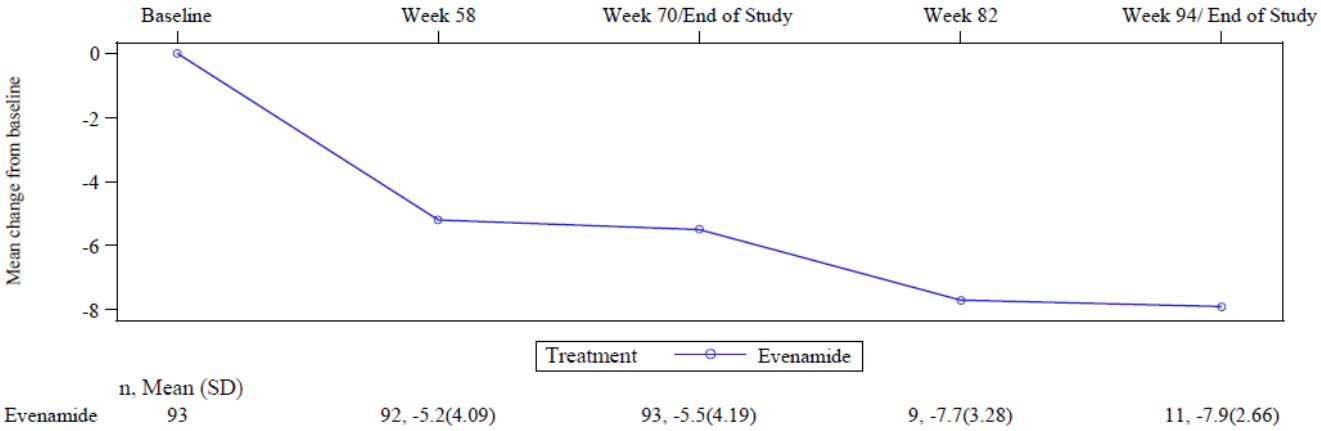
Table 12-5 Change from Baseline in the PANSS General Psychopathology Subscale Score - mITT Population Overall

		Evenamide (N=93)		
Visit	Statistic	Observed	Change from Baseline	% Change from Baseline
Baseline	n	93		
	Mean (SD)	35.5 (3.48)		
	Median	35.0		
	Min, Max	29, 49		
Week 58	n	92	92	92
	Mean (SD)	30.4 (5.30)	-5.2 (4.09)	-14.6 (11.41)
	Median	30.0	-5.0	-13.5
	Min, Max	20, 44	-17, 6	-45, 16
Week 70/ End of Study	n	93	93	93
	Mean (SD)	30.1 (5.32)	-5.5 (4.19)	-15.5 (11.74)
	Median	29.0	-5.0	-16.7
	Min, Max	20, 44	-17, 6	-44, 16
Week 82	n	9	9	9
	Mean (SD)	24.4 (4.25)	-7.7 (3.28)	-23.9 (9.96)
	Median	25.0	-6.0	-20.0
	Min, Max	19, 34	-13, -5	-41, -15
Week 94/ End of Study	n	11	11	11
	Mean (SD)	25.0 (3.46)	-7.9 (2.66)	-23.9 (7.59)
	Median	25.0	-8.0	-21.6
	Min, Max	20, 33	-13, -5	-39, -17

Source: *Listing 16.2.6.1.1*; Adapted from *Table 14.2.1.3c*.
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified Intent-to-treat,
SD = Standard Deviation, Min = Minimum, Max = Maximum,
Change from Baseline = Post Dose – Baseline. % Change from Baseline = 100*[(Post Dose – Baseline)/Baseline].
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

A decreasing trend in the mean change from baseline on the PANSS General Psychopathology subscale score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study was observed and is depicted in Figure 12-4.

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



Source: *Listing 16.2.6.1.1, Table 14.2.1.1c, Table 14.2.1.3c, Figure 14.2.1.1*

12.1.2. Clinical Global Impression Results

The Clinical Global Impression (CGI) has two components, the CGI-Severity (CGI-S) measures the global severity of illness at a given point in time, and the CGI-Change (CGI-C) measures the 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.

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

The CGI-S results for the mITT population in the overall combined evenamide dose group are presented in Table 14.2.2.1c and by subject details in Listing 16.2.6.2. A summary of mean values and mean changes from baseline on the CGI-S by visit for the mITT Population in the overall combined evenamide dose group is shown in Table 12-6, and the mean change from baseline on the CGI-S score by visit for the mITT Population in the overall combined evenamide dose group is shown in Figure 12-5.

A steady decrease in the CGI-S score for the mITT Population was recorded at all study visits (Week 58, 70/End of Study, 82 and 94/End of Study) compared to baseline in the overall combined evenamide dose group (Figure 12-5). In the overall combined evenamide dose group, the mean (SD) of CGI-S score recorded was 4.5 (0.62), 3.5 (0.73), 3.5 (0.75), 3.1 (0.33) and 3.0 (0.45) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline on the CGI-S was -1.0 (0.70), -1.0 (0.72), -1.0 (0.00) and -1.1 (0.30) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-6).

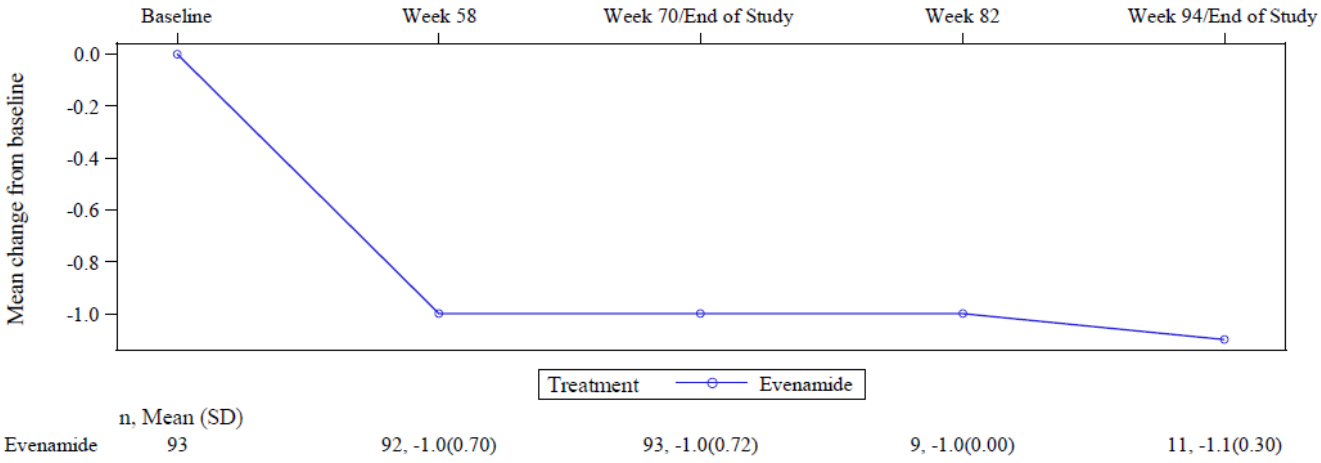
Table 12-6 Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	4.5 (0.62)	
	Median	4.0	
	Min, Max	4, 6	
Week 58	n	92	92
	Mean (SD)	3.5 (0.73)	-1.0 (0.70)
	Median	3.0	-1.0
	Min, Max	2, 6	-3, 1
Week 70/End of Study	N	93	93
	Mean (SD)	3.5 (0.75)	-1.0 (0.72)
	Median	3.0	-1.0
	Min, Max	2, 6	-3, 1
Week 82	N	9	9
	Mean (SD)	3.1 (0.33)	-1.0 (0.00)
	Median	3.0	-1.0
	Min, Max	3, 4	-1, -1
Week 94/End of Study	N	11	11
	Mean (SD)	3.0 (0.45)	-1.1 (0.30)
	Median	3.0	-1.0
	Min, Max	2, 4	-2, -1

Source: *Listing 16.2.6.2*; Adapted from *Table 14.2.2.1c*.
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, Change from Baseline = Post Dose – Baseline.
Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

The steady decrease in the mean change from baseline on the CGI-S score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study is depicted in Figure 12-5.

Figure 12-5 Mean Change from Baseline by Visit in CGI-S Score - mITT Population Overall



Source: *Listing 16.2.6.2*, *Table 14.2.2.1c*, *Figure 14.2.2.1*

12.1.2.1.1. Clinical Global Impression – Severity of Illness (CGI-S) Responder analysis

The responder analysis for the CGI-S was performed by summarizing the proportion of patients in the overall combined evenamide dose group with improvement from baseline to endpoint. The improvement categorizations for the CGI-S of "at least 2-category improvement" and "at least 1-category improvement" were analyzed at Weeks 58, 70/End of Study, Week 82 and Week 94/End of Study for the mITT population. The results are presented in Table 14.2.2.3, and by subject details in Listing 16.2.6.2. A summary of the results of the CGI-S responder analyses are given in Table 12-7.

Responders (CGI-S score reduction from baseline of ≥ 2)

The responder analysis was performed considering the change in the subject's condition from baseline, as indicated by a reduction from baseline on the CGI-S of ≥ 2, indicating at least a 2-category improvement.

In the Additional Period I, the number (%) of responders (improvement on the CGI-S from baseline of at least 2 categories) in the overall combined evenamide dose group in the mITT population was 20 (21.5%) and 20 (21.5%) at Week 58 and Week 70/End of Study, respectively. In the Additional Period II, the number (%) of responders (improvement on the CGI-S from baseline of at least 2 categories) in the overall combined evenamide dose group in the mITT population was 0 (0.0%) and 1 (1.1%) at Week 82 and Week 94/End of Study, respectively (Table 12-7).

Responders (CGI-S score reduction from baseline of ≥ 1)

An additional responder analysis was performed a CGI-S score reduction from baseline of ≥ 1, indicating at least a 1-category improvement.

In the Additional Period I, the number (%) of responders (improvement on the CGI-S from baseline of at least one category) in the overall combined evenamide dose group in the mITT population was 76 (81.7%) and 77 (82.8%) at Week 58 and Week 70/End of Study, respectively. In the Additional Period II, the number (%) of responders (improvement on the CGI-S from baseline of at least one category) in the overall combined evenamide dose group in the mITT population was 9 (81.8%) and 11 (100.0%) at Week 82 and Week 94/End of Study, respectively (Table 12-7).

Table 12-7 Responder analysis (Improvement) by Visit - Clinical Global Impression - Severity of Illness (CGI-S) Score - mITT Population Overall

Visit	Improvement Category	Statistic	Evenamide*(N=93)
Additional Period I			
Week 58	Improvement of at least 2 categories	n (%)	20 (21.5)
	Improvement of at least 1 category	n (%)	76 (81.7)
Week 70/End of Study	Improvement of at least 2 categories	n (%)	20 (21.5)
	Improvement of at least 1 category	n (%)	77 (82.8)
Visit	**Improvement Category**	**Statistic**	**Evenamide* (N=11)**
Additional Period II			
Week 82	Improvement of at least 2 categories	n (%)	0 (0.0)
	Improvement of at least 1 category	n (%)	9 (81.8)

Week 94/End of Study	Improvement of at least 2 categories	n (%)	1 (9.1)
	Improvement of at least 1 category	n (%)	11 (100.0)

Source: *Listing 16.2.6.2*; Adapted from *Table 14.2.2.3*.
N - Total number of subjects in the mITT Population, n = number of patients, mITT = Modified intent-to-treat.
Improvement of at least 2 categories = change (post dose - baseline) of CGI-S score is equal to or lower than -2.
Similarly, Improvement of at least 1 category = change (post dose - baseline) of CGI-S score is equal to or lower than -1.
Additional Period I: Additional 24-Week treatment period after Week 46 to Week 70; Additional Period II: Second additional 24-Week treatment period after Week 70 to Week 94.
*Percentages in Additional Period I are calculated using the N of patients in mITT population as denominator (N=93), while percentages in Additional Period II are calculated using the N of patients in the 'Rolled Over' population (N=11)

A similar responder analysis was conducted using the mITT (N=93) as denominator throughout the study duration till Week-94, see Table 14.2.2.3.

12.1.2.2. Clinical Global Impression – Change (CGI-C) score

The Clinical Global Impression – Change from baseline (CGI-C) score of the mITT Population in the overall combined evenamide dose group is presented in Table 14.2.3.1 and by subject details in Listing 16.2.6.3.

In the overall combined evenamide dose group, the mean (SD) of CGI-C score observed was 2.7 (0.83), 2.7 (0.79), 2.1 (0.78) and 2.2 (0.60) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Table 12-8).

Table 12-8 Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population Overall

Visit	Statistic	Evenamide (N=93)
Week 58	n	92
	Mean (SD)	2.7 (0.83)
	Median	3.0
	Min, Max	1,5
Week 70/End of Study	n	93
	Mean (SD)	2.7 (0.79)
	Median	3.0
	Min, Max	1,5
Week 82	n	9
	Mean (SD)	2.1 (0.78)
	Median	2.0
	Min, Max	1,3
Week 94/End of Study	n	11
	Mean (SD)	2.2 (0.60)
	Median	2.0
	Min, Max	1,3

Source: *Listing 16.2.6.3*; Adapted from *Table 14.2.3.1*.
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

Responder Analysis - CGI-C score

The proportion of patients rated as improved from baseline on the CGI-C at each visit (Week 58/Week 70/Week 82/Week 94) is presented in Table 14.2.3.2 and by subject details in Listing 16.2.6.3. The responder analysis was performed by considering different categories of improvement such as 'any improvement' (CGI-C score ≤ 3) and 'at least much improved' (CGI-C score ≤ 2). A summary of the results is provided in Table 12-9.

Table 12-9 Responder Analysis - Clinical Global Impression - Change from Baseline (CGI-C) mITT Population Overall

Visit	Category	Statistic	Evenamide* (N=93)
Additional Period I			
Week 58	CGI-C score ≤ 3	n (%)	79 (84.9)
	CGI-C score ≤ 2	n (%)	39 (41.9)
Week 70/End of Study	CGI-C score ≤ 3	n (%)	81 (87.1)
	CGI-C score ≤ 2	n (%)	42 (45.2)
Visit	**Category**	**Statistic**	**Evenamide* (N=11)**
Additional Period II			
Week 82	CGI-C score ≤ 3	n (%)	9 (81.8)
	CGI-C score ≤ 2	n (%)	6 (54.5)
Week 94/End of Study	CGI-C score ≤ 3	n (%)	11 (100.0)
	CGI-C score ≤ 2	n (%)	8 (72.7)

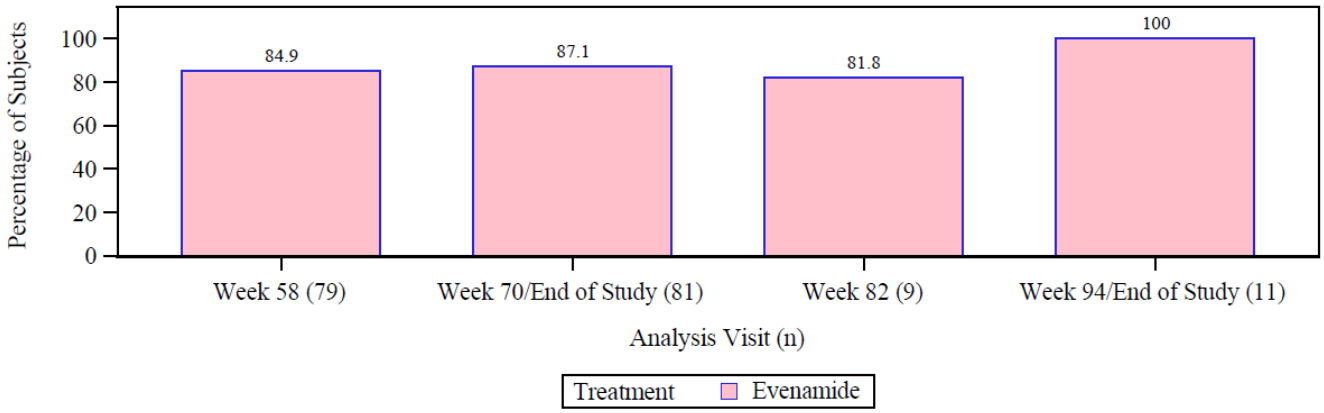
Source: *Listing 16.2.6.3*; Adapted from *Table 14.2.3.2*.
N - Total number of subjects in the mITT Population, n - number of patients, mITT = Modified Intent-to-treat.
CGI-C score ≤3 Category = patients rated as 1 = Very much improved, or 2 = Much improved, or 3 = Minimally improved.
CGI-C score ≤2 Category = patients rated as 1 = Very much improved, or 2 = Much improved.
Additional Period I: Additional 24-Week treatment period after Week 46 to Week 70; Additional Period II: Second additional 24-Week treatment period after Week 70 to Week 94.
*Percentages in Additional Period I are calculated using the N of patients in mITT population as denominator (N=93), while percentages in Additional Period II are calculated using the N of patients in the 'Rolled Over' population (N=11).

A similar responder analysis was conducted using the mITT (N=93) as denominator throughout the study duration till Week-94, see Table 14.2.3.2.

Responders - 'Any improvement' (CGI-C score ≤ 3)

The number (%) of subjects rated as improved (score ≤ 3) on the CGI-C in the overall combined dose group in the mITT population was 79 (84.9%), 81 (87.1%), 9 (81.8%) and 11 (100.0%) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Figure 12-6), showing an increasing proportion over time in each additional treatment period.

Figure 12-6 Bar Chart for Clinical Global Impression - Change from Baseline (CGI-C) Responder Analysis (CGI-C ≤ 3) mITT Population – Overall

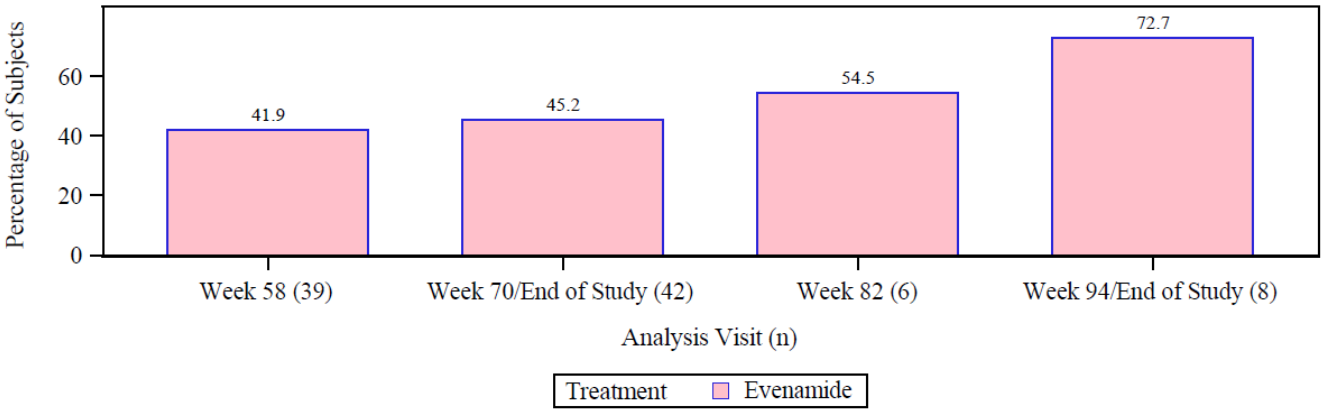


Source: *Listing 16.2.6.3, Table 14.2.3.2, Figure 14.2.3.1*

Responders - At least ' much improved' (CGI-C score ≤2)

The number (%) of subjects rated at least "much improved" (score ≤ 2) on the CGI-C in the overall combined dose group in the mITT population was 39 (41.9%), 42 (45.2%), 6 (6.5%) and 8 (8.6%) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively (Figure 12-7), showing an increasing proportion over time in each additional treatment period.

Figure 12-7 Bar Chart for Clinical Global Impression - Change from Baseline (CGI-C) Responder Analysis (CGI-C ≤ 2) mITT Population - Overall



Source: *Listing 16.2.6.3, Table 14.2.3.2, Figure 14.2.3.1*

12.1.2.3. Strauss-Carpenter Level of Functioning (LOF) Scale Results

The change from baseline on the Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score and Sub-Scales Score for the mITT Population in the overall evenamide dose group is presented in Table 14.2.4c and by subject details in Listing 16.2.6.4.

LOF Total Score

An increase in the LOF Total Score was observed at Week 70/94 compared to baseline in the overall combined evenamide dose group, indicating improvement in functionality of subjects after treatment. A summary of the results of the LOF Total Score for the mITT Population in the overall combined evenamide dose group is presented in Table 12-10.

At baseline, the mean (SD) LOF Total Score recorded was 18.3 (3.84), which increased to 20.5 (4.07), 20.6 (3.89), 20.6 (2.46) and 21.6 (3.83) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline on the LOF total score observed in the overall combined evenamide dose group was 2.2 (3.69), 2.3 (3.81), 3.1 (2.26) and 3.4 (2.91) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

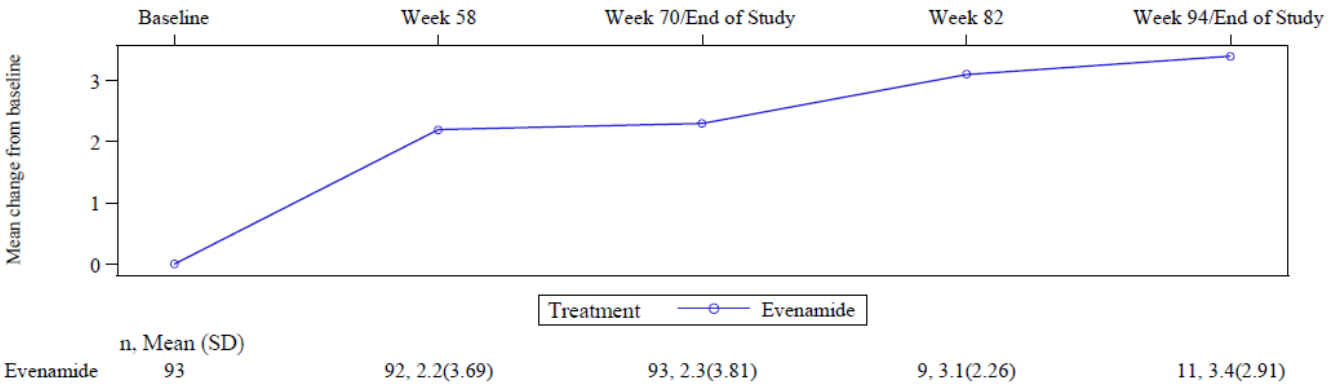
Table 12-10 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	18.3 (3.84)	
	Median	19.0	
	Min, Max	9.0, 30.0	
Week 58	n	92	92
	Mean (SD)	20.5 (4.07)	2.2 (3.69)
	Median	20.5	1.5
	Min, Max	12.0, 36.0	-11.0, 19.0
Week 70/End of Study	n	93	93
	Mean (SD)	20.6 (3.89)	2.3 (3.81)
	Median	20.0	2.0
	Min, Max	12.0, 35.0	-12.0, 19.0
Week 82	n	9	9
	Mean (SD)	20.6 (2.46)	3.1 (2.26)
	Median	20.0	3.0
	Min, Max	17.0, 25.0	1.0, 8.0
Week 94/End of Study	n	11	11
	Mean (SD)	21.6 (3.83)	3.4 (2.91)
	Median	21.0	3.0
	Min, Max	17.0, 31.0	0.0, 9.0

Source: *Listing 16.2.6.4*; Adapted from *Table 14.2.4c*.
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.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

There was a continuous increase in the mean change from baseline on the LOF Total Score at Week 58, Week 70/End of Study, Week 82 and Week 94/End of Study, as evident from the Figure 12-8, indicating improvement in functionality of subjects throughout the treatment period.

Figure 12-8 Mean Change from Baseline by Visit in Strauss-Carpenter - Level of Functioning Scale (LOF) Total Score - mITT Population



Source: *Listing 16.2.6.4, Table 14.2.3.2, Figure 14.2.3.1*

LOF Social Contact Subscale Score

An increase in the LOF Social Contact Subscale Score was observed at Week 70/94 compared to baseline in the overall combined evenamide dose group, indicating improvement in frequency and quality of social contacts of subjects after treatment. A summary of the results of the LOF Social Contact Subscale Score for the mITT Population in the overall combined evenamide dose group is presented in Table 12-11.

At baseline, the mean (SD) LOF Social Contact Subscale Score recorded was 1.4 (0.96), which increased to 1.9 (0.99), 1.9 (0.99), 2.2 (0.71) and 2.2 (0.68) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline on the LOF Social Contact Subscale Score observed in the overall combined evenamide dose group was 0.5 (0.77), 0.5 (0.80), 0.4 (0.78) and 0.4 (0.74) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

Table 12-11 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Social Contact Sub-Scale Score - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	1.4 (0.96)	
	Median	2.0	
	Min, Max	0.0, 4.0	
Week 58	n	92	92
	Mean (SD)	1.9 (0.99)	0.5 (0.77)
	Median	2.0	0.0

	Min, Max	0.0, 4.0	-1.5, 2.5
Week 70/End of Study	n	93	93
	Mean (SD)	1.9 (0.99)	0.5 (0.80)
	Median	2.0	0.0
	Min, Max	0.0, 4.0	-1.5, 2.5
Week 82	n	9	9
	Mean (SD)	2.2 (0.71)	0.4 (0.78)
	Median	2.0	0.0
	Min, Max	1.5, 4.0	0.0, 2.0
Week 94/End of Study	n	11	11
	Mean (SD)	2.2 (0.68)	0.4 (0.74)
	Median	2.0	0.0
	Min, Max	1.5, 4.0	0.0, 2.0

Source: *Listing 16.2.6.4*; Adapted from *Table 14.2.4c*.
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.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

LOF Work Subscale Score

An increase in the LOF Work Subscale Score was observed at Week 70/94 compared to baseline in the overall combined evenamide dose group, indicating improvement in the quantity and quality of useful work in subjects after treatment. A summary of the results of the LOF Work Subscale Score for the mITT Population in the overall combined evenamide dose group is presented in Table 12-12.

At baseline, the mean (SD) LOF Work Subscale Score recorded was 1.2 (0.97), which increased to 1.4 (1.03), 1.4 (1.01), 1.1 (1.0.5) and 1.5 (1.29) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline on the LOF Work Subscale Score observed in the overall combined evenamide dose group was 0.2 (0.86), 0.2 (0.94), 0.3 (0.71) and 0.5 (0.82) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

Table 12-12 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Work Sub-Scale Score - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	1.2 (0.97)	
	Median	2.0	
	Min, Max	0.0, 3.0	
Week 58	n	92	92
	Mean (SD)	1.4 (1.03)	0.2 (0.86)
	Median	2.0	0.0
	Min, Max	0.0, 4.0	-3.0, 3.0
Week 70/End of Study	n	93	93
	Mean (SD)	1.4 (1.01)	0.2 (0.94)

	Median	2.0	0.0
	Min, Max	0.0, 4.0	-3.0, 3.0
Week 82	n	9	9
	Mean (SD)	1.1 (1.05)	0.3 (0.71)
	Median	2.0	0.0
	Min, Max	0.0, 2.0	0.0, 2.0
Week 94/End of Study	n	11	11
	Mean (SD)	1.5 (1.29)	0.5 (0.82)
	Median	2.0	0.0
	Min, Max	0.0, 4.0	0.0, 2.0

Source: *Listing 16.2.6.4*; Adapted from *Table 14.2.4c*.
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.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

LOF Symptomatology Subscale Score

An increase in the LOF Symptomatology Subscale Score was observed at Week 70/94 compared to baseline in the overall combined evenamide dose group, indicating improvement in the symptoms and need for hospitalization of subjects after treatment. A summary of the results of the LOF Symptomatology Subscale Score for the mITT Population in the overall combined evenamide dose group is presented in Table 12-13.

At baseline, the mean (SD) LOF Symptomatology Subscale Score recorded was 2.8 (0.39), which increased to 3.2 (0.39), 3.2 (0.39), 3.4 (0.17) and 3.4 (0.20) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline in the LOF Symptomatology Subscale Score observed in the overall combined evenamide dose group was 0.3 (0.45), 0.4 (0.48), 0.5 (0.00) and 0.5 (0.15) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

Table 12-13 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Symptomatology Sub-Scale Score - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	2.8 (0.39)	
	Median	3.0	
	Min, Max	1.0, 4.0	
Week 58	n	92	92
	Mean (SD)	3.2 (0.39)	0.3 (0.45)
	Median	3.0	0.5
	Min, Max	2.0, 4.0	-1.0, 2.5
Week 70/End of Study	n	93	93
	Mean (SD)	3.2 (0.39)	0.4 (0.48)

	Median	3.5	0.5
	Min, Max	2.0, 4.0	-1.0, 2.5
Week 82	n	9	9
	Mean (SD)	3.4 (0.17)	0.5 (0.00)
	Median	3.5	0.5
	Min, Max	3.0, 3.5	0.5, 0.5
Week 94/End of Study	n	11	11
	Mean (SD)	3.4 (0.20)	0.5 (0.15)
	Median	3.5	0.5
	Min, Max	3.0, 3.5	0.0, 0.5

Source: *Listing 16.2.6.4*; Adapted from *Table 14.2.4c*.
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.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

LOF Function Subscale Score

The LOF Function Subscale Score increased at Week 70 compared to baseline in the overall combined evenamide dose group, indicating improvement in the ability to meet basic needs, fullness of life, and overall level of functioning in subjects after treatment. A summary of the results of the LOF Function Subscale Score for the mITT Population in the overall combined evenamide dose group is presented in Table 12-14.

The mean (SD) LOF Function Subscale Score recorded was 2.5 (0.42), 2.5 (0.44), 2.6 (0.42), 2.4 (0.37) and 2.5 (0.43) at Baseline, Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively. The mean (SD) change from baseline in the LOF Function Subscale Score observed in the overall combined evenamide dose group was 0.1 (0.40), 0.1 (0.46), 0.2 (0.49) and 0.3 (0.47) at Week 58, Week 70/End of Study (Additional Period I), Week 82 and Week 94/End of Study (Additional Period II), respectively.

Table 12-14 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Function Sub-Scale Score - mITT Population Overall

		Evenamide (N=93)	
Visit	Statistic	Observed	Change from Baseline
Baseline	n	93	
	Mean (SD)	2.5 (0.42)	
	Median	2.7	
	Min, Max	1.3, 4.0	
Week 58	n	92	92
	Mean (SD)	2.6 (0.44)	0.1 (0.40)
	Median	2.7	0.0
	Min, Max	1.3, 4.0	-1.3, 1.3
Week 70/End of Study	n	93	93
	Mean (SD)	2.6 (0.42)	0.1 (0.46)
	Median	2.7	0.0

	Min, Max	1.3, 4.0	-2.0, 1.3
Week 82	n	9	9
	Mean (SD)	2.4 (0.37)	0.2 (0.49)
	Median	2.7	0.0
	Min, Max	2.0, 2.7	-0.7, 0.7
Week 94/End of Study	n	11	11
	Mean (SD)	2.5 (0.43)	0.3 (0.47)
	Median	2.7	0.0
	Min, Max	2.0, 3.3	-0.7, 0.7

Source: *Listing 16.2.6.4*; Adapted from *Table 14.2.4c*.
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.
Total score is calculated as the sum of scores of the nine items in LOF.
Change from Baseline = Post Dose - Baseline. Baseline: Pre-dose of 014, Post-Baseline intervals of 015 beyond week 46 are after week 46 of 015 study dosing.

12.1.3. Statistical/Analytical Issues

Detailed documentation of statistical methods is presented in Section 9.7.1 and in the Statistical Analysis Plan (Appendix 16.1.9.1). There were no statistical/analytical issues reported.

12.1.3.1. Handling of Dropouts or Missing Data

Handling of missing data is described in Section 9.7.1.3.

12.1.3.2. Interim Analyses and Data Monitoring

No interim analysis was performed during the treatment period in Study 015 beyond Week 46.

12.1.3.3. Multicenter Studies

Study 015 beyond Week 46 was conducted in 6 centers only in India.

12.1.3.4. Multiple Comparisons/Multiplicity

Multiplicity adjustment is described in Section 9.7.1.4.

12.1.4. Tabulation of Individual Response Data

Individual efficacy response data are provided in Appendix 16.2.6.

12.1.5. Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

12.1.6. Drug-Drug and Drug-Disease Interactions

Not applicable.

12.1.7. By-Subject Displays

Not applicable.

12.2. Efficacy Conclusions

The secondary objectives of the study were to evaluate the preliminary evidence of long-term efficacy of evenamide, based on improvement of symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS), and on changes in the overall severity of illness, as assessed by the Clinical Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S). Secondarily, efficacy was determined by the long-term effect of evenamide on daily functioning based on changes in the Strauss-Carpenter Level of Functioning (LOF) scale.

Positive and Negative Syndrome Scale (PANSS) Total Score

A steady improvement in the PANSS total score was recorded at all study visits compared to baseline in the overall combined evenamide dose group for the mITT population, as well as for the mITT-C1 and mITT-C2 populations, reflecting a continuation of improvement in the symptoms of schizophrenia. Improvements were also observed on all three PANSS Subscales (Positive Syndrome, Negative Syndrome, and General Psychopathology).

These results were confirmed by the Supportive Efficacy Estimand Hypothetical analysis of the mITT Population in the overall combined evenamide dose group.

Moreover, these results were supported by the proportion of patients in the mITT population achieving a clinically meaningful level of improvement on the PANSS (Total score reduction ≥ 20%, as described by Rosenheck et al., 1997 and Meltzer et al., 2008, and ≥ 4 points improvement on PANSS Positive Symptoms sub-scale score), which increased over time in each additional treatment period.

Clinical Global Impression - Severity of illness (CGI-S)

Similarly, a steady decrease in the CGI-S score was observed at all study visits compared to baseline in the overall evenamide dose group for the mITT population.

Results of responders analysis on the CGI-S showed an increasing proportion of patients meeting the responder criteria (at least 1- or 2-category improvement) in each additional treatment period.

Clinical Global Impression - Change from baseline (CGI-C)

The mean rating on the CGI-C showed a decrease by visit in the overall evenamide dose group for the mITT population. Furthermore, an increasing proportion of patients over time were considered responders in each additional period, based on the definitions of at least “minimally improved” and at least “much improved” on the CGI-C.

Strauss-Carpenter - Level of Functioning Scale (LOF)

An increase in the LOF Total Score was observed at Weeks 70 and 94 compared to baseline in the overall combined evenamide dose group, indicating improvement in functionality of patients after treatment with evenamide in addition to their background antipsychotic.

Improvement was also observed in the LOF Subscales (Social Contact, Work, Symptomatology and Function Subscales) at Weeks 70 and 94 compared to baseline in the overall combined evenamide dose group.

Overall Efficacy Conclusions

The long-term treatment with evenamide [7.5 mg (up-titrated to 15 mg *BID*), 15 mg and 30 mg *BID*] as add-on to first and second generation antipsychotics (excluding clozapine) in patients with TRS was associated with an improvement in symptoms of schizophrenia assessed by the PANSS (total score and subscales), a decrease in disease severity assessed by the CGI-S score, overall improvement from baseline assessed by the CGI-C, and enhancement in functionality of patients assessed by the LOF. These benefits, which increased over time, were observed in patients with TRS not responding adequately to their stable, therapeutic dose of a single antipsychotic medication.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

Data from the two additional 24-week treatment periods that were available after completion of Study 015 (Week 46) for patients at sites in India confirm the high retention rate observed in Studies 014 and 015, as 96 (79.3%) subjects out of the 121 who completed Study 015 at Week 46 rolled over into the first 24-week additional treatment period (Additional Period I), and 92 (95.8%) out of the 96 completed treatment until Week 70. Although the number of patients who continued treatment with evenamide in the second 24-week additional period (Additional Period II) was reduced to 11 due to delays in approval of the protocol amendment that allowed this further extension, retention in this period remained high, with 9 (81.8%) of the patients completing the study until Week 94.

Safety results collected during Additional Period I and Additional Period II in Study 015 suggest that evenamide was very well tolerated at all doses during long-term treatment for a total duration of 100 weeks (6 weeks in core Study 014 + up to 94 weeks in extension Study 015). Add-on treatment with evenamide in patients with TRS was not associated with any pattern of clinically notable effects in any of the safety measures assessed, including laboratory tests, vital signs, physical, neurological and eye examinations, ECG evaluations, extrapyramidal symptoms (ESRS-A), or depressive symptoms (CDSS).

During the Additional Periods I and II, only one subject experienced a SAE of dilutional hyponatremia leading to seizures 26 days after he received his last dose of evenamide (15 mg *BID*); according to the judgement of the investigator, the event was related to the ingestion of a large volume of water and was controlled by administration of 100 mL i.v. bolus of 3 percent saline. Overall, no severe adverse events suggestive of involvement of evenamide were reported.

All efficacy measures continued to show improvement over time up to 94 weeks in the mean change from baseline (Study 014) in the overall combined evenamide dose group. Similarly, the proportion of patients reaching a clinically meaningful level of response on the PANSS (≥ 20% improvement from baseline, as defined by Rosenheck et al., 1997 and Meltzer et al., 2008) increased by visit in each

additional treatment period. A similar trend was observed in the proportion of responders on the CGI-S (at least a 1- or 2- category improvement) and on the CGI-C, not only those with "any improvement" from baseline (score ≤ 3) but also those who were rated at least "much improved" (score ≤ 2).

The same limitations acknowledged in the discussion of efficacy results from Study 014 and Study 015 up to Week 46 need to be taken into account to justify the acceptability of the efficacy data from these additional treatment periods. Firstly, because the study treatments were not blinded and not controlled by a placebo arm, rater bias in efficacy ratings or a placebo effect cannot be excluded. However, the Sponsor is unaware of any study performed in patients with schizophrenia where the placebo (spontaneous) responder rate doubles or triples over a period of 1-year and above. Furthermore, the pattern of change from baseline is consistent across all efficacy measures, although the magnitude of the benefit varied among the PANSS, CGI-S, CGI-C and LOF.

In addition, a relatively small number of patients (96) were enrolled in Study 015 beyond Week 46 (out of the 161 patients originally randomized to treatment in Study 014), and all of them were from India, raising the possibility that local practices may preclude the generalizability of these results to a global patient population. However, review of data from published placebo-controlled studies in patients with psychotic disorders with significant contribution from India did not detect any trend indicating that the results in India were more positive than in other countries (Khanna et al., 2005; Potkin et al., 2006; Geffen et al., 2012; Cantillon et al., 2017).

Furthermore, the efficacy data should not be considered statistically conclusive for the periods beyond Week 46, considering the lower number of subjects rolled over in Additional Period I up to Week 70, which was further reduced in Additional Period II up to Week 94. The major reason for this decreased roll-over was that, by the time the regulatory approvals were obtained for protocol amendments 4.1 (dated 30 November 2021) and 4.2 (dated 08 July 2022), which allowed enrollment of patients in the additional treatment periods, many of the subjects had already completed Week 46 or Week 70 and had discontinued treatment before getting a chance to be enrolled in Additional Period I or Additional Period II, respectively.

13.2. Overall Conclusions

The results of Study 015 beyond Week 46 indicate that evenamide at doses of 7.5 mg *BID* (up-titrated to 15 mg *BID*), 15 mg *BID* and 30 mg *BID* is well tolerated for up to 100 weeks of treatment, based on the data from multiple safety assessments, including ECGs, vital signs, laboratory tests and the incidence of TEAEs. Furthermore, there was no Serious and Treatment-Related TEAE and none of the subjects discontinued due to a TEAE in Study 015 beyond 46 weeks. Treatment with evenamide at doses of 7.5, 15 and 30 mg *BID* as an add-on for up to 100 weeks in patients with TRS was associated with a sustained improvement and clinically relevant benefits noted across all efficacy measures, although the lack of a control arm and the small sample size limit the interpretability of the efficacy results.

14. NARRATIVES OF DEATHS, OTHER SERIOUS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

Serious Adverse Events (SAEs)

One SAE was reported during the study and is described below.

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

Study Number:	NW-3509/015/II/2019
Country of Origin:	India
Type of Narrative:	Serious Adverse Event
Subject Number:	311006
MFR Case ID	2022NEW000003
Treatment Group:	Evenamide 15 mg *BID*
Reported Term [Preferred Term]:	Dilutional hyponatremia [Hyponatraemia] and Acute symptomatic seizure [Seizure]

This 35-year-old Asian male subject with chronic schizophrenia received the first dose of study medication (evenamide 7.5 mg *BID*) in Study 014 on 12 Apr 2021 (Day 1); he completed the study on 24 May 2021 (Day 43) and entered in the extension Study 015 on the same day on 7.5 mg *BID*, which was up-titrated to 15 mg *BID* on 26 Feb 2022. The subject received evenamide in the extension Study 015 for 385 days; due to the study medication supply disruption the subject received the last dose on 2 May 2022. Twenty-six days after the last dose of study medication (28 May 2022), the patient experienced a seizure, later diagnosed as due to dilutional hyponatremia.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug.*

This 35-year-old Asian male subject with chronic schizophrenia was randomized to receive evenamide. The first dose of study medication (7.5 mg *BID* of evenamide) was administered on 12 Apr 2021. The subject completed Study 014 on 24 May 2021 (Day 43) and entered in Study 015 (46-week extension) on the same day on 7.5 mg *BID*, which was up-titrated to 15 mg *BID* on 26 Feb 2022. On 11 Apr 2022 the subject completed the planned 46-week treatment period (365 days on evenamide) and entered a further period (24-week) of treatment with evenamide. The subject was continuing his antipsychotic medications (haloperidol 5 mg *BID*).

On 02 May 2022 (385 days on evenamide), the subject received the last dose of study medication, due to unavailability of the investigational product at the study site (last 3 kits of study medication were dispensed on 11 Apr 2022). The haloperidol 5 mg *BID* was continued.

On 28 May 2022 (Day 411) 26 days after receiving the last dose of evenamide, the subject had an episode of tonic-clonic convulsions at 5:30 p.m., associated with a fall, along with one episode of vomiting and bed wetting. He also had a contused lacerated wound on the mandible. The patient was brought to hospital

around 7:00 p.m. in a confused state (post ictal confusion). In the Emergency Room he was treated with antiepileptic medication brivaracetam at a dose of 100 mg i.v., followed by a dose of 50 mg i.v. *BID* for seizure, pantoprazole 40 mg *BID* qd, ondansetron 4 mg iv *TID* ceftriaxone/ sulbactam 1 mg iv *BID*. The subject regained his consciousness and was oriented by night.

The subject had attended a party (marriage ceremony) during which he consumed copious amounts of water for two days and was sleep deprived. Laboratory findings included severe hyponatremia (103.6 mmol/L normal range 135-155 mEq/L) and elevated Alanine transaminase (ALT) 139.7 IU/l (normal range 0-45 IU/L) (for these laboratory results, see Table 1). The ECG report had indicated possible myocardial ischemia changes (ST abnormality, possible transmural injury (anterolateral) and T wave inversion); however, they were considered not clinically significant. Brain CT Scan and an electroencephalogram (EEG) were normal. The hyponatremia was treated with 100 mL i.v. bolus of 3 percent saline.

On 29 May 2022 (Day 412), a neurologist examined the subject and concluded that the seizure was due to dilutional hyponatremia caused by excessive water intake. There was no prior history of seizure or hyponatremia in the subject. A single dose of oral 15 mg tolvaptan, for hyponatremia was administered. Subject vital signs were stable, and sodium levels improved to 128.9 mEq/L (normal range 135-155 mEq/L).

On 30 May 2022 (Day 413) the subject's vitals were stable, the EEG was normal, ALT level was high at 213.7 IU/L (normal range 0-45 IU/L), and sodium level was 133.5 mEq/l (normal range 135-155 mEq/L). Brivaracetam was discontinued and ceftriaxone/sulbactam was replaced with cefoparazone/sulbactam.

On 31 May 2022, the laboratory results indicated that the sodium level was almost normalized 134.9 mEq/l (normal range 135-155 mEq/L), however the ALT indicated continued increase (232.4 IU/l normal range 0-45 IU/L); HCV Ab and Hbs Ag tests were negative, and no other significant hepatic laboratory findings were detected. An abdominal ultrasound (USG) indicated mild hydronephrosis, with three small calculi in the left kidney and cystitis.

Intravenous administration of cefoperazone/sulbactam, ondansetron and pantoprazole were discontinued. Oral pantoprazole at a dose of 40 mg *BID* and domperidone at a dose of 30 mg *BID* were initiated, as prophylaxis for acidity and vomiting.

The same day, the events of acute symptomatic seizure and dilutional hyponatremia were considered resolved and the subject was discharged as stable, oriented, and conscious. As the subject was off the study medication (evenamide) since 02 May 2022, there was no need for action to be taken with study medication.

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

Medical History and Concomitant Medication:

The subject's concurrent conditions included schizophrenia (since 12 Jan 2015) and type 2 diabetes mellitus since 08 Dec 2021. The patient had been receiving haloperidol since 24 Feb 2018 at a dose of 5 mg *BID* daily. Other concomitant medications included metformin 250 mg daily for diabetes mellitus type 2 and lorazepam 2 mg as needed for exacerbation of psychosis.

Treatment of events included: 100 mL iv bolus of 3 percent saline, brivaracetam 100 iv once, followed by a 50 mg iv *BID* for seizure, pantoprazole, ondansetron, ceftriaxone/sulbactam iv, vitamin C, ursodeoxycholic acid and oral silymarin, zinc amino acid, and vitamin suspension of Syrup Heptagon as prophylaxis for liver.

Investigator Assessment:

The investigator considered the SAE of acute symptomatic seizure and dilutional hyponatremia as moderate in intensity, with seriousness criteria of hospitalization, and as an important medical event. The investigator considers the SAE as not related to the study drug evenamide, as the subject was off the IP for 26 days (due to unavailability of IMP on site), prior to the events.

Sponsor Assessment:

The Sponsor agrees with the investigator's causality assessment that this event is not related to the study medication (evenamide).

Pertinent Positives and Negatives:

A 35-year-old Asian male subject with history of chronic schizophrenia and type 2 diabetes mellitus, receiving haloperidol 5 mg at stable dose, received evenamide 15 mg *BID* for more than one year up to 2 May 2022 (Day 385). On 28 May 2022 (Day 411), 26 days after the last dose of study medication, the patient experienced a seizure, later diagnosed as due to dilutional hyponatremia caused by excess water intake. Prior to the event, the subject attended a marriage party at home, was unsupervised, slept very little, and drank too much water for two days. Based on the evidence that evenamide half-life is approx. 1 hour, does not have accumulation, and the subject had been off the study medication (evenamide) for 26 days (since 02 May 2022) before the onset of the events, a temporal relationship between evenamide and the event can be excluded; therefore, the events are not related to evenamide. The events are possibly related to the excess water intake by the patient, that led to dilutional hyponatremia (common in patients with chronic schizophrenia), and to an acute symptomatic seizure.

Table 1 - Key laboratory data for Subject Number: 311006

Timepoints		**Sodium**	**ALT**	**AST**	**Bilirubin total**	**CPK**	**LDH**
Date	**Day**	**136-145 mmol/L**	**0-41 U/L**	**0-40 U/L**	**0-1.2 mg/dL**	**0-189 U/L**	**0-250 U/L**
22-Mar-21 (screening)	-21	140	24	28	0.24	**253 H**	227

Timepoints		Sodium	ALT	AST	Bilirubin total	CPK	LDH
Date	**Day**	**136-145 mmol/L**	**0-41 U/L**	**0-40 U/L**	**0-1.2 mg/dL**	**0-189 U/L**	**0-250 U/L**
12-Apr-21 (study day 1)	1	▼ 1st dose of study medication					
		139	20	22	0.16	**204** H	232
19-Apr-21	8	**135** L	20	22	0.2	**201** H	251
26-Apr-21	15	**134** L	20	23	0.45	**259** H	227
10-May-21	29	137	24	26	0.17	**221** H	226
24-May-21	43	**134** L	37	35	0.39	**283** H	248
16-Aug-21	127	139	28	27	0.19	**306** H	249
11-Nov-21	214	**133** L	22	25	0.33	**467** H	250
29-Jan-22	293	**135** L	27	26	0.28	**261** H	225
11-Apr-22	365	**125** LN	32	29	0.33	**273** H	204
02-May-22	386	▽ last dose of study medication prior to the AE *					
28-May-22	412	**103.6** LN	**139.7** HN	.	.	.	.
29-May-22	413	**128.9** L	**213.7** HN	.	.	.	.
31-May-22	415	**133.5** L	**232.4** HN	.	.	.	.
06-Jun-22	421	**134.9** L	**105** H	**87.3** H	.	.	.
15-Jun-22	430	.	**68** H	37	.	.	.
		▼ re-start of study medication					
30-Jun-22	445	▽ last dose of study medication *					
05-Jul-22	450	**130** L	24	24	0.4	189	224
13-Jul-22 (end of study visit)	458	136	16	21	0.15	**193** H	185

*Legend: L=below lower limit; LN=below lower limit notable; H=above upper limit; HN=above upper limit notable. * due to unavailability of IP kits, IP was not dispensed.*

15. REFERENCE LIST

1. Addington D, Addington J, Maticka-Tindale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry. 1993; 163:S39-S44.
2. Cantillon M, Prakash A, Alexander A, Ings R, Sweitzer D, Bhat L. Dopamine serotonin stabilizer RP5063: A randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. Schizophr Res. 2017 Nov;189:126-133.
3. Chahine M, Chatelier A, Babich O and Krupp JJ. Voltage-Gated Sodium Channels in Neurological Disorders. CNS & Neurological Disorders - Drug Targets, 2008; 7:144-158.
4. Chouinard G, Ross-Chouinard A, Annable L, Jones, BD. The extrapyramidal symptom rating scale. Can J Neurol Sci 1980; 7: 233.
5. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res 2005;76(2-3) :247-65.
6. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington, DC: American Psychiatric Association; 2013.
7. Geffen Y, Keefe R, Rabinowitz J, Anand R, Davidson M. Bl-1020, a new γ-aminobutyric acid-enhanced antipsychotic: results of 6-week, randomized, double-blind, controlled, efficacy and safety study. J Clin Psychiatry. 2012 Sep;73(9):e1168-74.
8. Guy W (Ed). Clinical Global Impressions. In ECDEU Assessment Manual for Psychopharmacology, revised, U.S. Department of Health, Education and Welfare Pub. No. (ADM) 76-338. Rockville, MD: NIMH, 1976; 217-222.
9. Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry 2015; 2(5):452-464.
10. Kay SR, Fiszbein A, Opler L. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophrenia Bulletin 1987; 13:261-276.
11. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry. 2005 Sep;187:229-34.
12. Meltzer HY, Bobo WV, Roy A, Jayathilake K, Chen Y, Ertugrul A, Anil Yağcioğlu AE, Small JG. A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. J Clin Psychiatry. 2008 Feb;69(2):274-85.
13. NW-3509 (Evenamide) Investigator's Brochure.
14. Potkin SG, Gharabawi GM, Greenspan AJ, et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing and acute exacerbation requiring hospitalization. Schizophr Res 2006; 85:254-265.
15. Riordan H, Antonini P, Murphy MF. Atypical antipsychotics and metabolic syndrome in patients with schizophrenia: Risk factors, monitoring and healthcare implications. Am Health Drug Benefits 2011; 4(5):292-302.

16. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, Fye C, Charney D. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med. 1997 Sep 18;337(12):809-15.
17. Strauss JS, Carpenter WTJ. Prediction of outcome in schizophrenia: III. Five-year outcome and its predictors. Arch Gen Psychiatry 1977; 34:159-163.

16. APPENDICES

16.1. Study Information

16.1.1. Protocol and Protocol Amendments (for Study 015 beyond Week 46)

16.1.2. Sample Electronic Case Report Form

16.1.3. List of Institutional Review Boards and Independent Ethics Committees and Representative Written Information for Subject and Sample Consent Forms

16.1.4. List and Description of Investigators and Other Important Participants in the Study, including Brief Curriculum Vitae

16.1.5. Signatures of Sponsor's Responsible Medical Officer and Principal Investigator

16.1.6. Listing of Subjects Receiving Test Drug(S)/IP(s) from Specific Batches

16.1.7. Randomization Scheme and Codes

16.1.8. Audit Certificates

16.1.9. Documentation of Statistical Methods

16.1.9.1. Statistical Analysis Plan

16.1.9.2. Lab Data SI Unit Conversion and Normalization

16.1.10. Documentation of Inter-Laboratory Standardization Methods and Quality assurance Procedures

16.1.11. Publications based on the study

16.1.12. Important Publications Referenced in the Report

16.1.13. Analysis Population List

16.1.14. Protocol Clarification Letters

- Protocol Clarification Letter dated 23rd November 2023

16.2. Subject Data Listings

16.2.1. Subject Eligibility and Disposition

Listing 16.2.1.1. Subject Enrollment

Listing 16.2.1.2. Subject Disposition - Safety Population

16.2.2. Protocol Deviations

Listing 16.2.2. Major and Critical Protocol Deviations - Safety Population

16.2.3. Patients Excluded from the Efficacy Analysis

16.2.4. Subject Demographics and Baseline Characteristics

16.2.5. Investigational Product Accountability and Exposure

16.2.6. Individual Efficacy Response Data

16.2.7. Adverse event listings

16.2.14. Extrapyramidal Symptom Rating Scale

Listing 16.2.14 Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) - Safety Population

16.2.15. Calgary Depression scale of Schizophrenia

Listing 16.2.15 Calgary Depression Scale for Schizophrenia (CDSS) - Safety Population

16.3. Electronic Case Report Forms

Electronic CRF's for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.4. Individual Subject Data Listings

16.5. Source Tables, Figures and Graphs

16.6. Study 015 CSR up to and including Week 46