Clinical Study Report

1. TITLE PAGE

A PHASE II/III, MULTI-CENTER, OPEN-LABEL, EXTENSION STUDY TO DETERMINE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF EVENAMIDE IN PATIENTS WITH PSYCHIATRIC DISORDERS WHO PARTICIPATED IN A PREVIOUS TRIAL WITH EVENAMIDE

Investigational Medicinal Product	Evenamide (NW-3509)
Indication studied	Schizophrenia
Protocol number	NW-3509/020/III/2021
EudraCT number	2021-002093-34
Development Phase	Phase II/III
First subject in	23-Mar-2023
Last subject last 30-day safety follow up visit	16-Oct-2024
Company/Sponsor signatory	Ravi Anand MD, Chief Medical Officer Newron Pharmaceuticals S.p.A. Via Antonio Meucci, 3 20091 Bresso (Milano), Italy
Date of Report	24-May-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 Finished Product: Evenamide (NW-3509)		
Name of Active Ingredient: Evenamide		

Title of Study:

A phase II/III, multi-center, open-label, extension study to determine the long-term safety, tolerability, and efficacy of evenamide in patients with psychiatric disorders who participated in a previous trial with evenamide

Study Number:

NW-3509/020/III/2021

Investigators:

A total of 8 Principal Investigators (6 in Argentina and 2 in Italy) took part in the study.

Study Centers:

The study was conducted at 8 centers (6 in Argentina and 2 in Italy).

Publication (Reference):

None

Study Period: 23-Mar-2023 to 16-Oct-2024	**Phase of Development:** II/III

Study Objectives:

Study 020 was initially designed to include patients with other psychiatric disorders, such as bipolar disorder, in addition to those with schizophrenia. However, only patients with schizophrenia ultimately rolled over into the study. As a result, the study objectives outlined in the protocol were revised in the ***Statistical Analysis Plan*** *(SAP), which was finalized before the database lock (DBL).*

Primary:

Safety

- To evaluate the long-term safety and tolerability of evenamide 30 mg twice daily (*BID*) in patients with schizophrenia.

  All patients, regardless of the treatment they received during the core study (008A), were treated initially with evenamide 15 mg BID for 4 weeks in Study 020 (titration period).

Efficacy

- To evaluate the long-term efficacy of evenamide 30 mg *BID*, based on improvement in symptoms of psychosis, as assessed by the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the total score on the Positive and Negative Syndrome Scale (PANSS).

Secondary:

- To evaluate the long-term efficacy of evenamide, based on the rating of the Clinical Global Impression - Change from Baseline (CGI-C) at endpoint (Week 52 or early discontinuation).
- To evaluate the long-term efficacy of evenamide, as assessed by the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the CGI - Severity of illness (CGI-S).

Other Secondary Efficacy

- To determine the long-term effect of evenamide on general functioning, based on the change from Baseline to endpoint (Week 52 or early discontinuation) on the Global Assessment of Functioning (GAF) scale.
- To determine the long-term effect of evenamide on daily functioning, based on the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the Strauss-Carpenter Levels of Functioning (LOF) scale.
- To evaluate the patients' satisfaction with the study medication, compared to their previous treatment, using the Patient's Medication Satisfaction Questionnaire (MSQ).

Study Design and Methods:

This was a 52-week, multicenter, open-label, extension study designed to determine the long-term safety, tolerability, and efficacy of evenamide (NW-3509), in patients with psychiatric disorders who participated in a prior study with evenamide. Studies with evenamide that were expected to enroll patients into this open-label extension study were Study NW-3509/008A/II/2020 (Study 008A) and other ongoing and planned studies in patients with schizophrenia or bipolar disorder (*Amendment 1.0, Protocol version 2.0, dated 26 October 2021*). However, only the patients who completed Study 008A, a 4-week, randomized, double-blind, placebo-controlled trial in patients with schizophrenia, were enrolled into this open-label extension study. Patients randomized to receive evenamide 30 mg *BID* or placebo *BID* in Study 008A received treatment with evenamide in this open-label extension study, starting with a titration period of 4 weeks with evenamide 15 mg *BID*.

Study 008A was designed to determine the safety, tolerability, EEG effects and efficacy of oral doses of 30 mg *BID* of evenamide compared to placebo in patients with chronic schizophrenia who were symptomatic on their current second-generation antipsychotic medication. A total of 291 subjects were randomized and dosed in Study 008A, and 280 subjects completed the 4-week treatment period. Evenamide 30 mg *BID* showed statistically significant improvement, compared to placebo, in terms of the primary and key secondary efficacy endpoints. Additional details on Study 008A are available in the Clinical Study Report of Study 008A, as well as in the current edition of the NW-3509 (Evenamide) Investigator's Brochure.

This extension study (Study 020) was requested by the health authorities (HAs) of Italy and Argentina to allow patients who completed 4 weeks of treatment in Study 008A to have the opportunity to receive long-term treatment with evenamide.

All patients who completed Study 008A from Italy and Argentina, including those originally randomized to placebo, who were compliant with study procedures, were not experiencing moderate/severe adverse events, and had not shown significant worsening of their symptoms during their prior treatment period, were eligible to continue long-term treatment with evenamide in this separate 52-week, open-label, extension study (Study 020).

Upon entry into this open-label study, all patients underwent dose titration with evenamide, starting at a dose of 15 mg *BID*, and had their dose increased to 30 mg *BID* after a 4-week interval, provided the 15 mg *BID* dose was well tolerated. If intolerance developed at either the 15 or 30 mg *BID* dose, the patient had a dose reduction to once daily (*OD*) dosing. The patient could return to *BID* dosing if the intolerance resolved, or continue for the remainder of the study at the reduced dose, if necessary. Patients unable to tolerate 30 mg *OD* could have a further reduction to the starting dose of 15 mg *BID*. Patients unable to tolerate a dose of 15 mg *OD* were to be discontinued from the study (Synopsis Table 1).

Synopsis Table 1: Dosing in the Initial 52-Week Treatment Period

Dose Type	Study Weeks (Days)	Planned Dose	Dose Reduction
Starting Dose	1-4 (1-28)	15 mg *BID*	15 mg *OD**
	5-52 (29-364)		15 mg *BID***

Target Dose	5-52 (29-364)	30 mg *BID*	30 mg *OD**
	5-52 (29-364)		15 mg *BID****

**Patients unable to tolerate the starting dose (15 mg BID) or the target dose (30 mg BID) had a dose reduction to once daily (OD) dosing.*

*** If the Starting Dose (15 mg BID) was not well tolerated, but the tolerability issues were not severe enough to require a dose reduction to OD dosing, the patient remained on 15 mg BID.*

**** If the Target Dose (30 mg BID) was not well tolerated, and after the patient had a dose reduction to 30 mg OD, tolerability issues persist, the patient had a further reduction to 15 mg BID.*

When patients were taking their medication at their residence, they were instructed to take their dose of study medication at least 10 minutes after the time of dosing for their concomitant antipsychotic medication (if oral). 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, containing any unused medication, with them to the clinic. After all safety and efficacy assessments were completed, if there were no safety or tolerability issues, the patient was dispensed their study medication according to the planned dosing schedule. When they were discharged from the clinic, patients were reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

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. If the patient reported any of these symptoms, he/she was asked to contact the Principal Investigator, who would decide based on the symptoms/signs that have been identified, whether the patient should come in for an evaluation, whether their dosing regimen should be modified, and/or whether a concomitant medication should be added. If further evaluation of the patient confirmed symptoms or signs suggestive of treatment toxicity, the Investigator was to decide on the appropriate therapeutic and diagnostic measures to be completed. These might include hospitalization, performance of a full neurological examination, EEG, ECG, etc.

Baseline (OL Baseline, Day 29 of Study 008A/Day 0 of Study 020)

All patients provided written informed consent prior to their participation in this extension trial. The evaluations performed at the final visit in the prior Study 008A served as the OL Baseline (*Day 29 of Study 008A/Day 0 of Study 020*) assessments for this extension study. Patients who completed all the final safety and efficacy evaluations in Study 008A were considered eligible for continuing in this extension study. Patients who completed all the Baseline evaluations, gave consent for this extension study, and met the eligibility criteria for continuing treatment, received their first dose of study medication in this study in the clinic on Day 1, with a post-dose safety assessment (vital signs, ECG, AEs) approximately 2 hours after dosing. The post-dose assessments of the Study 020 Baseline visit have been considered as 'Day 1'. If there were no safety concerns, they were dispensed a supply of study medication for the initial 4-week treatment period and discharged from the clinic. Patients were instructed to begin *BID* dosing the following morning (Day 2) at their residence.

Initial 52-Week Open-Label Treatment Period

Patients returned to the clinic for scheduled visits at Weeks 4, 8, 12, 20, 28, 36, 44 and 52 (or at early discontinuation). The following evaluations were performed at each of these visits: vital signs, Columbia Suicide Severity Rating Scale (C-SSRS - "Since Last Visit" version), adverse events, and concomitant medications and therapies. All efficacy assessments (PANSS, CGI-S, CGI-C, GAF, LOF and MSQ) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A physical examination was performed at Weeks 28 and 52 (or at early discontinuation). A neurological examination, routine laboratory tests (hematology, biochemistry, urinalysis), and a 12-lead ECG were performed at Weeks 4, 12, 28 and 52 (or at

early discontinuation). The standard eye examination and Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A 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 who were surgically sterilized, at Weeks 12, 28 and 52 (or at early discontinuation). Measurement of serum prolactin was performed at Weeks 28 and 52. Measurement of HbA1c and an assessment of substance abuse, along with a urine drug screen, were conducted only at the final visit (Week 52 or early discontinuation).

At the completion of each visit, if there were no safety or tolerability issues noted after dosing that would necessitate a dose reduction, the patient was dispensed a supply of medication to cover the next period of dosing at the planned dose.

Telephone Contacts

Patients were contacted by the Investigator or a member of their staff at Weeks 2 and 6, between scheduled clinic visits, during the initial dose titration period to inquire about the occurrence of any adverse events or changes in use of concomitant medication. If necessary, based on the information collected, a reduction in the patient's dose was performed, or if there were any significant safety concerns, a clinic visit was scheduled for appropriate follow-up.

Safety Follow-up Visit

For patients who discontinued prematurely, as well as those who completed 52 weeks of open-label treatment in this extension study and did not continue further treatment, a safety follow-up visit was performed approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. In addition, the patient was contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

Additional 52-Week Treatment Period

The duration of this extension study was increased by one-year, based on the assessment of safety data on evenamide and approval by the Independent Safety Monitoring Board (ISMB). For this subsequent one-year treatment period, there was no dose titration, and patients continued with the same dose of evenamide. During this additional period, visits at the site were conducted every 13 weeks, with telephone contacts with the patient performed between scheduled visits. However, as this study was terminated by the Sponsor prematurely, the additional 52-week period could not be completed.

Schedule of Evaluations –52-Week Treatment Period

The schedule of evaluations for all visits in the initial 52-week and subsequent one-year open-label treatment period are summarized in Table 9-7 and Table 9-8, respectively.

Study Population: Only eligible patients with schizophrenia who completed Study 008A in Argentina and Italy were enrolled in this open-label extension study.

Subjects Rolled over into Study 020:	52 subjects
Subjects Excluded:	None from the Safety Population and 1 subject from the mITT Population
Subjects Analyzed:	**Safety Population:** 52 subjects **mITT population:** 51 subjects

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

Patients meeting all the following inclusion criteria were eligible for enrollment into the study:

1. Patient was at least 18 years of age and (*Amendment 1.1, Protocol version 2.1, dated 05 April 2022*) completed the specified treatment period in their prior evenamide study [e.g., Study 008A, (*Amendment 1.0, Protocol version 2.0, dated 26 October 2021*)],
2. Patient provided written informed consent for this extension study,
3. If female, the patient had a negative pregnancy test at Baseline and was not lactating.
   a. If of childbearing potential, the patient agreed to continue using a highly effective method of contraception, (i.e., a method that could achieve a failure rate of less than 1% per year when used consistently and correctly) during the trial until the final follow-up visit. Highly effective methods of contraception include:
      i. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal),
      ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable),
      iii. Intrauterine device (IUD),
      iv. Intrauterine hormone-releasing system (IUS),
      v. Bilateral tubal occlusion,
      vi. Vasectomized partner (with surgical success confirmed by medical assessment).
   b. A woman was considered to be of non-childbearing potential if she met one of the following criteria:
      i. was post-menopausal (the last menstrual period was at least 12 months ago; confirmed by FSH measurement),
      ii. had no uterus, ovaries or fallopian tubes.
   c. Women who were taking hormone replacement therapy (HRT) were required to use contraception (as described above) during the trial.
   d. Sexual abstinence was not considered an acceptable method of contraception.
4. Male patients who were not sterilized but agreed to not have sex without using a condom, if their partner was a woman of childbearing potential, during the trial (from the first dose until the final follow-up visit). Male patients also agreed not to attempt to father a child and not to donate sperm from the first dose until the final follow-up visit.

Exclusion Criteria:

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

1. Patient demonstrated substantial non-compliance with any requirement of the protocol in the prior study, as judged by the Investigator, that would put him/her at risk for continuing treatment in Study 020.
2. In the Investigator's opinion, the patient had a significant worsening of risk for suicidality during the prior study.
3. Patient experienced any moderate/severe neurological adverse events.
4. Patient had shown significant worsening of symptoms of his/her psychiatric disorder between Baseline and the final assessment during the treatment period in the prior study.
5. Patient demonstrated substantial non-compliance with dosing of the study medication or the concomitant antipsychotic medication in the prior study, as judged by the Investigator.

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

The study medication was administered orally as capsules of 15-mg and 30-mg dosage strengths of evenamide. Study medication with each different dosage (15 and 30 mg evenamide) was provided in 30-ml HDPE bottles. All patients received open-label treatment with evenamide, starting at a dose of 15 mg *BID*, with a dose increase

to 30 mg *BID* after 4 weeks, dependent on tolerability. Details of the study medication are 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.	15 mg	19795/3 19795/8
				30 mg	19795/9 19795/11 19795/13

An adequate supply of study medication was dispensed at the appropriate dose level for the patient at each visit to cover the period until the next dispensing visit.

Planned Study Duration:

The study was planned to last up to 53 weeks (371 days), including a 52-week (364-day) open-label treatment period, and a 7-day safety follow-up period. The duration of this extension study was planned to be increased in one-year segments, contingent on approval by the ISMB based on an assessment of safety data from ongoing evenamide studies.

Comparator, Dose and Mode of Administration:

No placebo or other comparator was used in this open-label extension study.

Criteria for Evaluation and Endpoints:

Safety Evaluations – Primary Safety Objective

Safety was assessed by the following:

- Incidence (%) of treatment-emergent adverse events (TEAEs)
- Incidence (%) of serious adverse events (SAEs)
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, body temperature, respiratory rate, BMI)
- Laboratory evaluations (hematology, blood chemistry, and urinalysis; HbA1c and 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).
- Substance use assessment
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)

Efficacy Evaluations

The change from Baseline to endpoint for all efficacy measures was calculated using both Baselines [the double-blind baseline of core Study 008A (Study 008A Day 0, referred to as "DB Baseline") and the open-

label baseline of the extension Study 020 (Study 008A Day 29/Study 020 Day 0, referred to as "OL Baseline")]. Efficacy was assessed by the following measures:

- *Primary Efficacy Objective*
  - PANSS total score – mean change from Baseline to endpoint (Week 52 or early discontinuation)
- *Secondary Efficacy Objectives*
  - CGI-S – Mean change from Baseline to endpoint (Week 52 or early discontinuation)
  - CGI-C – Mean rating at endpoint and proportion of patients with improvement from Baseline to endpoint (score of 1, 2, or 3)
  - PANSS total score – proportion of patients with at least 20% improvement and at least 30% improvement from Baseline(s) to endpoint
- *Other Secondary Efficacy Objectives*
  - LOF – mean change from Baseline to endpoint (Week 52 or early discontinuation)
  - MSQ – mean change from Baseline to endpoint (Week 52 or early discontinuation)
  - GAF – mean change from Baseline to endpoint (Week 52 or early discontinuation)

Independent Safety Monitoring Board

Safety data from all patients were examined periodically by an Independent Safety Monitoring Board (ISMB). The ISMB did not request any modifications to the study design, as there were no significant safety concerns identified in the periodic reviews of the accumulating safety data for evenamide.

Statistical Methods:

***Sample Size*:**

It was anticipated that approximately 500 patients with psychiatric disorders who completed prior studies in which they received evenamide at doses of 7.5, 15 or 30 mg *BID*, or placebo *BID*, would continue treatment with evenamide in this open-label extension study. However, Study 020 was required only by health authorities in Argentina and Italy as an extension of Study 008A, therefore a lower number of patients (52) was included in the study. No a priori assumptions on sample size and statistical power were made.

Patient Characteristics:

The demographic characteristics and baseline characteristics (age, sex, childbearing potential, height, weight, race, ethnicity, education, marital status, employment, housing status, substance use) collected at Baseline(s) were summarized by 'subjects randomized to evenamide in the core study continuing with evenamide in this extension study' (EVN-EVN), 'subjects randomized to placebo in the core study switched over to evenamide in this extension study' (PLC-EVN), and overall, for the Safety and mITT populations. Race, ethnicity, education, marital status, employment, and housing status data were taken from Study 008A Baseline. Age, sex, childbearing potential, and height data were taken from Study 020 Baseline. Weight data were taken from Study 008A for EVN-EVN subjects and from Study 020 for PLC-EVN subjects. The disease characteristics, including duration of illness, duration of current episode, number of psychiatric hospitalizations, family history of schizophrenia, were summarized for the Safety population. Continuous variables were summarized by minimum, maximum, mean, median, and standard deviation, and categorical variables were summarized using frequencies and percentages.

Analysis Populations:

The Safety population consisted of all subjects who took at least one dose of study medication in this extension study. The efficacy analyses were performed using the mITT population comprising those subjects who had an OL Baseline *(Day 29 of double-blind Study 008A/Day 0 of Study 020)* efficacy assessment, received at least one dose of the study medication in this extension study and had at least one post-OL-Baseline efficacy assessment for the PANSS.

Safety Analysis:

Two Baselines were considered for the analyses: the double-blind Baseline of core Study 008A (Study 008A Day 0, referred to as "DB Baseline") and the open-label Baseline of the extension Study 020 (Study 008A Day 29/Study 020 Day 0, referred to as "OL Baseline"). These two baselines were used in a mixed approach for safety analyses depending on the treatment received in the double-blind Study 008A, with the rationale that baseline values are the last ones collected prior to the administration of the first dose of evenamide. Therefore, the DB Baseline (Study 008A Day 0) was used for subjects randomized to evenamide in Study 008A and continuing treatment with evenamide in Study 020, while the OL Baseline (Study 008A Day 29/Study 020 Day 0) was used for subjects randomized to placebo in Study 008A and switched to evenamide in Study 020. The Safety population was used for the analysis of all safety variables. The safety analysis for patients enrolled in Study 020 included all safety data collected from the time of the first dose of study medication in this study, in addition to safety data collected at the Baseline visit of Study 008A (used as DB Baseline values for EVN-EVN subjects) and the final values for all safety parameters collected at Day 29 of Study 008A (used as OL Baseline values for PLC-EVN subjects). Results were displayed for the overall evenamide 30 mg *BID* treatment group.

All adverse events (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 were assessed and presented. Changes from Baseline at each visit and at endpoint (Week 52 or early discontinuation) in vital signs, ECG and laboratory values, and physical/neurological examinations and standard eye examination findings were summarized, with abnormal and clinically notable values/findings being identified. Mean changes from Baseline in the total score and sub-scale scores on the ESRS-A were presented. Descriptive statistics were provided for the C-SSRS.

Efficacy Analysis:

Efficacy analyses were repeated using both Baselines [DB Baseline (Study 008A Day 0) and OL Baseline (Study 008A Day 29/Study 020 Day 0] based on the mITT population for the overall evenamide 30 mg *BID* group. Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) were provided for all continuous efficacy measures (PANSS and CGI-S) for actual values and changes from Baseline at each visit. PANSS 'Responder' analyses were performed by summarizing the proportion of patients with improvement from Baseline(s) to endpoint on the PANSS total score (i.e., PANSS Total score reduction $\geq$ 20% and $\geq$ 30%). The patient's condition at the time of OL Baseline (Study 020) was considered when assessing the CGI-C. Summary statistics (mean rating) of CGI-C at open-label post-Baseline visits (Weeks 12, 28 and 52) were provided. CGI-C 'Responder' analyses were performed by summarizing the proportion of patients with different categories of improvement ("any improvement" defined as CGI-C score $\leq$ 3, and "at least much improved" defined as CGI-C score $\leq$ 2) from OL Baseline to endpoint on the CGI-C. The change from Baseline to endpoint (Week 52 or early discontinuation) for the other continuous measures, i.e., GAF, LOF, and MSQ, was summarized for evenamide 30 mg *BID* at each post-Baseline time point of the Initial 52-Week period (i.e., Weeks 12, 28 and 52) for the mITT population. For categorical variables, the number and percentage of patients in each category were presented at each time-point.

Demonstration of a clinically relevant improvement from Baseline to endpoint (Week 52 or early discontinuation) on the PANSS total score for evenamide 30 mg *BID*, would be considered as preliminary evidence of long-term benefit of evenamide as adjunctive therapy in patients with chronic schizophrenia showing inadequate response to their current antipsychotic medication. If patients showed significant worsening, the investigators took whatever measures they deemed necessary, e.g., administration of rescue medication. 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 post-intervention safety and efficacy data were collected.

Summary – Results and Conclusions:

Patient Population and Study Disposition:

Clinical study NW-3509/020/III/2021 (Study 020) was a 52-week, multi-center, open-label, extension study designed to determine the long-term safety, tolerability, and efficacy of evenamide (NW-3509) in patients with psychiatric disorders who participated in a prior study with evenamide. However, only Study NW-3509/008A/II/2020 (Study 008A), a 4-week, randomized, double-blind, placebo-controlled trial in patients with schizophrenia, enrolled patients into this open-label extension study. Two-hundred-eighty (280) subjects completed the core Study 008A, and 52 of these subjects from sites in Argentina and Italy were enrolled in the open-label extension Study 020. Among these 52 subjects, 29 subjects who were randomized to the placebo arm started treatment with evenamide 30 mg *BID*, while the remaining 23 subjects continued treatment with evenamide 30 mg *BID* in Study 020 (after a 4-week titration period at the dose of 15 mg *BID*). Subjects were predominantly males [38 (73.1%)], Hispanic or Latino [49 (94.2%)], White [51 (98.1%)], single [34 (65.4%), not employed [44 (84.6%)], with 9-16 years of education [35 (67.3%), and living with a family [48 (92.3%)]. The mean (SD) age of the subjects was 43.3 (14.55) years, ranging from 18 to 76 years. The mean (SD) weight and body mass index were 81.3 (16.69) kg and 28.0 (5.06) kg/m^2, respectively.

Efficacy Results:

Positive and Negative Syndrome Scale (PANSS)

Patients treated with evenamide 30 mg *BID* experienced an improvement of symptoms of schizophrenia, as assessed by the change from DB Baseline and OL Baseline on the PANSS Total score, which was steadily decreasing (indicating improvement) visit by visit. The mean (SD) changes from DB Baseline in the PANSS Total score were -12.5 (9.28), -16.5 (9.58) and -18.6 (9.77) at Weeks 12, 28 and 52, respectively, and the mean (SD) changes from OL Baseline in the PANSS Total score were -6.1 (6.18), -9.4 (8.22) and -12.3 (9.01) at Weeks 12, 28 and 52, respectively, indicating improvement in the symptoms of Schizophrenia.

The proportion of responders with ≥20% improvement (i.e., lowering of score) in the PANSS Total Score of the mITT Population increased at each visit, with more than 50% of patients meeting this criterion at Week 52, compared to the DB Baseline. Similarly, an increasing proportion of patients achieved an even greater improvement of ≥30% from Baseline at each visit, with 27.5% of patients meeting this criterion at Week 52, compared to the DB Baseline.

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

In the analysis of the secondary efficacy measures, evenamide 30 mg *BID* treatment was associated with a decrease in the CGI-S score over time from Baseline(s) till Week 52, indicating the efficacy of add-on treatment with evenamide in reducing the overall severity of illness in patients with chronic schizophrenia. The mean (SD) DB Baseline CGI-S score of 4.8 (0.53) decreased by -1.0 (0.67), -1.5 (0.70) and -1.5 (0.83) at Weeks 12, 28 and 52, respectively. Similarly, the mean (SD) OL Baseline CGI-S score of 4.4 (0.57) decreased by -0.6 (0.64), -1.1 (0.77) and -1.1 (0.82) at Weeks 12, 28 and 52, respectively.

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

The CGI-C mean rating at post-baseline visits indicated that patients treated with evenamide 30 mg *BID* were considered, on average, minimally to much improved, as evident from the mean scores at Weeks 12 [2.8 (0.86)], 28 [2.6 (0.93)] and 52 [2.6 (1.01)]. The proportion of patients rated as improved (score ≤ 3) on the CGI-C in the evenamide treated group was greater than 70% at all post-baseline visits [n (%): 39 (76.5%), 37 (72.5%) and 36 (70.6%) at Weeks 12, 28 and 52, respectively], while the proportion of patients rated as at least "much improved" (score ≤ 2) in the evenamide treated group was greater than 40% at all post-baseline visits [n (%): 22 (43.1%), 24 (47.1%) and 23 (45.1%) at Weeks 12, 28 and 52, respectively].

Strauss-Carpenter - Level of Functioning Scale (LOF)

Treatment with evenamide 30 mg *BID* was associated with an improvement in the LOF Total score at all visits from the DB Baseline and OL Baseline till Week 52. The mean (SD) LOF Total Score increased from 17.0 (6.82) at DB Baseline by 2.1 (5.38), 2.7 (5.13) and 2.5 (5.13) at Weeks 12, 28 and 52, respectively. Similarly, the mean (SD) LOF Total score increased from 16.8 (6.77) at OL Baseline by 2.3 (4.89), 2.8 (5.65) and 2.7

(5.95) at Weeks 12, 28 and 52, respectively. A similar trend was seen in the LOF sub-scale scores, i.e., Social Contact, Symptomatology, Work and Function.

Patient's Medication Satisfaction Questionnaire (MSQ)

Improvement in the MSQ mean change from Baseline(s) was observed in the evenamide 30 mg *BID* treatment group at each visit till Week 52, except for MSQ at Week 12 which remained unchanged compared to OL Baseline. The DB Baseline mean (SD) MSQ score increased from 4.6 (0.98) by 0.6 (1.59), 1.1 (1.03), and 1.1 (1.18) at Weeks 12, 28 and 52, respectively. Similarly, the OL Baseline mean (SD) MSQ score changed from 5.2 (1.07) by 0.0 (1.65), 0.6 (1.24), and 0.6 (1.20) at Weeks 12, 28 and 52, respectively.

Global Assessment of Functioning Scale (GAF)

A steady improvement from Baseline in the GAF category mean scores (on a scale of 1 to 10) was recorded at each visit from Week 12 till Week 52. The GAF category mean (SD) score (on a scale of 1 to 10) at OL Baseline was 6.6 (1.18), and it increased to 7.1 (1.07), 7.6 (0.91) and 7.7 (0.87) at Weeks 12, 28 and 52, respectively, indicating an overall improvement in functioning. The mean (SD) changes from OL Baseline score at Weeks 12, 28 and 52 were 0.5 (0.89), 1.0 (1.01), and 1.0 (1.09), respectively.

Overall Efficacy Summary

Overall, the long-term efficacy of evenamide 30 mg *BID* was demonstrated by improvement in the symptoms of schizophrenia assessed by the PANSS Total Score, a decrease in the disease severity assessed by the CGI-S score, and improvement in overall severity of illness assessed by the CGI-C. In addition, evenamide enhanced functionality of patients as evident from improvements in the LOF Total and subscale scores and improvement in the individual's social, occupational, and psychological functioning as assessed by the Global Assessment of Functioning (GAF). An increase in patient's satisfaction with their medication, as assessed by the Patient's Medication Satisfaction Questionnaire (MSQ), was also noted. In addition, the proportion of patients with clinically meaningful improvement, defined based on responder criteria for the PANSS total score and CGI-C increased through 52 weeks of treatment. These long-term beneficial effects of evenamide treatment, which increased over time, were observed in patients with chronic schizophrenia who have been symptomatic on their current single second-generation antipsychotic (SGA) medication.

Safety Results:

The primary safety objective of the study was to evaluate the long-term safety and tolerability of an oral dose of evenamide of 30 mg *BID* [60 mg/day], achieved after a 4-week titration starting with 15 mg *BID* in patients with schizophrenia.

A total of 22 (42.3%) subjects reported at least 1 TEAE. The most common TEAEs (incidence by PT ≥2%) were nasopharyngitis [5.8% (3/52)], influenza [3.8% (2/52)], tooth infection [3.8% (2/52)], akathisia [3.8% (2/52)], headache [3.8% (2/52)], and anemia [3.8% (2/52)].

Treatment-related TEAEs were reported in 4 (7.7%) subjects, and the same proportion experienced at least one serious TEAE, although two of these events occurred more than 30 days after the last dose of study medication. None of the reported serious TEAEs were considered related to the study medication. Treatment-related TEAEs included akathisia, headache, dry mouth, and psychotic disorder in 1 (1.9%) subject each.

Overall, 4 subjects had at least 1 serious TEAE, with cellulitis, pneumonia, femur fracture, intentional overdose, acute myocardial infarction (leading to death) and sudden death in 1 (1.9%) subject each in the evenamide treated group. However, 'pneumonia' and 'myocardial infarction' occurred more than 30 days after the last dose of study medication.

The number of subjects with any TEAE leading to study drug discontinuation was 3 (5.8%), with cellulitis, intentional overdose, and psychotic disorder reported in 1 (1.9%) subject each. Cellulitis and intentional overdose were considered serious TEAEs not related to the study medication, and both recovered; whereas psychotic disorder did not resolve and was deemed as possibly related to the study drug.

Two (3.8%) subjects had a TEAE resulting in death. One subject died due to cardiorespiratory arrest, and the other subject died due to acute myocardial infarction 2 months and 15 days after the administration of the last dose of study medication. The Investigator considered both of these events as not related to study medication.

The majority of TEAEs were of mild [10 (19.2%)] or moderate [8 (15.4%)] intensity, and only 4 (7.7%) subjects had severe TEAEs, including tooth infection, femur fracture, intentional overdose, acute myocardial infarction (occurred more than 30 days after the last dose of study medication), and sudden death.

Very few clinical laboratory test results were deemed clinically significant by the Principal Investigator, and no notable trends in the occurrence of laboratory abnormalities were noted in the evenamide 30 mg *BID* treated subjects.

Vital signs data did not indicate any clinically significant effects of evenamide 30 mg *BID*, with the number of treatment-emergent clinically notable abnormalities being very low. At endpoint (Week 52) clinically notable weight gain was reported in only 3 (5.8%) subjects.

In the analysis of data from the ECGs, there was no significant increase in mean QTcF value from baseline at any post-dose timepoint in the study. There were no clinically meaningful changes from baseline in mean values for any ECG parameters (Mean Heart Rate, RR Interval, PR Interval, QRS Axis, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval). In the categorical analysis of ECG parameters, Aggregate (ms) of >450 and ≤480 ms in QTcB Interval was noted in 1 subject at Week 52, but no significant abnormal QTcF interval aggregate or an abnormal change from baseline in QTcF values were noted. These findings are consistent with ECG data available from previous studies.

No safety concerns were noted on the physical or neurological examinations and standard eye examinations. On the ESRS-A, the vast majority of patients either did not show any extrapyramidal symptom or showed "minimal"/"mild" symptoms, with very few exceptions in which a "moderate" symptom was reported, and there was no evidence of worsening of EPS with evenamide treatment. On the Columbia-Suicide Severity Rating Scale (C-SSRS), the Suicidal Ideation categories 'Non-Specific Suicidal Thought' and 'Wish to be Dead' were reported in a small number of patients, and only one reported a 'Non-suicidal Self-injurious Behavior'.

Overall, the results from all safety parameters indicated that evenamide 30 mg *BID* as add-on treatment in patients with chronic schizophrenia who have been symptomatic on their current single SGA medication was well tolerated when taken orally concomitantly with the patients' background SGA for up to 52 weeks.

Conclusions:

The results of this study confirm previous clinical evidence and suggest that evenamide at a dose of 30 mg *BID* for 52 weeks as add-on treatment in moderately to severely ill patients with schizophrenia, who were experiencing worsening symptoms of psychosis and demonstrating inadequate response to their current therapeutic dose of a SGA, is well tolerated, based on the data from multiple safety assessments, including vital signs, laboratory tests, ECGs, and incidence of TEAEs, with no patterns of safety abnormalities detected. Furthermore, there were no Serious and Treatment-Related TEAEs reported in this study. Treatment with evenamide for up to 52 weeks at a dose of 30 mg *BID* given as add-on to SGAs (including clozapine) in patients with schizophrenia was associated with a sustained improvement and clinically relevant benefits across all efficacy measures, although the lack of a control arm and the small sample size limit the interpretability of the efficacy results.

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

3-BPAA	(3-butoxy-phenyl)-acetic acid
ADaM	Analysis dataset model
ADO	Adverse dropout (discontinuation due to adverse event)
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine-aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate-aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma drug concentration vs. time curve
$AUC_{(0-\infty)}$	AUC from time zero extrapolated to infinity
$AUC_{(0-t)}$	AUC from time zero to the last quantifiable concentration
BID	Twice daily
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CDSS	Calgary Depression Scale for Schizophrenia
CGI-C	Clinical Global Impression - Change from Baseline
CGI-S	Clinical Global Impression - Severity of illness
C_{max}	Maximum post-dose plasma drug concentration
CMO	Chief Medical Officer
CNS	Central Nervous Systems
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CYP	Cytochrome P450
CYP2D6	Cytochrome P450 2D6
DB	Double blind
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EPS	Extrapyramidal symptoms
ESRS-A	Extrapyramidal Symptom Rating Scale - Abbreviated Version
EVN	Evenamide
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HA	Health authority
HbA1c	Blood glycosylated hemoglobin
HDL	High density lipoprotein
HDPE	High density polyethylene
hERG	human *Ether-a-go-go* Related Gene
HRT	Hormone replacement therapy
h.s.	*hora somni* (at bed time)
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
i.p.	Intraperitoneal
IRB	Institutional Review Board
ISMB	Independent Safety Monitoring Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LATAM	Latin America
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOF	Strauss-Carpenter Level of Functioning Scale
MED	Minimal effective dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MSQ	Medication Satisfaction Questionnaire
ms	Milliseconds
MTD	Maximum tolerated dose
NMDAr	N-Methyl-D-Aspartate receptor
NOAEL	No Observed Adverse Effect Level
OC	Observed Cases
OD	Once daily
OL	Open label
OLE	Open-label extension
OTC	Over-The-Counter
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PK	Pharmacokinetics
PK-PD	Pharmacokinetics-Pharmacodynamics

PLC	Placebo
PPI	Pre-Pulse Inhibition
prn	As needed
PT	Preferred Term
QM	Once a month
QRS	QRS duration; measured from the start of the Q wave until the end of the S wave (J point)
QT	QT interval; measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcB	QT corrected using Bastet's formula
QTcF	QT corrected using Fridericia's formula
RBC	Red blood cells
RDO	Retrieved dropout
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SGA	Second-generation antipsychotic
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
t_{max}	Time of maximum plasma concentration post-dose
TLF	Table, Listing and Figure
TQT	Thorough QT
TRS	Treatment-resistant schizophrenia
TST	Tail suspension test
VGSCs	Voltage-gated sodium channels
VLDL	Very low density lipoprotein
WBC	White Blood Cells
WHO	World Health Organization

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 conducted in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza Brazil, 2013 (Appendix 1A of the study protocol presented in Appendix 16.1.1) and ICH E6 Guideline (Good Clinical Practice). However, where applicable, the principles of the 1996 version of the Declaration of Helsinki were adhered to (Appendix 1B of the study protocol presented in Appendix 16.1.1).

5.3. Patient Information and Consent

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

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

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

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

No study procedure was performed (including the screening visit) before the ICF was signed. The informed consent procedure was done according to the guidelines provided in the Declaration of Helsinki and the 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. A sample ICF is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was conducted at 8 sites, 6 in Argentina and 2 in Italy. 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. All people involved at clinical centers were qualified to perform their roles. The study administrative structure is described in Table 6-1.

Table 6-1 Study Administrative Structure

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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).

In schizophrenia, VGSC blockers are frequently used as “add-on” therapy to antipsychotics, with their success being attributed not only to their mood-stabilizer effects, but also to their enhancement of the onset of antipsychotic action, increasing the overall efficacy of the antipsychotic drugs (Casey et al., 2003; Citrome, 2003; Tiihonen et al., 2003). Based on its effect on VGSCs, NW-3509 used in combination with current neuroleptics should improve their efficacy, allowing a reduction of their dosage, and thereby reducing associated side effects (e.g., metabolic syndrome, tardive dyskinesia, and extra-pyramidal symptoms [EPS]).

7.2. Pharmacology

It is hypothesized that there is a dysfunction of the glutamatergic and dopaminergic systems in schizophrenia and bipolar disorders. Current antipsychotic drugs target the dysregulation of mesolimbic and mesocortical dopaminergic/serotoninergic systems. However, this approach to treating the symptoms of schizophrenia still appears to be inadequate, with a very high proportion (~70%) of patients discontinuing their antipsychotic (first or second generation) due to intolerance, inadequate benefit, or both within 18 months of starting treatment (Lieberman et al., 2005). This suggests a failure to modulate other important mechanisms that are critical for anti-psychotic benefit. Aberrant electrical connectivity in schizophrenia leads to abnormal cortical activity and glutamate transmission largely contributes to the pathophysiology of this psychiatric disorder; however, it is not targeted by existing therapies.

NW-3509 normalizes glutamate release induced by aberrant sodium channel activity (veratridine-stimulated), without affecting basal glutamate levels, due to its inhibition of VGSCs. The minimal effective dose in an *in vivo* microdialysis study in rats was 2.5 mg/kg i.p., which overlaps with the effective doses in preclinical models of psychiatric illnesses.

NW-3509 appears to be highly selective in its effects on VGSCs. Radio-ligand binding assays demonstrated that NW-3509 showed less than 20% inhibition against a panel of >150 receptors, ion channels, transporters and kinases when tested at 10 µM, i.e., at concentrations many fold higher than likely to be achieved in humans. Acute treatment with doses of NW-3509 (oral 2.5 mg/kg p.o.) active in preclinical models, did not alter monoamines (dopamine, serotonin, norepinephrine) or their metabolite levels in the brain, while functional electrophysiology studies did not detect any significant activity of NW-3509 on other ion channels, such as voltage-gated Ca^{2+} channels and NMDA receptor channels, up to extremely high concentrations (IC_{50} >100 µM). Evenamide showed an affinity for the human sigma-1 receptor (Sig-1R) in a radioligand binding assay in the range of 0.49-1.11 µM. However, evenamide showed antagonist activity at the Sig-1R only at concentrations 140 times the anticipated maximum therapeutic exposure of 0.02 µM.

The potential benefits of NW-3509 were demonstrated in a battery of animal models predictive of efficacy in psychiatric diseases, including models of schizophrenia, mania, psychosis, depression, compulsivity and aggressiveness, and cognition. NW-3509 was effective when administered alone and in combination with marketed antipsychotics.

In the schizophrenia model of impaired sensorimotor gating and information processing (Pre-Pulse Inhibition [PPI] deficit), NW-3509 was effective, irrespective of whether the impairment was spontaneous or induced by amphetamine, NMDA-receptor antagonists (MK-801, PCP, or ketamine), or sleep deprivation. The minimal effective dose (MED) in reversing PPI deficits ranged from 0.5 mg/kg i.p. (sleep deprivation model) to 1.25 mg/kg p.o. (MK-801/ amphetamine-induced deficits).

The potential anti-manic and antipsychotic effects of NW-3509 were demonstrated in the mouse models of amphetamine + chlordiazepoxide- and amphetamine- induced hyperactivity, respectively, at MEDs of 5-20 mg/kg p.o. Antidepressant activity was evaluated using the tail suspension test (TST) in mice (MED 10 mg/kg p.o.), and effects on aggressive behavior were evaluated in the resident-intruder paradigm (MED 0.25 mg/kg i.p.). The marble burying test was used to evaluate compulsive behavior (MED 20 mg/kg p.o.).

A key feature of these experiments was that sub-threshold doses of NW-3509 added to ineffective doses of typical (haloperidol) or atypical (risperidone) antipsychotics in models of schizophrenia (PPI deficit), mania (amphetamine + chlordiazepoxide hyperactivity), and psychosis (amphetamine-induced hyperactivity) demonstrated significant efficacy of the combination.

In the rat model of PPI deficit induced by amphetamine (2.5 mg/kg, s.c.), ineffective doses of NW-3509 (0.625 mg/kg and 1.25 mg/kg p.o.) in combination with sub-threshold doses of

haloperidol (0.05 mg/kg i.p.) or risperidone (0.05 mg/kg i.p.) produced a reversal of the PPI deficit. The combination of haloperidol (0.3 mg/kg i.p.) and inactive doses of NW-3509 (10 and 20 mg/kg p.o.) also significantly increased PPI compared to haloperidol alone in a model of spontaneous PPI deficit in C57BL/6J mice.

The above experiments suggest that NW-3509, when added to sub-therapeutic doses of antipsychotics, may confer antipsychotic efficacy or augments their effects, thus indicating that doses of antipsychotic drugs can be reduced, which should result in a reduction in their dose-dependent side-effects.

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

The mean effective dose of evenamide when used as monotherapy across different PPI deficits is 6 mg/kg; this corresponds to a mean plasma concentration of 100 ng/ml in the rat. However, a series of add-on studies have demonstrated that lower/ineffective doses of evenamide (producing plasma levels approx. 20 ng/ml in the rat) are sufficient to effectively counteract the PPI deficit induced by different sources, when combined with ineffective doses of first or second-generation antipsychotics.

Extrapolated plasma concentrations of NW-3509 at the minimal effective doses (0.65 mg/kg – 1.25 mg/kg p.o., given as add-on to antipsychotics) in schizophrenia models range from 10 to 20 ng/ml. Physiological PK/PD modelling, using input information of NW-3509 LogP, solubility, permeability, *in vitro* clearance, plasma protein binding, and effective concentrations in animal models of PPI, indicated that a steady state plasma concentration of 20-40 ng/ml would likely be effective in humans.

In summary, preclinical data indicated that NW-3509, through modulation of the firing abnormalities, has the potential to normalize the aberrant spread of excitatory transmission and the excessive release of glutamate that occur as a consequence of the hypothesized dysfunction of the glutamatergic and dopaminergic systems in schizophrenia. As NW-3509 will be administered in conjunction with $5HT_2/D_2$ blocking antipsychotics, it may add to or synergize with these drugs to bring about a combined therapeutic effect on glutamate release and dopaminergic and serotoninergic systems, thus modulating these major neurotransmitter systems that have been associated with schizophrenia symptoms.

7.3. Safety Pharmacology

Evenamide (NW-3509) was evaluated for its potential to induce exaggerated pharmacology, i.e. CNS side effects in a range of *in vitro* and *in vivo* safety pharmacology and respiratory studies [modified Irwin study in rats, rotarod test, spontaneous locomotor activity, rat whole body plethysmography]; effects on the cardiovascular system [cardiac channels Na^+ 1.5, Ca^{2+} 1.2 and hERG, canine Purkinje fibers and telemetry in the conscious dog], as well its potential to induce phospholipidosis *in vitro*. The safety pharmacology studies did not reveal any findings that pose a risk for humans; the most conservative safety margin was greater than x20; this was based on the lowest efficacious concentration in any of the add-on experimental paradigms (i.e., 20 ng*h/mL in the rat and risperidone PPI model), and the most conservative No Observed Adverse Effect Level (NOAEL) dose in any of the species tested (i.e., 5.0 mg/kg/*BID* in the 4-week dog study C_{max} = 414 ng/mL). A single-dose study in healthy male volunteers did not detect any pattern of treatment-related adverse changes at doses up to and including 30 mg (mean C_{max} = 93 ng/mL; range 65.3-113 ng/mL). Similarly, multiple doses of 15, 20 and 25 mg *BID* were well tolerated in patients with schizophrenia (Study 002 – see details below under Clinical Studies).

7.4. Pharmacokinetics and Metabolism

The pharmacokinetics (PK) of NW-3509 following intravenous and oral administration was studied in mice, rats, dogs and cynomolgus monkeys. Generally, in all species, NW-3509 was rapidly absorbed, with maximal concentrations reached within 0.25 to 1.25 hours following oral dosing and was cleared with a terminal half-life of 0.5 to 1.5 hours. The oral bioavailability was 18% in mice, 7% in rats, 15-30% in dogs, and 20% in cynomolgus monkeys.

In the rat NW-3509 showed high penetration into the brain; the concentration ratio brain/plasma was 13 at 0.25 hours after oral dosing and 5.7 at 1 hour. The clearance of NW-3509 was similar in both plasma and the brain (1.5-2.0 hours). Plasma protein binding was 91.0% in rats and 94.2% in humans.

In the 4-week rat toxicity study, exposure to NW-3509 was higher in females than in males and increased in a dose over-proportional manner. Accumulation ratios were >1 in both sexes. In the 4-week dog study, no gender effect was noted, and no accumulation was seen. The kinetics were linear over the dose range of 2.5 to 10 mg/kg/*BID*.

In the first Phase I study, single oral doses of 1, 2, 5, 10, 20 and 30 mg of NW-3509 were administered to 6 healthy subjects per dose level. Absorption was rapid, and t_{max} was reached between 0.75 and 2.0 hours. C_{max}- and AUC-values kept increasing with increasing doses. The mean terminal elimination half-life observed in the six cohorts ranged between 1.6 and 4.0 hours.

Based on the short half-life, a *BID* dosing schedule was used in the multiple ascending dose study in patients with schizophrenia (Study 002). In Study 002, all patients randomized to evenamide started at a dose of 15 mg *BID*, and had subsequent weekly dose increases to 20 and 25 mg *BID*, based on tolerability. Peak plasma concentrations [C_{max}; mean (SD)] of 40.4 (20.4), 65.7 (31.3) and 94.1 (51.3) ng/mL were achieved after the first administration of doses of 15, 20 and 25 mg, respectively, with a t_{max} of 1-2 hours and a half-life of 2.2-2.5 hours. Although there are no data available on the effect of food on plasma concentrations of NW-3509, because of the rapid rise to C_{max}, a recommendation was made to dose with food or after a meal.

In vitro, NW-3509 was extensively metabolized in rat, dog, minipig, cynomolgus monkey and human hepatocytes; metabolic stability was highest in dog and human. Metabolic reactions included demethylation, di-demethylation, hydroxylation (major), di-hydroxylation, oxidation (major) and various combinations thereof, as well as glucuronidation. The number of metabolites detected was 16 in rat, 15 in minipig, 12 in monkey, 8 in dog and 5 in human hepatocytes.

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

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

7.4.1. Clinical Pharmacology Study NW3509-007

Study 007 (NW3509-007) assessed the mass balance recovery after a single oral dose of 25 mg of Carbon 14 NW-3509 ([^{14}C] NW-3509) in 6 healthy male subjects, of whom 2 were CYP2D6 poor metabolizers. There was a complete recovery of the radioactivity, the majority of which was recovered in the urine, indicating renal excretion was the main route of elimination. Exposure to NW-3509 accounted for approximately 5% of circulating plasma total

radioactivity based on AUC(0-inf), indicating extensive biotransformation of NW-3509 following oral administration. The whole blood plasma total radioactivity concentration ratios indicated very limited distribution of total radioactivity to the cellular components of whole blood. Only 1 AE, mild in intensity and not related to evenamide, was reported (catheter site bruise). There were no clinically significant findings in any laboratory assessments, vital signs, urinalysis, ECGs, or physical examinations.

Detailed results of Study 007 are provided in the current edition of the NW-3509 (Evenamide) Investigator's Brochure.

7.4.2. Toxicology studies

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

In rat toxicity studies, severe CNS symptoms with convulsions and death were found at high doses while underactivity, unsteady gait, unresponsive, poor righting reflex, and prostrate posture were noted at lower doses. These signs persisted for up to 60 minutes after dosing and the frequency tended to increase with the treatment duration. In the 1st 4-week toxicity study (ONP0049), the only histopathological finding was urothelial hyperplasia (minimal or slight severity) in males given 150 mg/kg/day. In the 2nd 4-week toxicity study (ONP0105), rats were treated twice daily 8 hours apart, in order to achieve continuous exposure to quantifiable concentrations of NW-3509; there was no urothelial hyperplasia. In the 13-week toxicity study (ONP0103), the doses were: male 0, 10, 25, 50 mg/kg/*BID* and female 0, 10, 15, 20 mg/kg/*BID*. There were no deaths which were considered to be treatment related. A CNS sign (chin rubbing) was noted at all doses. There were no treatment-related histopathological findings.

The doses in the 26-week toxicity study (CG15GG) were the same as those in the 13-week study. There were 13 decedent animals, most of which were attributable to gavage errors. However, there were unexplained deaths in the low-dose (1) and high-dose (4) male groups. In females, there was 1 unexplained death at the low dose. In the absence of unexplained deaths in the mid- and high-dose groups of females, this single death was regarded as a chance event. In males, the lack of a mid-dose unexplained death suggests that the low-dose unexplained death may also be a chance event. A few animals sporadically exhibited CNS clinical signs. There was no effect of treatment on body weight gain, food consumption or in the ophthalmic examinations. There were minor changes in various hematology and clinical pathology

parameters, but in the absence of corroborative pathology; and as there was evidence of recovery following 4 weeks off-dose, these alterations were considered not adverse. The pathology examinations revealed no test item-related lesions (main study and recovery period). In view of the low dose unexplained deaths, a precise no observed adverse effect level (NOAEL) in the rat could not be established based on the 26-week study. However, 2 additional studies in rats were conducted:

- The first of these was a 6-week rat toxicity study conducted at the request of the FDA (OVZ0013). The dose levels were 0, 5, 10 and 20 mg/kg *BID* in females and 0, 5, 10 and 40 mg/kg *BID* in males, and included frequent observations (up to 8 times/post each dose of the *BID* schedule) as requested by the FDA. There were no premature decedents or test item-related clinical signs, including seizures, noted during the study. Body weights, food intake, clinical pathology parameters, ophthalmoscopy, organ weights, and macroscopic and microscopic pathology were unaffected by treatment. The NOAEL is therefore considered to be 20 mg/kg *BID* for females and 40 mg/kg *BID* for males.
- The second study was a 3-week rat neurotoxicity study (1019-4501). The effects on brain electrophysiology were examined in conscious male telemetered rats at 50 mg/kg *BID*. Electroencephalography (EEG) and electromyography records were obtained continuously for 24 hours/day. There were no seizures observed or inferred from the EEG recordings. Clinical signs noted included: salivation, partial ptosis, decreased activity, weakness, uncoordination and retching, however, EEGs remained normal. The dose of 50 mg/kg *BID* was considered to be the NOAEL for this study.

The results of these 2 rat explanatory studies reinforce the NOAELs (females 20 mg/kg *BID*, males 40 mg/kg *BID*) and further suggest that the low-dose unexplained deaths in the 26-week study were chance (probably mis-dosing) events.

In dog toxicity studies, CNS symptoms again predominated (underactivity, uncoordinated movement and unsteadiness). Dogs were treated twice daily 8 hours apart. In the 4-week toxicity study (ONP0081), 1 female at 10 mg/kg/*BID* was sacrificed moribund on Day 18 due to severe CNS signs. There were no treatment-related histopathological changes.

In the 13-week toxicity study (ONP0104), the doses were: 0, 2.5, 5, 7.5, mg/kg/*BID*. There were no deaths and no treatment-related histopathological findings. Clinical signs (tremor, activity) were recorded at ≥2.5 mg/kg/*BID*.

The 39-week toxicity study (1017-5022) was performed with the same doses as in the 13-week study. The analysis of this study indicates that 7.5 mg/kg *BID* was associated with adverse CNS effects including convulsions in three females. CNS signs and gastrointestinal toxicity

declined in frequency and severity after the first three weeks of dosing. At 2.5 and 5 mg/kg *BID*, evenamide was well tolerated although there were minor clinical signs. There were no effects on body weights, body weight gains, food consumption, clinical pathology parameters, ophthalmology, electrocardiography, organ weights, macroscopic or microscopic evaluations at any dose level. At 2.5 and 5 mg/kg *BID*, evenamide was generally well-tolerated with minimal treatment-related CNS clinical signs (uncoordinated ataxia, weakness, tremor). Based upon the relatively low incidence and minimal to mild severity of CNS clinical findings at 5 mg/kg *BID*, the NOAEL in the dog was considered to be 5 mg/kg *BID* following 39 weeks of administration.

The standard test battery of mutagenicity studies Ames (ONP0072), chromosome aberration (ONP0048) and micronucleus (ONP0050) were completed, and none of the assays conducted revealed evidence of genotoxic potential. For phototoxic potential of evenamide (WJ43NB), the ultraviolet/visible spectra of evenamide were determined and there was no absorbance which could indicate that further testing was necessary. The rat embryo-fetal developmental study (RV17CG) showed no evidence of teratogenicity and the NOAEL for maternal toxicity and embryo-fetal survival and development was 20 mg/kg *BID*. In the rabbit embryo-fetal developmental study (QP91NQ), three high-dose (10 mg/kg *BID*) females were killed with respiratory impairment. There was no evidence of teratogenicity and the NOAEL for maternal effects was 7.5 mg/kg *BID*, and for embryo-fetal survival, growth and development was 10 mg/kg *BID*. In the rat fertility and early embryonic development study (CW27WN) there were no effects of evenamide on any parameter and the NOAELs were 50 mg/kg *BID* for males and 20 mg/kg *BID* for females.

The major metabolite of NW-3509, (3-butoxy-phenyl)-acetic acid (3-BPAA), was found to be devoid of pharmacological and mutagenic activity. Repeated dose toxicity with the major metabolite, 3-BPAA, had also been evaluated: dose levels of up to 500 mg/kg/day were very well tolerated in the dose range finding study (OVZ0018). The 100 mg/kg/day dose was further evaluated in a 4-week study in rats and was found to be devoid of any toxicological activity (OVZ0019). The NOAEL for 3-BPAA in rats was established to be 100 mg/kg/day.

Based on the exposure to 3-BPAA observed in humans following a 60-mg evenamide dose (C_{max} of 633 ng/mL and AUC of 5520 ng.h/mL) and 3-BPAA exposure in a 4-week oral toxicity study in rats (PD57CS), a Safety Ratio (SR) of at least xl50 was calculated for C_{max} and more than x50 for AUC [C_{max} = xl77 (males), x341 (females); AUC = x66 (males), x212 (females)].

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

7.5. Clinical studies

7.5.1. Phase I studies

7.5.1.1. Study NW3509A/001/I/2011 (Study 001)

Study 001, a first-in-human phase 1 study, was a single dose, randomized, placebo-controlled, independent, sequential cohort (9 subjects in each cohort) study that evaluated the safety, tolerability, and the maximum tolerated dose (MTD) of escalating single oral doses of evenamide (1, 2, 5, 10, 20 and 30 mg; n=6 at each dose) or placebo (n=3 in each cohort) in healthy male volunteers. Results of standard safety assessments (ECGs, laboratory results, vital signs, physical and neurological examinations) including Holter recordings did not indicate any adverse effects of any dose of evenamide on any of these measures.

Overall, a total of 33 non-serious adverse events (AEs) were reported in 21 subjects. All the AEs were rated as mild intensity, except for two (2) moderate AEs (headache and somnolence at 30 mg evenamide; both resolved). The C_{max} and AUC increased with the dose.

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

7.5.1.2. Study NW-3509/011/I/2019 (Study 011)

Study 011 was a double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of a supratherapeutic dose of evenamide 60 mg. Six subjects received evenamide and 3 placebo. No deaths, SAEs, other significant AEs, discontinuations due to AEs, or any clinically significant changes in laboratory tests, ECGs, vital signs, physical and neurological examinations, suicidality assessment, or findings on the seizure checklist were reported during this study. There were no adverse effects of evenamide on the morphology of the ECGs or QTc measurements at the dose of 60 mg; the concentration-QTcF analysis revealed a small QTcF shortening with increasing plasma concentration with evenamide, and its major metabolite, 3-BPAA. The safety and tolerability of the 60 mg dose was considered acceptable and was selected as the supratherapeutic dose for TQT Study 010.

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

7.5.1.3. Study NW-3509/010/I/2019 (Study 010)

TQT-Study 010 was a phase 1, randomized, partially blinded, placebo- and positive-(moxifloxacin 400 mg) controlled, 4-way balanced crossover study to assess the effect of single oral therapeutic (30 mg) and supratherapeutic (60 mg) doses of evenamide on the QT/QTc interval in healthy male and female subjects. Fifty-six subjects (25.0% female) were

randomized to 1 of 4 treatment sequences. No deaths, SAEs, other significant AEs, or discontinuations due to AEs, or any clinically significant changes in laboratory tests, ECGs, vital signs, physical and neurological examinations, suicidality assessment, or findings on the seizure checklist were reported during this study.

Analysis of change from Baseline in QTcF values indicated that both evenamide (30 and 60 mg) and its metabolite 3-BPAA were associated with an increase in QTcF of less than 6 ms, while placebo and moxifloxacin produced increases of 7.6 and 17.3 ms, respectively. Concentration-QTc analysis of plasma concentrations of evenamide and its major metabolite, 3-BPAA, and QTc intervals indicated a small, dose-dependent reduction of the QTcF. There were no QTcF observations associated with the evenamide treatments that exceeded 450 ms or an increase > 30 ms from Baseline.

These results indicate that evenamide administered at doses of 30 mg and 60 mg is likely to be devoid of the risk of QTc prolongation and arrhythmias.

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

7.5.2. Completed phase II-III studies

7.5.2.1. Study NW3509A/002/II/2015 (Study 002)

Study 002 was a four-week, double-blind, placebo-controlled, randomized, multi-center protocol designed to investigate the tolerability, safety, and preliminary evidence of efficacy of evenamide as an add-on treatment to either risperidone or aripiprazole in 89 patients with a DSM-5 diagnosis of schizophrenia. Patients included in the study were primarily males (86%) from 19 to 60 years of age. The study was conducted in US (n=61) and India (n=28), and enrolled patients with schizophrenia with a mean duration of illness of approximately 18 years and an average of three psychiatric hospitalizations. The starting daily dose in this trial was 15 mg *BID*, which was increased at weekly intervals to 20 and 25 mg *BID*, contingent on tolerability. The completion rate for evenamide-treated patients was 84%, with 2 patients discontinuing for serious adverse events (seizure, atrial fibrillation). The seizure occurred at a dose of 20 mg *BID*, resolved spontaneously, and the patient refused to undergo an EEG or any further evaluation. Atrial fibrillation occurred at a dose of 25 mg *BID* in a patient with pre-existing atrial premature complex (APC).

The most common AEs reported in this study were somnolence, insomnia, overdose, dry mouth, headache, and cold sweat/hyperhidrosis; there were no major differences in the incidence of these AEs between evenamide and placebo. There were no AEs indicative of extrapyramidal symptoms, dizziness, metabolic effects, endocrine changes, or abnormalities

in laboratory results, vital signs, or ECGs in evenamide-treated subjects, compared with placebo subjects.

The results of the study indicated a preliminary signal of efficacy despite its limitations (i.e., small sample size, unequal randomization, short duration of treatment, and limited to milder patients). Patients treated with evenamide showed a consistent pattern of greater improvement compared to placebo on the PANSS total (mean change from Baseline) and positive symptoms sub-scale (mean change from Baseline and responder analysis), and CGI-C (responder analysis).

Pharmacokinetic analysis indicated a C_{max} ranging from 40.4 ng/mL (15 mg *BID* dose) to 94.1 ng/mL (25 mg *BID* dose); similarly, the AUC also increased with dose.

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

7.5.2.2. Study NW-3509/008/II/2019 (Study 008)

Study 008 was a 4-week, double-blind, placebo-controlled, multi-center study performed in 138 outpatients with schizophrenia in India and US, which evaluated the safety, tolerability, including EEGs, and preliminary efficacy of multiple fixed doses of 7.5 and 15 mg *BID* of evenamide as add-on to a single atypical antipsychotic.

The mean age of the patients was 38 years, and the majority of patients were males (76.1%) and Asian (81.9%). The most common atypical antipsychotics that patients were taking concomitantly were risperidone (35.5%), olanzapine (29.7%) and clozapine (16.7%). Six (4.4%) patients discontinued the study prematurely, but none were due to AEs.

There was no evidence of any seizurogenic activity for evenamide based on interpretations of EEG recordings (approximately 360) performed by the Investigators, as well as assessments of the Seizure Checklist (approximately 1000).

Only 1 patient reported an asymptomatic potential overdose/medication error (classified as a SAE). A total of 37 (26.8%) of the 138 patients experienced at least 1 TEAE in the study; there were no meaningful differences in the incidence of TEAEs between treatment groups. The only TEAEs reported in patients treated with evenamide with an incidence greater than 5% were somnolence and headache. All TEAEs reported were mild or moderate in intensity, except for 4 laboratory abnormalities reported as severe TEAEs in 1 subject in the placebo group. Overall, there was no meaningful difference in the pattern of TEAEs, or incidence of new abnormalities in laboratory results, ECGs, vital signs, physical, neurological and eye examinations, EPS (ESRS-A), suicidal ideation and behavior (C-SSRS), or depressive symptoms (CDSS) between treatment groups.

No statistically significant differences were noted between either of the evenamide groups and placebo for any of the efficacy measures, including the PANSS and CGI-S. Analysis of plasma PK samples for evenamide showed good dose proportionality, with increases of 2.21, 2.37 and 2.34-fold for Cmax, AUC(0-t) and AUC(0-inf), respectively, between the 7.5 and 15 mg *BID* doses. The mean exposures at the 15 mg dose are below the expected efficacious levels. This supports the need to use a higher dose of evenamide to achieve efficacy in patients showing inadequate response to antipsychotics.

Detailed results of Study 008 are provided in the current edition of the NW-3509 (Evenamide) Investigator's Brochure.

7.5.2.3. Study NW-3509/014/II/2019 (Study 014)

Study 014 was a 6-week, open-label, randomized, rater-blinded, multi-center study designed to evaluate the safety, tolerability, and preliminary efficacy of fixed doses of evenamide of 7.5, 15 and 30 mg *BID* as add-on treatment in patients with treatment-resistant schizophrenia (TRS) on a stable therapeutic dose of single antipsychotic. A total of 161 patients were randomized (1 subject was not dosed) into the study conducted in India, Sri Lanka, and Italy.

Eight (8) subjects discontinued the study (the reported primary reasons for discontinuation were: withdrawal of consent [7] and adverse event [1] pyrexia, headache, and vomiting, not considered related to evenamide) and 153 completed the treatment period. One hundred forty-four (144) of the 153 patients who completed Study 014 continued into the long-term extension Study 015 (NW-3509/015/II/2019) treatment period. One hundred forty-four (144) of the 153 patients who completed Study 014 continued into the long-term extension Study 015 (NW-3509/015/II/2019).

In Study 014 evenamide, at doses of 7.5, 15 and 30 mg *BID* as add-on therapy to a stable therapeutic dose of an antipsychotic, was well tolerated. No serious adverse event was reported, and no meaningful differences among treatment groups were observed in the incidence of TEAEs, notable abnormalities in laboratory tests, vital signs or ECGs, or the incidence of abnormal physical, neurological, or standard eye examination findings. No adverse effects of evenamide were observed on other safety measures assessing EPS (ESRS-A), or depressive symptoms (CDSS). No TEAEs and/or symptoms, suggestive of seizure, were identified.

Efficacy at 6 weeks

The PANSS total score was reduced significantly ($p<0.001$, paired t-test; LOCF) by 11.6% from baseline to Week 6, with 15.4% of the patients considered “responders” (≥ 20% improvement from baseline). Approximately 25% of the patients had a rating of at least “much improved” on the CGI C; and 10% of the patients were rated as “responders” on the CGI-S (2-category improvement). Mean improvement from baseline was 1.3 and 0.9 for the LOF and

MSQ, respectively, indicating improvements in patients' functioning and satisfaction with their current medication.

Detailed results of Study 014 are provided in the current edition of the NW-3509 (Evenamide) Investigator's Brochure.

7.5.2.4. Study NW-3509/015/II/2019 (Study 015)

Study 015 (NW-3509/015/II/2019) is 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 TRS not responding adequately to their current antipsychotic medication.

One hundred forty-four (144) of the 153 patients who completed Study 014 continued into the long-term extension Study 015 (NW-3509/015/II/2019). Patients continued on the same dose of evenamide they had received during Study 014. The treatment durations for this study were 94 weeks for India and 46 weeks for the other countries (Italy and Sri Lanka) for a total treatment with evenamide of 100 and 52 weeks, respectively, including the initial 6-week treatment period in Study 014. Twenty-three (23) subjects discontinued the study prematurely: 17 due to withdrawal of consent, 4 due to lost to follow-up, 1 for a non-serious adverse event (somnolence), and 1 due to sudden death. In addition, 1 SAE (dilutional hyponatremia, and acute symptomatic seizure) occurred 26 days after the last dose of evenamide, which was considered by the Investigator to be not related. Results indicate that evenamide was very well tolerated at all doses, and the efficacy data showed a pattern of gradual and increasing improvement over time. Overall, no meaningful differences among treatment groups (7.5, 15, and 30 mg *BID*) were observed in any of the safety measures.

Efficacy at 1-year

The PANSS total score was reduced significantly ($p<0.001$, paired t-test; primary estimand treatment policy) by 20.0% from baseline to 1-year, with 41.8% of the patients considered "responders" (≥ 20% improvement from baseline). Approximately 38% of the patients had a rating of at least "much improved" on the CGI-C; and 24.1% of the patients were rated as "responders" on the CGI-S (2-category improvement). Mean improvement from baseline was 2.5 for the LOF, indicating improvements in patients' functioning.

Summary of efficacy and safety results beyond 1-year

Patients from India were offered the opportunity to roll over into two additional extension periods for a total of 48 weeks of additional treatment with evenamide beyond 1-year: Additional Period I from 1-year till Week 70, and Additional Period II from Week 70 till Week 94, for a total of 76 and 100 weeks of total treatment with evenamide, respectively. 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. 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).

7.5.2.5. Study NW-3509/008A/II/2020 (Study 008A)

Study 008A (NW-3509/008A/II/2020), which was recently completed (April 2024), was a Phase II/III, prospective, multi-center, randomized, 4-week, double-blind, placebo-controlled study, designed to determine the safety, tolerability, EEG effects and efficacy of oral doses of 30 mg *BID* of evenamide (NW-3509) in patients with chronic schizophrenia who are symptomatic despite being on a therapeutic and stable dose of their current second-generation antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone) medication. The study was conducted in 45 centers in Europe, Asia, and Latin America. Two hundred-ninety-one (291) patients were randomized to receive either evenamide 30 mg *BID* (N=132) or placebo (N=159). Two-hundred-eighty-one (281) patients completed the 4-week treatment period with only 11 patients discontinuing (8 due to withdrawal of consent, and 3 for an adverse event).

The results indicate that evenamide was well-tolerated, with 3 SAEs (2 on evenamide and 1 death on placebo), and only 3 dropouts for adverse events (ADOs), 2 on evenamide and 1 on placebo, and approximately 25% of patients experiencing at least 1 TEAE, with no differences in incidence between evenamide and placebo. No pattern of abnormality was detected in any safety measure, including vital signs, laboratory tests, ECGs, EEGs, standard eye examinations, suicidality, depressive symptoms or seizure-like symptoms in evenamide 30 mg *BID* treated patients compared to placebo, and no other clinically important AEs, or abnormalities in physical or neurological (including assessment of extrapyramidal symptoms) examinations were noted. One patient on placebo died on Day 28 of the study due to an accidental fall/ suspected suicide.

Both the primary (PANSS Total score) and the key secondary (CGI-S) efficacy endpoints were met, as evenamide demonstrated a statistically significant improvement and clinically meaningful benefits compared to placebo in most of the efficacy measures tested, including

the sensitivity analyses. Similarly, these benefits were reflected by the CGI-C mean rating and the proportion of patients considered as "responders", i.e. at least 'minimally improved' or 'much improved'. The efficacy of evenamide 30 mg *BID* was demonstrated by improvement in the symptoms of schizophrenia as assessed by the PANSS (total score and subscales), a decrease in the disease severity assessed by the CGI-S score, improvement in overall severity of illness assessed by the CGI-C, and enhancement in functionality of patients in the symptomatology sub-scale of the LOF. The proportion of responders on the PANSS and CGI-C was significantly higher in the evenamide 30 mg *BID* treated group compared with the placebo *BID* treated group at Day 29. These beneficial effects were observed over the 4-week treatment period in patients with chronic schizophrenia who were symptomatic on their current single second-generation antipsychotic (SGA) medication.

Detailed results of Study 008A are provided in the current edition of the NW-3509 (Evenamide) Investigator's Brochure.

8. STUDY OBJECTIVES

The objectives of the study were as follows:

8.1. Primary

Safety

- To evaluate the long-term safety and tolerability of evenamide 30 mg *BID* in patients with schizophrenia.

  All patients, regardless of the treatment they received during the core study (Study 008A), were treated initially with evenamide 15 mg BID for 4 weeks in Study 020 (titration period).

Efficacy

- To evaluate the long-term efficacy of evenamide 30 mg *BID*, based on improvement in symptoms of psychosis, as assessed by the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the total score on the Positive and Negative Syndrome Scale (PANSS).

8.2. Secondary Efficacy

- To evaluate the long-term efficacy of evenamide, based on the rating of the Clinical Global Impression - Change from Baseline (CGI-C) at endpoint (Week 52 or early discontinuation).

- To evaluate the long-term efficacy of evenamide, as assessed by the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) as assessed by the CGI - Severity of illness (CGI-S).

8.3. Other Secondary Efficacy

- To determine the long-term effect of evenamide on general functioning, based on the change from Baseline to endpoint (Week 52 or early discontinuation) on the Global Assessment of Functioning (GAF) scale.
- To determine the long-term effect of evenamide on daily functioning, based on the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the Strauss-Carpenter Levels of Functioning (LOF) scale.
- To evaluate the patients' satisfaction with the study medication, compared to their previous treatment, using the Patient's Medication Satisfaction Questionnaire (MSQ).

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan - Description

This was a 52-week, open-label, extension to prior studies with evenamide, that was designed to evaluate the long-term safety, tolerability, and efficacy of evenamide in patients with psychiatric disorders who participated in a prior study with evenamide. Studies with evenamide that were expected to enroll patients into this open-label extension study include Study NW-3509/008A/II/2020 (Study 008A) and other ongoing and planned studies in patients with schizophrenia or bipolar disorder (*Amendment 1.0, Protocol version 2.0, dated 26 October 2021*). However, only patients who completed Study 008A, a 4-week, randomized, double-blind, placebo-controlled trial were enrolled into this open-label extension study. Patients randomized to receive evenamide 30 mg *BID* or placebo *BID* in Study 008A received treatment with evenamide in this open-label extension study, starting with a titration period with evenamide 15 mg *BID* for 4 weeks.

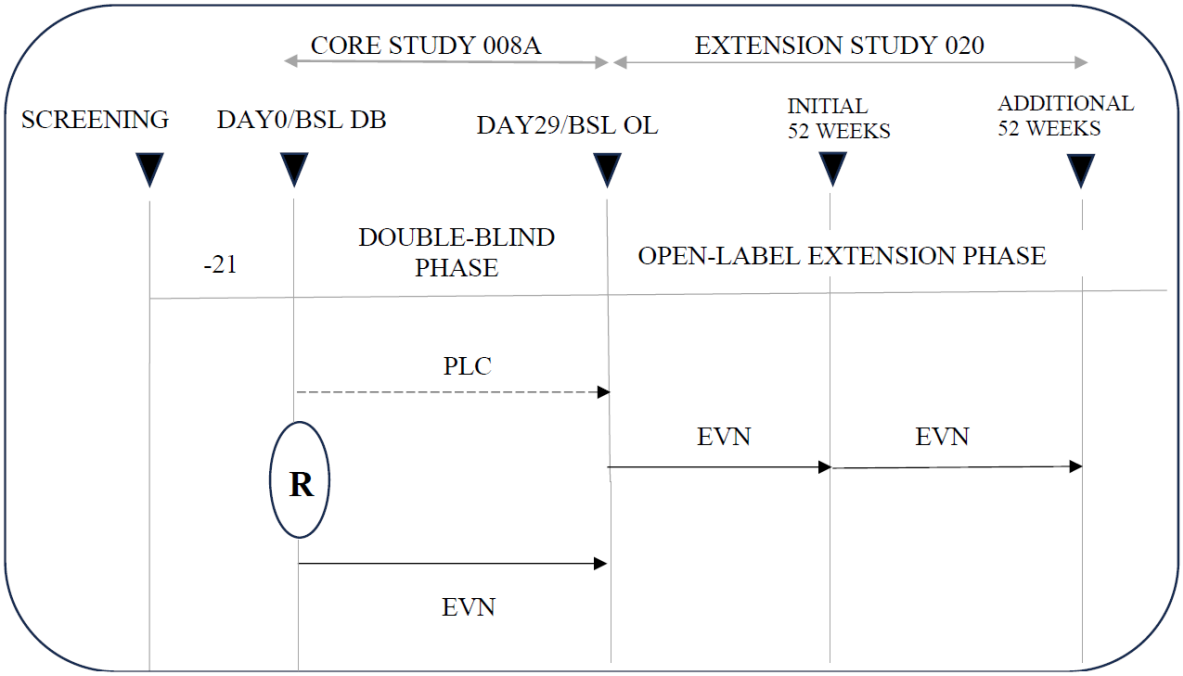
All patients who completed Study 008A from Italy and Argentina, including those originally randomized to placebo, who were compliant with study procedures, were not experiencing moderate/severe adverse events, and had not shown significant worsening of their symptoms during their prior treatment period, were eligible to continue long-term treatment with evenamide in this separate 52-week, open-label, extension study (Study 020). The duration of this extension study was increased by one-year, based on the approval of the ISMB after the assessment of safety data from ongoing evenamide studies.

The Sponsor communicated to participating investigational sites the decision to discontinue Study 020 on 30 July 2024 in Argentina, and 02 September 2024 in Italy. The primary reasons

for this discontinuation were non-compliance and protocol deviations identified at the sites in Argentina during the study, along with administrative reasons for a site in Italy. However, it is important to note that no pattern of safety abnormalities was identified during the course of Study 020.

Upon entry into this open-label study, all patients underwent dose titration with evenamide, starting at a dose of 15 mg *BID*, and had their dose increased to 30 mg *BID* after a 4-week interval, if the 15 mg *BID* dose was well tolerated. If intolerance developed at either the 15 or 30 mg *BID* dose, the patient had a reduction to once daily (*OD*) dosing. The patient could return to *BID* dosing if the intolerance resolved or continued for the remainder of the study at the reduced dose, if necessary. Patients unable to tolerate 30 mg *OD* had a further reduction to the starting dose of 15 mg *BID*. Patients unable to tolerate a dose of 15 mg *OD* were to be discontinued from the study. Table 9-1 depicts the combined study design of the double-blind core study (Study 008A) and the open-label extension study (Study 020).

Table 9-1 Combined study design schema



BSL DB: Baseline of double-blind 008A study, BSL OL: Baseline of open-label 020 study, R: Randomization, EVN: Evenamide 30 mg *BID* add-on to antipsychotics, PLC: Placebo *BID* add-on to antipsychotics
008A Week 1: 15 mg *BID* starting dose, followed by the 30 mg *BID* target dose from Week 2 through Week 4, based on tolerability.
020 Weeks 1 to 4: 15 mg *BID* starting dose, followed by 30 mg *BID* from Week 5 till end of study, based on tolerability.

All patients provided written informed consent prior to their participation in this extension trial. The evaluations performed at the final visit in the prior Study 008A served as the OL Baseline (*Day 29 of Study 008A/Day 0 of Study 020*) assessments for this extension study. Patients who completed all the final safety and efficacy evaluations were considered eligible for continuing in this extension study. Patients who completed all the Baseline evaluations, gave consent for this extension study, and met the eligibility criteria for continuing treatment, received their first dose of study medication in the clinic on Day 1, with a post-dose safety assessment (vital signs, ECG, AEs) approximately 2 hours after dosing. The post-dose assessments of the Study 020 Baseline visit were considered as 'Day 1'. If there were no safety concerns, they were dispensed a supply of study medication for the initial 4-week treatment period and discharged from the clinic. Patients were instructed to begin twice daily dosing the following morning (Day 2) at their residence.

Patients returned to the clinic for scheduled visits at Weeks 4, 8, 12, 20, 28, 36, 44 and 52 (or at early discontinuation). The following evaluations were performed at each of these visits: vital signs, Columbia Suicide Severity Rating Scale (C-SSRS - "Since Last Visit" version), adverse events, and concomitant medications and therapies. All efficacy assessments (PANSS, CGI-S, CGI-C, GAF, LOF, and MSQ) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A physical examination was performed at Weeks 28 and 52 (or at early discontinuation). A neurological examination, routine laboratory tests (hematology, biochemistry, urinalysis), and a 12-lead ECG were performed at Weeks 4, 12, 28 and 52 (or at early discontinuation). The standard eye examination and Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A 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 who were surgically sterilized, at Weeks 12, 28 and 52 (or at early discontinuation). Measurement of serum prolactin was performed at Weeks 28 and 52. Measurement of HbA1c and an assessment of substance abuse, along with a urine drug screen, were conducted only at the final visit (Week 52 or early discontinuation).

At the completion of each visit, if there were no safety or tolerability issues noted after dosing that would necessitate a dose reduction, the patient was dispensed a supply of medication to cover the next period of dosing at the planned dose.

Patients were contacted by the Investigator or a member of their staff at Weeks 2 and 6, between scheduled clinic visits, during the initial dose titration period, to inquire about the occurrence of any adverse events or changes in use of concomitant medication. If necessary, based on the information collected, a reduction in the patient's dose could be performed, or if

there were any significant safety concerns, a clinic visit was scheduled for appropriate follow-up.

For patients who discontinued prematurely, as well as those who completed 52 weeks of open-label treatment in this extension study and did not continue further treatment, a safety follow-up visit was performed approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events was performed. In addition, the patient was contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

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. If the patient reported any of these symptoms, he/she was asked to contact the Principal Investigator, who would decide, based on the symptoms/signs that have been identified, whether the patient should come in for an evaluation, whether their dosing regimen should be modified, and/or whether a concomitant medication should be added. If further evaluation of the patient confirmed symptoms or signs suggestive of treatment toxicity, the Investigator decided on the appropriate therapeutic and diagnostic measures to be completed. These might include hospitalization, performance of a full neurological examination, EEG, ECG, etc.

Additional 52-Week Treatment Period

The duration of this extension study was increased by one-year, based on approval by the ISMB after an assessment of safety data available on evenamide. In this additional one-year extension there was no dose titration, and patients continued on the same dose of evenamide. During this additional period, clinic visits were conducted every 13 weeks, with telephone contacts with the patient to be performed between scheduled visits.

An overview of the study design is provided in Table 9-2 and Table 9-3.

Table 9-2 Summary of Study Design - Initial 52-Week Open-Label Treatment Period (adapted from protocol)

Period	Pre-Treatment	Initial 52-Week, Open-Label, Treatment Period								Post-Treatment	
Visit	**OL Baseline#**	**Week 4**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Final $ (Week 52 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	0/1	1 to 28	29 to 56	57 to 84	85 to 140	141 to 196	197 to 252	253 to 308	309 to 364	7 days after last dose	30 days after last dose
Duration	1 day	28 days	28 days	28 days	56 days	56 days	56 days	56 days	56 days	7 days	30 days
Treatment/ Procedures	Informed consent; final evaluations from prior study served as Baseline assessments for this study; confirmed I/E criteria met; dispensed medication; patient took first dose of 15 mg in clinic, with 2-hr post-dose safety assessment	Selected safety and efficacy assessments; increased dose to 30 mg *BID*, if starting dose was well tolerated; patient took first dose of 30 mg at residence in PM	Selected safety and efficacy assessments; reduced dose if target dose of 30 mg *BID* was not well tolerated	All safety and efficacy assessments	Selected safety and efficacy assessments	All safety and efficacy assessments	Selected safety and efficacy assessments	Selected safety and efficacy assessments	Last dose of study medication; performed all safety and efficacy assessments	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 2** (AEs, Conc. Medication)	**Week 6** (AEs, Conc. Medication)							If patient did not return for scheduled visit, contacted to assess AEs	Information collected via telephone contact

#Day 0, pre-first dose assessments (Baseline), and Day 1, post-first dose, were to be completed on the same day, if possible.
$ Final evaluation for patients who discontinued prematurely and those who completed 52 weeks of treatment.
* Performed for patients who discontinued prematurely, and those who completed 52 weeks of treatment and did not continue treatment in the additional period.

Table 9-3 Summary of Study Design – Additional 52-Week Open-Label Treatment Period (adapted from protocol)

Period	Pre-Treatment	Additional 52-Week, Open-Label, Treatment Period				Post-Treatment	
Visit	**Baseline**	**Week 13**	**Week 26**	**Week 39**	**Final [$] (Week 52 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	1	1 to 91	92 to 182	183 to 273	274 to 364	7 days after last dose	30 days after last dose
Duration	1 day	91 days	91 days	91 days	91 days	7 days	30 days
Treatment/ Procedures	Informed consent; confirmed I/E criteria met; dispensed medication; patient took first dose in clinic	Selected safety and efficacy assessments; reduced dose if target dose of 30 mg *BID* was not well tolerated	Selected safety and efficacy assessments	Selected safety and efficacy assessments	Last dose of study medication; performed all safety and efficacy assessments	Safety evaluations (vital signs and AEs) and study completion 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 6** (AEs, Conc. Medication)	**Week 19** (AEs, Conc. Medication)	**Week 32** (AEs, Conc. Medication)	**Week 45** (AEs, Conc. Medication)	If patient does not return for scheduled visit, contact to assess AEs	Information was collected via telephone contact

$ Final evaluation for patients who discontinued prematurely and those who completed 52 weeks of treatment.
*Performed for patients who discontinued prematurely, and those who completed 52 weeks of treatment.

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

Preliminary evidence of efficacy in treating the symptoms of schizophrenia was obtained in Study 002, a 4-week, randomized, double-blind, placebo-controlled, multiple ascending dose study evaluating the safety, tolerability and preliminary efficacy of evenamide in patients with chronic schizophrenia not responding adequately to their current antipsychotic (risperidone or aripiprazole). In this study, doses of evenamide in the range of 15-25 mg *BID* (30-50 mg/day) were well tolerated [see detailed summary of the results in the current edition of the NW-3509 (Evenamide) Investigator's Brochure].

In a 4-week safety study (Study 008), evenamide at doses of 7.5 mg and 15 mg *BID* given to patients receiving concomitant antipsychotic treatment was shown to be well tolerated, with no safety risks identified based on an analysis of the safety data, including EEG, from the 138 patients who were randomized to treatment in the study. Only 1 patient reported a serious AE (potential overdose/medication error); there were no signs or symptoms detected, and the patient completed the study. Six (4.4%) patients discontinued prematurely, but none were due to AEs. There was no evidence of any seizurogenic activity for study medication based on interpretations of EEG recordings by the Investigators, as well as assessment of the Seizure Checklist. No pattern of TEAEs related to either the 7.5 mg *BID* or 15 mg *BID* dose of evenamide, compared to placebo, was observed. No meaningful differences among treatment groups were observed in the incidence of treatment-emergent notable abnormalities in laboratory tests or vital signs parameters, the proportion of patients with abnormal ECGs, the incidence of abnormal physical or neurological examination findings or results from other safety assessments (see Section 7.1 of the protocol provided in the Appendix 16.1.1 for a detailed summary).

The current study (Study 020) was designed as an open-label study design so that all patients who completed their prior study, including those previously randomized to placebo, had the opportunity to benefit from treatment with evenamide in this study. The assessment of long-term safety and efficacy were based on changes from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation), rather than comparison to a control group. The initial treatment period of the study was 52 weeks, with the option of extending the study by one-year. The endpoint for assessment of efficacy was at the final Week 52 (or at early discontinuation) time-point in the initial period.

The study incorporated a design in which patients were titrated from a starting dose of 15 mg evenamide *BID* to a target dose of 30 mg evenamide, *BID* after 4 weeks, if the starting dose was well tolerated. This was done to maintain the blind in the prior study and to ensure that patients randomized to placebo in Study 008A started at a dose of 15 mg *BID*, before having their dose increased to the target dose of 30 mg *BID*, if tolerability permitted. The dose was to

be reduced to once daily dosing if the *BID* dose was poorly tolerated. If the reduced dose was well tolerated, investigators were encouraged to reattempt *BID* dosing at the next scheduled visit, so that as many patients as possible received the target dose of 30 mg *BID*. Restarting *BID* dosing was only allowed on a clinic visit day. If intolerance again developed, the patient had a dose reduction and continued on once daily dosing for the remainder of the study. Patients who qualified for the study received their first dose of study medication in the clinic on the Baseline day (Day 0/1), after all final safety and efficacy evaluations from the prior study had been completed and their eligibility for the study had been confirmed. A safety assessment (vital signs, ECG, AEs) was performed approximately 2 hours after dosing. Patients were dispensed medication for the initial 4-week period of dosing and instructed to begin *BID* dosing at 15 mg on the following morning (Day 2) at their residence.

It was originally planned that the patients who participated in prior studies with evenamide would be enrolled in this open-label trial. Only patients who completed the prior study, provided informed consent in writing, did not show significant worsening of their underlying psychiatric illness during the prior study, had no safety issues that would put them at risk for continuing treatment with evenamide, and were compliant with procedures and dosing, were eligible for participating in this trial. However, only the patients who completed Study NW-3509/008A/II/2020 (Study 008A), a 4-week, randomized, double-blind, placebo-controlled trial in patients with schizophrenia, were enrolled into this open-label extension study.

The safety and efficacy evaluations performed at the final visit in the prior study served as the Baseline (Day 0) assessments for this extension study, and did not need to be repeated. Patients returned to the clinic for scheduled visits at Weeks 4, 8, 12, 20, 28, 36, 44 and 52 (or at early discontinuation) for the performance of safety and efficacy evaluations. In addition, to ensure safety during the initial dose titration period, patients were contacted by the Investigator or a member of their staff at Weeks 2 and 6, between scheduled clinic visits to inquire about the occurrence of any adverse events or changes in use of concomitant medication. If necessary, based on the information collected, a reduction in the patient's dose to once daily dosing was to be performed, or if there were any significant safety concerns, a clinic visit was to be scheduled for appropriate follow-up.

All patients who completed 52 weeks of treatment and did not continue treatment in the subsequent additional 1-year period, as well as those who discontinued prematurely, were required to return for a safety follow-up visit 7 days after the last dose of study medication to assess vital signs and any adverse events occurring following treatment discontinuation. If the patient did not attend his/her follow-up visit after 7 days, attempts were made to contact the patient to assess his/her condition. If the patient could not be reached, the caregiver was to be contacted. In addition, the patient was contacted 30 days after the last dose of study medication

to determine if any Serious Adverse Events (SAEs) occurred within 30 days after the final dose.

9.3. Selection of Study Population

The proposed indication for evenamide is add-on therapy in patients with schizophrenia not responding adequately to their current antipsychotic. The rationale for using evenamide in this patient population, based on its pharmacology, is presented in Section 7.1 of the protocol provided in the Appendix 16.1.1.

The primary purpose of this open-label study was to gather long-term safety and efficacy data; therefore, patients from multiple evenamide studies were permitted to enroll. To maximize patients' safety and the possibility of benefit from evenamide treatment, only those patients who completed their prior study, did not show significant worsening of their underlying psychiatric illness, and had no safety issues that would put them at risk, were eligible for continuing evenamide treatment in this trial. Female patients of childbearing potential, who were not using highly effective contraception, were excluded, as reproductive and embryo-fetal toxicity studies had not yet been completed with evenamide.

9.3.1. Inclusion Criteria

The patients who met all of the following inclusion criteria were enrolled into the study:

1. Patient was at least 18 years of age and (*Amendment 1.1, Protocol version 2.1, dated 05 April 2022*) completed the specified treatment period in their prior evenamide study [e.g., Study 008A, (*Amendment 1.0, Protocol version 2.0, dated 26 October 2021*)].
2. Patient provided written informed consent for this extension study.
3. If female, the patient had a negative pregnancy test at Baseline and was not lactating.
    a. If of childbearing potential, the patient agreed to continue using a highly effective method of contraception, (i.e., a method that could achieve a failure rate of less than 1% per year when used consistently and correctly) during the trial until the final follow-up visit. Highly effective methods of contraception included:
        i. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal),
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable),
        iii. Intrauterine device (IUD),
        iv. Intrauterine hormone-releasing system (IUS),

v. Bilateral tubal occlusion,

vi. Vasectomized partner (with surgical success confirmed by medical assessment).

b. A woman was considered to be of non-childbearing potential if she met one of the following criteria:

i. was post-menopausal (the last menstrual period was at least 12 months ago; confirmed by FSH measurement),

ii. had no uterus, ovaries, or fallopian tubes.

c. Women who were taking hormone replacement therapy (HRT) were required to use contraception (as described above) during the trial.

d. Sexual abstinence was not considered an acceptable method of contraception.

4. Male patients who were not sterilized agreed to not have sex without using a condom, if their partner was a woman of childbearing potential, during the trial (from the first dose until the final follow-up visit). Male patients also agreed not to attempt to father a child and not donated sperm from the first dose until the final follow-up visit.

9.3.2. Exclusion Criteria

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

1. Patient demonstrated substantial non-compliance with any requirement of the protocol in the prior study, as judged by the Investigator, that would put him/her at risk for continuing treatment in Study 020.
2. In the Investigator's opinion, the patient had a significant worsening of risk for suicidality during the prior study.
3. Patient was experiencing any moderate/severe neurological adverse events.
4. Patient had shown significant worsening of symptoms of his/her psychiatric disorder between Baseline and the final assessment during the treatment period in the prior study.
5. Patient demonstrated substantial non-compliance with dosing of the study medication or the concomitant antipsychotic medication in the prior study, as judged by the Investigator.

9.3.3. Removal of Patients from Therapy or Assessment

A subject was considered to have completed the initial treatment period of the study, and the additional 52-week treatment period, when he/she returned for the final evaluation at Week 52 of the period, regardless of whether the subject returned for the safety follow-up assessment (approximately 7 days after the last dose of study medication) if the patient completed 52

weeks of treatment in the current period and was not continuing additional open-label extension treatment. ‘Discontinuation' refers to any subject who did not complete the full 52 weeks of treatment in the period of the study, exclusive of missed doses during the period.

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

- The subject experienced any moderate/severe hypersensitivity or allergic reaction, that might 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.

The criteria for a subject to discontinue from the study prior to Week 52 in any treatment period 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 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 must be fully documented;
- The Sponsor, Institutional Review Board/Ethics Committee (IRB/EC), or regulatory agency terminated the study.

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

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

Patients who discontinued from the study prematurely (i.e., before completing the 52-week randomized treatment period) were to have their reason for discontinuation entered in the CRF. All patients who discontinued prematurely were asked to return for a final assessment at which time all final Week 52 assessments were performed. Patients were also requested to return for the safety follow-up assessment 7 days after their last dose of study medication. Additionally, patients were contacted by telephone for the safety follow-up assessment on any SAEs that might have occurred within 30 days after their last dose of study medication. A similar procedure was followed for patients who entered the additional 52-week treatment period and discontinued prematurely.

Retrieved Dropouts

Subjects who discontinued treatment but agreed to continue in the study and returned for scheduled visits for assessment of selected efficacy parameters (PANSS, CGI-S and CGI-C) were considered as 'retrieved dropouts'.

9.4. Treatments

9.4.1. Treatments Administered

The investigational product (evenamide) was provided by the Sponsor in the form of capsules at dosage strengths of 15 mg and 30 mg for oral administration. All study medication, together with relevant documentation, was supplied to the pharmacy at the investigational site.

The bottles of study medication were unblinded and had the dosage strength specified on the label. The appropriate medication for the starting dose (15 mg *BID*) was dispensed on Day 1. The first dose of study medication (15 mg) was administered in the clinic on Day 1, which was the same day as the final evaluation in the antecedent study. If the patient received the last dose of study medication for the prior study in the morning, the first dose in Study 020 was administered at least 6 hours later. If there were no post-dose safety issues, the patient was dispensed medication for the initial 4 weeks of dosing and was instructed to begin twice daily dosing with 15 mg at his/her residence on the following morning (Day 2).

The oral doses of evenamide taken by the patient according to the titration schedule are summarized in Table 9-4.

Table 9-4 Capsules of Study Medication Administered According to the Dose Titration in the Initial 52-Week Treatment Period

Dose Type	Study Weeks (Days)	Planned Dose	Dose Reduction
Starting Dose	1-4 (1-28)	15 mg *BID*	15 mg *OD**
	5-52 (29-364)		15 mg *BID***
Target Dose	5-52 (29-364)	30 mg *BID*	30 mg *OD**
	5-52 (29-364)		15 mg *BID****

*Patients unable to tolerate the starting dose (15 mg *BID*) or the target dose (30 mg *BID*) had a dose reduction to once daily (*OD*) dosing.
** If the Starting Dose (15 mg *BID*) was not well tolerated, but the tolerability issues were not severe enough to require a dose reduction to *OD* dosing, the patient remained on 15 mg *BID*.
*** If the Target Dose (30 mg *BID*) was not well tolerated, and after the patient had a dose reduction to 30 mg *OD* tolerability issues persisted, the patient had a further reduction to 15 mg *BID*.

Dosing During the Treatment Period

The study medication was administered as capsules of 15-mg and 30-mg dosage strengths of evenamide. Doses were administered as 1 capsule *BID* given at approximately 8:00 AM and 8:00 PM (these dosing times were flexible; however, the two doses were to be taken at least 6 hours apart). Patients were instructed to take 1 capsule from the bottle of study medication at each dosing time. Dose reductions to once daily dosing could be performed at any time if

intolerance developed. For these patients, an increase to the target *BID* dose at a subsequent scheduled visit was performed if the Investigator felt it was warranted.

If possible, the dose of study medication was taken with food or after a meal. Any other medications were taken according to their usual schedule. On the day of each scheduled clinic visit, patients were reminded to take their study medication at their residence, 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 patient was dispensed their study medication according to the planned dosing schedule. At discharge from the clinic, patients were reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

Overdose

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

Any instance of a suspected overdose (based on pill counting), that was asymptomatic and for which there was no explanation, was considered a ‘medication error’ and did not need to be reported as a SAE. Any confirmed overdose, whether symptomatic or not, was to be communicated to the CRO and Sponsor within 24 hours and fully documented as a SAE. Only symptomatic overdoses were submitted to Regulatory Authorities as expedited safety reports. Details of any signs or symptoms accompanying the overdose and their management were recorded, including details of any antidote(s) administered. The patient was reminded of the importance of taking the medication according to the dosing schedule and not discarding any of the medication or giving it to other individuals.

9.4.2. Identity of Investigational Product(s)

The evenamide capsules (15 mg and 30 mg), were 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 or 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 prior to the next scheduled visit for patients prescribed twice daily dosing. The bottles were properly labelled with the below information:

- Protocol No. NW-3509/020/III/2021
- Investigator's name and contact information (provided on a separate label based on country-specific requirements)
- Quantity of capsules
- Evenamide dosage strength: 15 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
- Inventory management number (Kit number)
- Patient's subject number (entered by site)
- Date of dispensing (entered by site)

Patients who had their dose reduced to once daily dosing received half the number of bottles of study medication that were used for twice daily dosing at the starting or target dose and were instructed to take only 1 capsule per day in the morning.

Detailed description of the drug packaging for the study medication is presented in Table 9-5 and Table 9-6.

Table 9-5 Drug Packaging and Dispensing According to the Planned Dosing Schedule: Initial 52-Week Treatment Period

	Planned Doses (*BID* dosing)			Dose Reductions (*OD* dosing)		
Study Weeks (Days)	**No. of Bottles***	**Evenamide**		**No. of Bottles***	**Evenamide**	
		Starting Dose 15 mg *BID*	**Target Dose 30 mg *BID***		**15 mg *OD***	**30 mg *OD***
1-4 (1-28)	4	64 caps x 15 mg	--	--	--	--
5-8 (29-56)	4	64 caps x 15 mg**	64 caps x 30 mg	2	32 caps x 15 mg	--
9-12 (57-84)	4	64 caps x 15 mg**	64 caps x 30 mg	2	32 caps x 15 mg	32 caps x 30 mg
13-20 (85-140)	8	128 caps x 15 mg**	128 caps x 30 mg	4	64 caps x 15 mg	64 caps x 30 mg

Study Weeks (Days)	Planned Doses (*BID* dosing)			Dose Reductions (*OD* dosing)		
	No. of Bottles*	Evenamide		No. of Bottles*	Evenamide	
		Starting Dose 15 mg *BID*	Target Dose 30 mg *BID*		15 mg *OD*	30 mg *OD*
21-28 (141-196)	8	128 caps x 15 mg**	128 caps x 30 mg	4	64 caps x 15 mg	64 caps x 30 mg
29-36 (197-252)	8	128 caps x 15 mg**	128 caps x 30 mg	4	64 caps x 15 mg	64 caps x 30 mg
37-44 (253-308)	8	128 caps x 15 mg**	128 caps x 30 mg	4	64 caps x 15 mg	64 caps x 30 mg
45-52 (309-364)	8	128 caps x 15 mg**	128 caps x 30 mg	4	64 caps x 15 mg	64 caps x 30 mg

*16 capsules/bottle
**Dispensed only for patients who had tolerability issues at the starting dose and were unable to have their dose increased to the target dose of 30 mg *BID*; or those who, after dropping back from 30 mg *BID* to 30 mg *OD*, were unable to tolerate this dose and required a further dose reduction to 15 mg *BID*.

Table 9-6 Drug Packaging and Dispensing According to the Planned Dosing Schedule: Additional 52-Week Treatment Period

Study Weeks (Days)	Planned Doses (*BID* dosing)			Dose Reductions (*OD* dosing)		
	No. of Bottles*	Evenamide		No. of Bottles*	Evenamide	
		Starting Dose 15 mg *BID*	Target Dose 30 mg *BID*		15 mg o*d*	30 mg o*d*
1-13 (1-91)	13	208 caps x 15 mg**	208 caps x 30 mg	7	112 caps x 15 mg	112 caps x 30 mg
14-26 (92-182)	13	208 caps x 15 mg**	208 caps x 30 mg	7	112 caps x 15 mg	112 caps x 30 mg
27-39 (183-273)	13	208 caps x 15 mg**	208 caps x 30 mg	7	112 caps x 15 mg	112 caps x 30 mg
40-52 (274-364)	13	208 caps x 15 mg**	208 caps x 30 mg	7	112 caps x 15 mg	112 caps x 30 mg

*16 capsules/bottle
**Dispensed only for patients who had tolerability issues at the starting dose and were unable to have their dose increased to the target dose of 30 mg *BID*; or those who, after dropping back from 30 mg *BID* to 30 mg *OD*, were unable to tolerate this dose and required a further dose reduction to 15 mg *BID*.

The patients were instructed to keep the study medication at room temperature (15 to 25° C), as it was stored at the investigational site. All unused study medication and medication bottles were returned to the Sponsor or their designee at the end of the trial or destroyed by the study site upon authorization by the Sponsor. The destruction of unused medication was documented in accordance with ICH E6(R2) GCP guideline.

9.4.3. Method of Assigning Patients to Treatment Groups

Subject Number

Each patient enrolled in the antecedent Study 008A received a six-digit subject number, with the first three digits specifying the center number and the last three digits specifying the subject

at the center. This same subject number was retained for Study 020 to identify the subject, with an additional 3 digits corresponding to the prior study number added at the beginning. For example, subject number 013-103-007 would correspond to the seventh subject enrolled (screened) at center 103 in prior study 013. The subject number was entered in the CRF and appeared in the header of each CRF page.

Patient Enrollment

Only eligible patients with schizophrenia who completed Study 008A were enrolled in this open-label extension study. In addition to violations of inclusion and exclusion criteria, reasons for not enrolling a patient include a major protocol deviation, lost to follow-up, voluntary withdrawal, and study termination; the primary reason was to be noted on the applicable Case Report Form (CRF). Enrollment in the study and dispensing of study medication was done on Day 1 after obtaining the informed consent and all Baseline evaluations (final evaluations from prior study) were completed.

Patient Randomization

Patients were randomized equally into two dose groups (evenamide 30 mg *BID* and placebo *BID*) in the core Study 008A. In Study 020 all the eligible subjects started at a dose of 15 mg *BID* of evenamide and had their dose increased to 30 mg *BID* after 4 weeks, based on tolerability, as per Protocol No. NW-3509/020/III/2021 (more details can be found in the overall design section).

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

9.4.4. Selection of Doses for the Study

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

Evenamide (NW-3509) has a short half-life ranging from 1.6 to 4 hours in volunteers (Study 001), and 2.2 to 2.5 hours in patients with schizophrenia receiving multiple doses of 15 to 25 mg *BID* (Study 002). Therefore, based on the above findings, twice daily (*BID*) dosing was used in the current study, with a decrease to once daily (*od)* dosing permitted if intolerance developed.

The target dose tested in the current study was 30 mg *BID* (60 mg/day). This dose was expected to be well tolerated and within the efficacious dose range, as single doses of 30 mg (Study 001 and Study 010) and 60 mg (Study 010 and Study 011), as well as multiple doses of 25 mg *BID* (Study 002), were well-tolerated. In addition, in a 4-week safety study (Study 008) evaluating doses of 7.5 and 15 mg *BID* in patients receiving concomitant antipsychotic treatment, evenamide was shown to be well tolerated, with no safety risks identified based on an analysis of the safety data, including EEGs, from the 138 patients who were enrolled in the study (see Section 7.1 of the study protocol presented in Appendix 16.1.1).

Systemic concentrations of the metabolite (3-BPAA) were not measured by a validated method in the chronic rat and dog studies. However, in dedicated oral rat toxicity studies with the metabolite, where exposure margins were well in excess of human clinical exposures at 60 mg (the highest single dose given to date), there were no adverse findings in the preliminary study (highest dose 500 mg/kg/day, 3 days, > 450-fold exposure margin). In the main 4-week study, no adverse findings were observed at 100 mg/kg/day (highest dose tested).

9.4.5. Selection and Timing of Dosing for Each Patient

As stated above, based on evenamide's short half-life, twice daily (*BID*) dosing was used in the current study, with a decrease to once daily (*OD*) dosing permitted if intolerance developed.

When patients were taking their medication at their residence, they were instructed to take their dose of study medication at least 10 min after the time of dosing for their concomitant antipsychotic medication (if oral). If possible, 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, containing any unused medication, with them to the clinic. After all safety and efficacy assessments were completed, if there were no safety or tolerability issues, the patient was dispensed their study medication according to the planned dosing schedule. When they were discharged from the clinic, patients were reminded to take their evening dose of the study medication at least 6 hours after the morning dose.

9.4.6. Blinding

This was an open-label study, therefore, the subject, the Investigator, the study staff, the CRO and the Sponsor were aware of the patient's treatment assignment. However, since the prior study was a blinded study, the treatment assignment from that study remained unknown, unless the blind had already been broken.

9.4.7. Prior and Concomitant Therapy

Any medication, in addition to the study medication, that was administered during the study from the time of signing of the consent form at Baseline through the final evaluations at Week 52 in each period must have been recorded in the CRF [including over-the-counter (OTC) medications]. Patients and their caregivers were instructed to contact the Investigator, if possible, for approval prior to taking any new medications, including OTC medications, while residing at home or in a residential care facility and prior to their final evaluation in each period. Restrictions on concomitant medications taken during the treatment period of the study followed the guidelines summarized in Appendix 6 of the protocol provided in the Appendix 16.1.1.

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 *h.s.*, was permitted as a soporific in patients who had been taking it at the time of entry into the study. However, patients were not allowed to start quetiapine (at doses up to 150 mg *h.s.*) for sleep post-Baseline during the study. Also, valproic acid was permitted, if used as a prophylaxis of clozapine-induced seizures, and/or maintenance treatment. Drugs that could increase the risk of seizures, e.g., bupropion, were not permitted.

Rescue Medication and Prohibited Medications

"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 increase of the patient's antipsychotic medication (if not currently at their maximum tolerated dose) or the administration of any other psychotropic medication required to treat the episode.

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

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

The need for administering 'rescue medication' to an individual patient was left to the clinical judgment of the Investigator; however, any of the following changes from Baseline in the patient's status were considered as adequate justification for considering a rescue by making a change in the patient's treatment regimen:

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

If the dose of the patient's current antipsychotic medication was increased by more than 25%, or the rescue medication administered was a drug prohibited by the protocol (e.g., an additional antipsychotic or a mood stabilizer), and use of the medication was not temporary (5 days or less), all final (Week 52) efficacy evaluations were to be performed prior to the start of dosing. Despite this intervention, the patient should have continued in the study and returned for all scheduled efficacy and safety evaluations.

If the dose of a patient's current antipsychotic medication was reduced by more than 25% for safety/tolerability reasons, all final (Week 52) efficacy evaluations were to be performed prior to the dose reduction. Despite this dose reduction, the patient should have continued in the study and returned for all scheduled efficacy and safety evaluations.

Benzodiazepines

Patients receiving chronic dosing with lorazepam or other benzodiazepine at Baseline could continue on this medication. Occasional *prn* dosing with benzodiazepines was also permitted. The lowest possible dose was to be used, and no dose was to be given within 8 hours of a scheduled efficacy assessment.

For patients not currently receiving chronic dosing with lorazepam or another benzodiazepine upon entry into the study, lorazepam 0.5 mg or an equivalent short half-life benzodiazepine (dose not higher than an equivalent of 2 mg/day of lorazepam) was to be used on an as-needed basis to treat episodes of agitation or severe restlessness during the study. The use of *i.m.* lorazepam for emergent agitation was permitted, but only if deemed necessary by the Investigator, and in consultation with the Medical Monitor, if possible.

9.4.8. Treatment Compliance

The first dose of the study medication was administered to the patient in the clinic in the presence of a licensed physician. Following administration of the study drug, appropriate hand

and/or mouth checks were to be performed to ensure that the dose was swallowed. The date, time and number of capsules taken during the in-patient period were recorded on the CRFs.

The study drug was only dispensed to subjects in accordance with the protocol. Monitoring of drug accountability records and information on medication dispensed to subjects in the study was done periodically by a monitor from the CRO.

A pill counting method was utilized to ensure dosing compliance at the subject level.

Dosing compliance (% compliance) was assessed by calculating the number of capsules consumed and comparing that to the number of capsules expected to be consumed as follows:

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

  Where, number of capsules consumed = Sum of number of capsules consumed per kit.

- Number of capsules consumed per kit is calculated as number of dispensed capsules in the kit – number of returned/lost capsules in the kit, if available.

9.5. Safety and Efficacy Variables

9.5.1. Safety and Efficacy Measurements Assessed and Flow Chart

Baseline (OL Baseline, Day 29 of Study 008A/Day 0 of Study 020)

All patients provided written informed consent prior to their participation in this extension trial. The safety and efficacy evaluations performed at the final visit in the prior Study 008A served as the OL Baseline (Day 29 of Study 008A/Day 0 of Study 020) assessments for this extension study. Patients who completed all the final safety and efficacy evaluations in Study 008A, provided informed consent in writing, and satisfied all of the selection criteria, were considered eligible for continuing in this extension study. At the Baseline visit (Day 0), the detailed Baseline schedule of evaluations outlined in Table 9-7 were completed. All patients who were taking clozapine agreed to routine blood monitoring (venipuncture for measuring absolute neutrophil count [ANC] - see Appendix 4 of the protocol presented in the Appendix 16.1.1), with weekly testing (if within 6 months of starting clozapine), bi-weekly testing (if clozapine was started from 6 to 12 months ago), or testing every 4 weeks (if clozapine has been taken for more than 12 months).

Initial 52-Week Extension Treatment Period

Patients who completed all the Baseline evaluations, gave consent for this extension study, and met the eligibility criteria for continuing treatment, received their first dose of study medication in the clinic on Day 1, with a post-dose safety assessment (vital signs, ECG, AEs) approximately 2 hours after dosing. The post-dose assessments of the Study 020 Baseline visit

have been considered as 'Day 1'. If there were no safety concerns, patients were dispensed a supply of study medication for the initial 4-week treatment period and discharged from the clinic. Patients were instructed to begin twice daily dosing the following morning (Day 2) at their residence.

Patients returned to the clinic for scheduled visits at Weeks 4, 8, 12, 20, 28, 36, 44 and 52 (or at early discontinuation). The following evaluations were performed at each of these visits: vital signs, Columbia Suicide Severity Rating Scale (C-SSRS - "Since Last Visit" version), adverse events, and concomitant medications and therapies. All efficacy assessments (PANSS, CGI-S, CGI-C, GAF, LOF and MSQ) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A physical examination was performed at Weeks 28 and 52 (or at early discontinuation). A neurological examination, routine laboratory tests (hematology, biochemistry, urinalysis), and a 12-lead ECG were performed at Weeks 4, 12, 28 and 52 (or at early discontinuation). The standard eye examination and Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A) were conducted at Weeks 12, 28 and 52 (or at early discontinuation). A 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 who were surgically sterilized, at Weeks 12, 28 and 52 (or at early discontinuation). Measurement of serum prolactin was performed at Weeks 28 and 52. Measurement of HbA1c and an assessment of substance abuse, along with a urine drug screen, were conducted only at the final visit (Week 52 or early discontinuation).

At the completion of each visit, if there were no safety or tolerability issues noted after dosing that would necessitate a dose reduction, the patient was dispensed a supply of medication to cover the next period of dosing at the planned dose.

The patient returned for the final evaluation at Week 52 (or at early discontinuation), at which time all final safety [adverse events, vital signs (including BMI), 12-lead ECG, laboratory tests (hematology, biochemistry, urinalysis, serum pregnancy test, HbA1c, serum prolactin), ESRS-A, C-SSRS, physical/neurological examinations, and standard eye examination] and efficacy evaluations were performed. A urine drug screen and assessment of substance use were also performed.

Telephone Contacts

Patients were contacted by the Investigator or a member of their staff at Weeks 2 and 6, between scheduled clinic visits, during the initial dose titration period to inquire about the occurrence of any adverse events or changes in use of concomitant medication. If necessary, based on the information collected, a reduction in the patient's dose was performed, or if there were any significant safety concerns, a clinic visit was scheduled for appropriate follow-up.

Safety Follow-up Evaluation

For patients who discontinued prematurely, as well as those who completed 52 weeks of open-label treatment in this extension study and did not continue further treatment, a safety follow-up visit was performed approximately one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events were performed. Patients who did not return for their 7-day safety follow-up visit were contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patient was contacted minimally 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

Additional 52-Week Extension Treatment Period

The duration of this extension study was increased by one-year, based on approval by the ISMB after an assessment of safety data from ongoing evenamide studies. For this subsequent one-year treatment period there was no dose titration, and patients continued on the same dose of evenamide. During this additional period, clinic visits were conducted every 13 weeks, and telephone contacts with the patient were performed between scheduled visits (Table 9-8). A safety follow-up evaluation, as described above, was performed for any patient who completed this additional period or discontinued prematurely.

Hospitalization

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

Schedule of Evaluations – Initial and Additional 52-Week Treatment Period

The study flow-chart with the schedule of evaluations performed at each visit in the initial 52-week open-label treatment period of study is provided in Table 9-7, and the schedule of evaluations performed at each visit in the additional 52-week open-label treatment period of the study is provided in Table 9-8. Detailed schedules of evaluations along with a narrative description of activities at each visit are provided in the protocol in Appendix 16.1.1.

Table 9-7 Schedule of Evaluations: Initial 52-Week Treatment Period

Assessment / Visit	Baseline (Final Visit of Prior Study) [A]	Week 2	Week 4	Week 6	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52 (Final)[B]	7-Day Safety follow-up[C]
Study Days(s)	**0/1[A]**	**1-14**	**15-28**	**29-42**	**43-56**	**57-84**	**85-140**	**141-196**	**197-252**	**253-308**	**309-364**	**365-371**
Informed consent (for extension study)	X											
Inclusion/Exclusion Criteria	X											
Vital Signs [I]	X[O]		X		X	X	X	X	X	X	X[J]	X
Physical Examination	X							X			X	
Neurological Examination	X		X			X		X			X	
Standard Eye Examination	X					X		X			X	
C-SSRS evaluation	X		X		X	X	X	X	X	X	X	
Substance Use Assessment	X										X	
Urine Drug Screen	X										X	
Laboratory (Hematology, Biochemistry, Urinalysis)	X		X			X		X			X	
Serum Pregnancy Test [D]	X					X		X			X	
HbA1c	X										X	
Serum prolactin	X							X			X	
ECG 12-lead	X[O]		X			X		X	X		X	
ESRS-A	X					X		X			X	
Dose administration and drug label record [H]	X[E]		X[F]		X	X	X	X	X	X	X	
Concomitant Medication and Significant Non-Drug Therapies	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X[O]	X	X	X	X	X	X	X	X	X	X[G]	X
Telephone Contact [K]		X		X								
PANSS [L]	X					X		X			X	
CGI-S [L]	X					X		X			X	
CGI-C [L]	X					X		X			X	

Assessment / Visit	Baseline (Final Visit of Prior Study) [A]	Week 2	Week 4	Week 6	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52 (Final)[B]	7-Day Safety follow-up[C]
Study Days(s)	**0/1[A]**	**1-14**	**15-28**	**29-42**	**43-56**	**57-84**	**85-140**	**141-196**	**197-252**	**253-308**	**309-364**	**365-371**
GAF [L]	X					X		X			X	
LOF [L]	X					X		X			X	
MSQ [L]	X					X		X			X	
Clozapine blood monitoring (venipuncture for measuring ANC) [N]	X	X	X	X	X	X	X	X	X	X	X	
Study Completion											X	X

[A] Final evaluations for the antecedent study served as the Baseline (Day 0) assessments for this extension study (Study 020) and were not repeated. Any listed procedure that was not done at the final visit in the prior study was to be performed at Baseline in this study. The post-dose period on this initial day was considered Day 1.

[B] All Week 52 (Final) evaluations were performed when a subject discontinued from the extension study prematurely.

[C] Performed approximately 7 days after the last dose of study medication for subjects who discontinued prematurely and those who completed the initial 52-week open-label extension treatment period and did not continue further treatment in a subsequent period of the study.

[D] A 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 who were surgically sterilized. Results of the serum pregnancy test performed as part of the final evaluations in the prior study was to be available within 7 days of Baseline for this initial treatment period; if positive, the patient was discontinued from the study.

[E] The first dose of evenamide in the extension study was given after all final evaluations were completed for the antecedent study. The dose was administered at least 6 hours after the morning dose on this day. All patients started on a dose of 15 mg *BID*. If subjects were unable to tolerate this dose, a dose reduction to once daily dosing (15 mg *OD*) might be performed, with an option to increase the dose to 15 mg *BID* if tolerability improved. Patients unable to tolerate 15 mg *OD* were discontinued from the extension study.

[F] All patients had their dose increased from 15 mg *BID* to 30 mg *BID* at Week 4, if the 15 mg *BID* dose was well tolerated. Subjects unable to tolerate 30 mg *BID*, had a dose reduction to 30 mg *OD*, with an option to increase the dose to 30 mg *BID*, if tolerability improved. If the 30 mg *OD* dose was not tolerated, a reduction to the starting dose of 15 mg *BID* was performed.

[G] Patients were contacted minimally 30 days after their final dose to follow up on the occurrence of any SAEs within the 30-day period.

[H] At each scheduled visit, patients were dispensed a sufficient supply of study medication to cover the period until the next scheduled visit. Additional medication was provided in case the visit was delayed.

[I] Vital signs were performed with pulse and blood pressure measured in each of 3 positions (supine, standing 1 min, standing 3 min).

[J] Height was measured at the final visit, in addition to routine vital signs.

[K] Patients were contacted by the Investigator or a member of their staff at Weeks 2 and 6 (between scheduled clinic visits) during the initial dose titration period to inquire about the occurrence of any adverse events or changes in concomitant medication. If necessary, based on the information collected, a reduction in the patient's dose was performed, or if there were any significant safety concerns, a clinic visit was scheduled for appropriate follow-up.
[L] Assessed in patients with schizophrenia.
[N] For patients receiving clozapine, routine blood monitoring (absolute neutrophil count [ANC]) was performed weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or monthly (every 4 weeks) if clozapine was started more than 12 months ago. At visits where routine laboratory testing was scheduled, measurement of ANC was performed as part of the hematology panel.
[O] On Day 1, a safety assessment consisting of vital signs, ECG and adverse events were performed approximately 2 hours after the first dose of study medication in the current study.

Table 9-8 Schedule of Evaluations: Additional 52-Week Treatment Period

Assessment / Visit	Baseline (Final Visit of Previous Period) [A]	Week 6	Week 13	Week 19	Week 26	Week 32	Week 39	Week 45	Week 52 (Final)[B]	7-Day Safety follow-up [C]
Study Days(s)	**1[A]**	**1-42**	**43-91**	**92-133**	**134-182**	**183-224**	**225-273**	**274-315**	**316-364**	**365-371**
Informed consent (for additional extension period)	X									
Inclusion/Exclusion Criteria	X									
Vital Signs	X		X		X		X		X[I]	X
Physical Examination	X				X				X	
Neurological Examination	X				X				X	
Standard Eye Examination	X		X		X				X	
C-SSRS evaluation	X				X		X		X	
Substance Use Assessment	X								X	
Urine Drug Screen	X								X	
Laboratory (Hematology, Biochemistry, Urinalysis)	X		X		X		X		X	
Serum Pregnancy Test [D]	X				X		X		X	
HbA1c	X								X	
Serum prolactin	X				X				X	
ECG 12-lead	X		X		X		X		X	
ESRS-A	X		X		X		X		X	

Assessment / Visit	Baseline (Final Visit of Previous Period) [A]	Week 6	Week 13	Week 19	Week 26	Week 32	Week 39	Week 45	Week 52 (Final)[B]	7-Day Safety follow-up [C]
Study Days(s)	**1[A]**	**1-42**	**43-91**	**92-133**	**134-182**	**183-224**	**225-273**	**274-315**	**316-364**	**365-371**
Dose administration and drug label record [H]	X [E]		X		X		X		X	
Concomitant Medication and Significant Non-Drug Therapies	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X [G]	X
Telephone Contact [F]		X		X		X		X		
PANSS [J]	X		X		X		X		X	
CGI-S [J]	X		X		X		X		X	
CGI-C [J]	X		X		X		X		X	
GAF [J]	X		X		X		X		X	
LOF [J]	X		X		X		X		X	
MSQ [J]	X		X		X		X		X	
Clozapine blood monitoring (venipuncture for measuring ANC) [L]	X	X	X	X	X	X	X	X	X	
Study Completion									X	X

[A] Day 1 of this treatment period corresponded to the final visit (Week 52) of the preceding treatment period, and the evaluations performed at this final visit were not repeated. Patients provided informed consent for this additional treatment period and met all criteria for continuing treatment.

[B] All Week 52 (Final) evaluations were performed when a subject discontinued from the extension study prematurely.

[C] Performed approximately 7 days after the last dose of study medication for subjects who discontinued prematurely and those who completed the 52-week open-label extension treatment period, and did not continue further treatment in a subsequent period of the study.

[D] A 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 who were surgically sterilized. Results of the serum pregnancy test performed as part of the final evaluations in the previous period was to be available within 7 days of Baseline for the current period; if positive, the patient was discontinued from the study.

[E] The first dose of evenamide in this period of the extension study was given after all final evaluations were completed for the preceding period. The dose was administered at least 6 hours after the morning dose on this day. All patients continued on the same dose of evenamide they were receiving at the end of the previous treatment period, unless tolerability issues necessitated a dose reduction.

[F] Patients were contacted by the Investigator or a member of their staff between scheduled clinic visits to inquire about the occurrence of any adverse events or change in concomitant medications. If necessary, based on the information collected, a reduction in the patient's dose was performed, or if there were any significant safety concerns, a clinic visit was scheduled for appropriate follow-up.

[G] Patients were contacted minimally 30 days after their final dose to follow up on the occurrence of any SAEs within the 30-day period.
[H] At each scheduled visit, patients were dispensed a sufficient supply of study medication to cover the period until the next scheduled visit. Additional medication was provided in case the visit was delayed.
[I] Height was measured at the final visit, in addition to routine vital signs.
[J] Assessed in patients with schizophrenia.
[K] Assessed in patients with bipolar disorder.
[L] For patients receiving clozapine, routine blood monitoring (absolute neutrophil count [ANC]) was performed weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or monthly (every 4 weeks) if clozapine was started more than 12 months ago. At visits where routine laboratory testing was scheduled, measurement of ANC was performed as part of the hematology panel.

9.5.1.1. Safety Assessments

The assessment of safety was based on the following:

- Adverse events (AEs) - subjective reporting and objective observation,
- Vital signs (systolic/diastolic blood pressure, pulse, body weight, body temperature, respiratory rate and BMI),
- Laboratory tests (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),
- C-SSRS,
- ESRS-A

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 subjects 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 Study 020 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 a highly effective contraception method (i.e., a method that can achieve a failure rate of less than 1% per year when used consistently) were not eligible for the study. The use of contraception should have been initiated at least 28 days before the first dose and continued until 30 days after stopping study medication. As a further precaution, a serum pregnancy test was performed for all women [excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or who had been surgically sterilized], at Baseline (final visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial period of the study and every 13 weeks in the additional period. The results of the serum test at Baseline in each treatment period were to be available within 7 days of starting treatment. Additional serum or urine pregnancy tests could be performed, as needed, based on local requirements.

If a patient became pregnant during the study, she was to be discontinued from the study immediately. The Investigator was to report all pregnancies, within 24 hours of discovery or notification by the patient, to the CRO by email or by fax using the Pregnancy Reporting Form. The timelines and other reporting requirements were the same as for 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 she 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 one year after delivery of the baby, and any premature terminations were to be 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 clinic visits in the initial and additional treatment periods of the study, as mentioned in the schedule of evaluations (Table 9-7 and Table 9-8). At OL Baseline, vital signs were assessed as part of the final visit of the prior study

(Study 008A Day 29) and approximately 2 hours after the first dose (Study 020 Day 1). Vital signs included body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. For all vital sign assessments, pulse and blood pressure were measured after the subject had been in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing. Additionally, height (used to calculate BMI) was measured at OL Baseline (final visit of prior study) and at Week 52 (or at early discontinuation) in each period of the study.

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 Baseline (final visit of prior study) and at Weeks 4, 12, 28 and 52 (or at early discontinuation) in the initial period, and every 13 weeks in the additional treatment period (Section 9.5.1). Evaluations of the hematology, blood chemistry and urinalysis analytes listed in Table 9-9 were performed at each of the visits. In addition, a serum pregnancy test was performed at Baseline (final visit of prior study) and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial period of the study and every 13 weeks in the additional period for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or surgically sterilized. Measurement of HbAlc was performed at Baseline and at the final visit (Week 52 or at early discontinuation) in each of the study periods. Serum prolactin was measured at Baseline and at Weeks 28 and 52 in the initial period and Weeks 26 and 52 in the additional period to assess the effect of the concomitant antipsychotic medication, as well as any potential effect of evenamide treatment, on prolactin levels.

Table 9-9 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

- *HbA1c*
- *Serum prolactin (Baseline and final visit)*
- *Serum pregnancy tests – for all women, excepting those who were post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or were surgically sterilized.*
- *Urine drug screen*

Subjects underwent a urine drug screen at Baseline (last visit of prior study/period) and at the final visit (Week 52 or early discontinuation) in each period of the study, along with an assessment of substance use. 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, propoxyphene, tricyclic antidepressants). Subjects with positive urine results for any substances of abuse (except THC) were excluded from the initial period of the study or from continuing in an additional treatment period. These cases should have been discussed with the Medical Monitor if the patient was being considered for enrollment.

The Investigator reviewed laboratory values from the prior study that were available at Baseline, prior to the first administration of the study medication, to ensure that the subject fulfilled the protocol's inclusion/exclusion criteria. Abnormal tests at any visit were repeated if necessary. 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 normal when it fell on or within the upper and lower limits of the reference range. A value was 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, 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 labelled 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 was symptomatic was recorded on the Adverse Events CRF.

Refer to Section 13.0 of the protocol presented in Appendix 16.1.1, "Reporting Safety Information" for further directions.

9.5.1.1.6. Electrocardiogram (ECG)

All the subjects had a standard 12-lead ECG performed at OL Baseline (final visit of the prior study – Pre-dose, and approximately 2 hours after first dose [Day 1]) and at Weeks 4, 12, 28 and 52 (or at early discontinuation) in the initial period, and every 13 weeks in the additional treatment period, as mentioned in the schedule of evaluations (Table 9-7 and Table 9-8, Section 9.5.1). If the ECG was abnormal at Baseline, the evaluation was repeated, and if no clinically significant abnormalities were noted, the patient was eligible for the study.

To ensure consistency in the data analysis across subjects, all ECGs were sent to a central ECG monitoring service (IQVIA) for review and interpretation; however, the 'real-time' review and interpretation of the 12-lead ECGs that were used for determination of a subject's eligibility for enrollment in the trial, as well as post-dose safety monitoring, were performed by a physician at the investigational site. The ECG parameters included numerical values for heart rate and RR, PR, QRS, QT, QTcB, and QTcF intervals, as provided by the central ECG service. One copy of the ECG tracing was retained in the subject's records, one was retrieved by the monitor, and a third one 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 used for all statistical analyses.

Each ECG tracing had the following information entered on it:

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

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

9.5.1.1.7. Physical Examinations

A physical examination was performed at OL Baseline (final visit of prior study), Weeks 4, 12 and 28, and at the final visit (Week 52 or at early discontinuation) in the initial period, and it every 26 weeks in the additional treatment period. 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 OL Baseline (final visit of prior study), Week 28, and at the final visit (Week 52 or at early discontinuation) in the initial period, and every 26 weeks in the additional treatment period. The findings were entered on the Neurological Examination section of the CRF. The neurological examination included the following assessments: evaluation of mental status, cranial nerves, muscle strength and tone, reflexes, the sensory system, coordination, and gait.

9.5.1.1.9. Standard Eye Examination

A standard eye examination, comprising assessments of visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and the front part of the eyes (eyelids, cornea, conjunctiva, sclera, and iris) were performed at OL Baseline (final visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial treatment period, and every 26 weeks in the additional treatment period. At the site, a physician with appropriate experience and training performed the examination. If a clinically significant abnormality was noted that required expert follow-up, an Ophthalmologist or Optometrist was consulted.

9.5.1.1.10. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al., 2007; Posner et al., 2011) is a standardized suicidal rating system. Its use is recommended by the US Food and Drug Administration (FDA). This version collects information on the lifetime history of suicidality, as well as information on ‘suicidal ideation’ over the past month and ‘suicidal behavior’ over the past 2 years. The ‘Since Last Visit' version of the C-SSRS was performed at every clinic visit in both the initial and additional treatment periods. Follow-up assessments were performed at each scheduled visit at Weeks 4, 8, 12, 20, 28, 36, 44, and at the final visit (Week 52 or early discontinuation).

9.5.1.1.11. Substance Use assessment

A substance use assessment was performed for summarizing the use of any abusive substance by any subject during the study period. The assessment was performed at Baseline and Week 52/early withdrawal for the initial and additional treatment periods of Study 020.

9.5.1.1.12. Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)

The ESRS-A is a 24-item symptom scale and 4-item CGI scale designed to examine changes in motor function associated with pharmacologic treatment (Alphs et al., 2010; Alphs and Chouinard, 2006). Major motor symptoms assessed included those of parkinsonism, dystonia, dyskinesia, and akathisia. Parkinsonism is further subclassified with assessments of rigidity, tremor, reduced facial expression, impaired gait, postural instability, and bradykinesia. All

items, including the Clinical Global Impressions of parkinsonism, dystonia, dyskinesia, and akathisia, were rated on a 0 to 5 scale (absent, minimal, mild, moderate, severe, extreme).

The ESRS-A was performed at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial treatment period, and every 13 weeks in the additional treatment period.

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 will develop these complications comprising a metabolic syndrome. Metabolic complications and obesity are commonly found in patients treated with clozapine (Zimbron et al., 2016). 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 had an extensive treatment history with antipsychotics and other psychotropic drugs, a number of parameters were evaluated to assess the presence of metabolic syndrome at screening, and to monitor its progress over the course of the study to assess any potential effects of evenamide. These parameters included HbA1c, in addition to the 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), measured during the study.

9.5.1.1.14. Independent Safety Monitoring Board (ISMB)

An independent board of knowledgeable experts appointed by Newron safeguarded subjects participating in this trial by reviewing unblinded safety data on an ongoing basis. The main reasons for the Sponsor 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 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 ISMB increased the effectiveness of safety monitoring by supplementing usual activities performed under the Sponsor's study-specific safety monitoring plan.

Details of Independent Safety Monitoring Board (ISMB) are provided in the Section 13.2 of the protocol provided in the Appendix 16.1.1.

9.5.1.2. Efficacy Assessments

All efficacy measures were assessed at Baseline (final visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial treatment period, and every 13 weeks in the additional treatment period.

Efficacy related Endpoints

Primary Efficacy Endpoint

PANSS total score – mean change from Baseline to endpoint (Week 52 or early discontinuation)

Secondary Efficacy Endpoint

The secondary efficacy endpoints were:

- CGI-S – mean change from Baseline to endpoint (Week 52 or early discontinuation)
- CGI-C – mean rating at endpoint and proportion of patients with improvement from Baseline to endpoint (score of 1, 2 or 3)
- PANSS total score – proportion of patients with at least 20% improvement and at least 30% improvement from Baseline to endpoint

Other Secondary Efficacy Endpoints

- LOF – mean change from Baseline to endpoint (Week 52 or early discontinuation)
- MSQ – mean change from Baseline to endpoint (Week 52 or early discontinuation)
- GAF – mean change from Baseline to endpoint (Week 52 or early discontinuation)

9.5.1.2.1. *Positive and Negative Syndrome Scale (PANSS)*

The PANSS (Kay et al., 1987) is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The 30 symptoms are each rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms, and gauge 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 assessment was conducted at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial period, and every 13 weeks in the

additional period, and was used as the primary efficacy measure in the trial. The rater for the PANSS was an MD, clinical psychologist, or other clinicians with extensive training and experience in performing the clinical interview and rating the scale.

9.5.1.2.2. Clinical Global Impression (CGI)

The CGI (Guy, 1976) is the general name for 2 scales: the CGI-Severity (CGI-S) measures global severity of illness at a given point in time, and the CGI-Change (CGI-C) measures change from the Baseline state at each post-Baseline visit. In this study, the ratings of the CGI-S and CGI-C were performed by a clinician who was involved in the management of patient care. Whenever possible, the CGI scales were completed by the same clinician for every assessment; if this was not possible, the rating clinician reviewed the subject's presentation (along with the review of clinical notes) with the rater who completed the initial evaluation.

The CGI rating scale permits a global evaluation of the patient's improvement over time. At Baseline, a CGI-S was performed in which the investigator had to rate the severity of a patient's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). At subsequent visits, the investigator assessed the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at Baseline using the CGI-C, a 7-point scale, ranging from 1 ('very much improved') to 7 ('very much worse'), with a score of 4 indicating "no change". The CGI-S and CGI-C assessments were conducted at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial 52-week treatment period, and every 13 weeks in the additional 52-week treatment period. The patient's condition at the time of OL Baseline (Study 020) was considered when assessing the CGI-C.

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. Notes were taken at the Baseline assessment for use in assessing change at subsequent visits.

9.5.1.2.3. Global Assessment of Functioning Scale (GAF)

The GAF (Jones et al., 1995) assigns a clinical judgment in numerical fashion to the individual's overall level of functioning. It is a clinician-rated scale that takes only seconds to complete after a patient has been evaluated. It is very widely used in clinical and research settings with reliability ranging from 0.62 to 0.82. Impairments in psychological, social, and occupational functioning are considered, but those related to physical or environmental limitations are not. The GAF should be used to rate functioning for the current period (i.e., the level of functioning at the time of the evaluation).

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

The GAF assessment was performed at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial 52-week period, and every 13 weeks in the additional 52-week period.

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

The LOF has been widely used as an instrument to evaluate clinical outcomes 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 were 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 are calculated as the mean scores for items in each scale. A total score is calculated as the sum of the raw scores across the nine items. Interrater 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 assessment was conducted at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial period, and every 13 weeks in the additional 52-week period.

9.5.1.2.5. Patient's Medication Satisfaction Questionnaire (MSQ)

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

controlled study comparing antipsychotic treatments in patients with schizophrenia experiencing an acute exacerbation and was able to show a statistically significant difference between treatment groups in satisfaction with the medication (Potkin et al., 2006). The MSQ was assessed at OL Baseline (last visit of prior study), and at Weeks 12, 28 and 52 (or at early discontinuation) in the initial 52-week period, and every 13 weeks in the additional 52-week period.

9.5.1.2.6. Rater Training

The raters, who must have demonstrated competence in administering scales used in clinical trials, were trained and certified for the PANSS and CGI using the Newron dedicated platform and its training program to minimize the inter- and intra- rater variability. The same rater performed all the ratings for a given patient throughout the study; this applies to the PANSS and CGI raters.

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 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 12.3.8 of the Study Protocol presented in Appendix 16.1.1.

9.5.2. Appropriateness of Measurements

Assessment of long-term efficacy of evenamide is an objective of this study. The efficacy of evenamide in treating symptoms in patients with schizophrenia was assessed using the Positive and Negative Syndrome Scale (PANSS) as the primary measure, and the Clinician's Global Impression - Change from Baseline (CGI-C) and Severity of illness (CGI-S) as secondary measures. The PANSS is a standard scale for assessing the individual symptoms of schizophrenia and has been widely used as the primary efficacy measure in many antipsychotic trials.

The effect of evenamide on general functioning was assessed using the Global Assessment of Functioning (GAF) scale. The effect of evenamide on patients' daily functioning was evaluated using the Strauss-Carpenter Levels of Functioning scale (LOF). The Medication Satisfaction Questionnaire (MSQ) was completed by the patient and used to evaluate the patients' satisfaction with the study medication, compared to their previous treatment.

A benefit/risk assessment for evenamide, based on preclinical and clinical data collected to date, is provided in Appendix 5 of the protocol provided in Appendix 16.1.1.

9.5.3. Primary Efficacy Variable(s)

The efficacy of evenamide in treating the symptoms of schizophrenia was assessed using the PANSS, which was used as the primary efficacy measure in this study. Additionally, the CGI-C and CGI-S were used as the secondary efficacy 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 Investigator made and would make all pertinent records, including source documentation, available for inspection by regulatory authorities and for auditing by the Sponsor. This information was considered confidential. Audits/Inspections might occur any time from start to after conclusion of the study. When an Investigator signs the protocol, he/she agrees to allow regulatory authorities and Newron auditors to inspect his/her study records. 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 were recorded on electronic Case Report Form (eCRF) for all subjects who signed the ICF. 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 Investigator, or designated representative, was requested to complete the source document/eCRF as soon as possible after information was collected, preferably on the same day that a study subject was seen for an examination, treatment, or any other study procedure. Any outstanding entries were to be completed immediately after the final examination. An explanation was given for all the missing data. No section of the eCRF was left blank without an appropriate explanation by the Investigator, since the lack of such an explanation might necessitate discarding an otherwise usable observation. Paper copies of the eCRFs for the patient rating scales (e.g. PANSS, CGI, GAF, LOF, MSQ, ESRS-A, and C-SSRS) were printed and used by the Investigator or designated staff during the assessment of the patient. Data recorded on these paper forms were transcribed into the eCRF, and the original forms stored in the patient's file as source documents. If requested, copies of the eCRFs were made available to the appropriate regulatory agencies. The eCRFs were only considered to be completed when each eCRF had been reviewed and electronically confirmed

by the Investigator, indicating his/her assurance of the accuracy of all recorded data. A sample eCRF is provided in Appendix 16.1.2.

9.6.1.2. Study Monitoring

A CRO was selected by the Sponsor to oversee the conduct of the trial. An appropriate representative of the CRO (Study Monitor) maintained contact with the Investigator and visited the study site to discuss and/or retrieve data. An initiation visit 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 was required to allow the Study Monitor to perform these periodic, interim monitoring visits. The purposes of these visits were:

- To verify that written Informed Consent was obtained before each subject's participation in the trial,
- 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 CRFs for accuracy and completeness,
- To validate the contents of the CRFs against source documents,
- To assess the status of drug storage, dispensing and retrieval.

The Investigator made available the source documents for inspection. This information was considered confidential. Violations of and deviations from the protocol were notified to the Study Monitor as soon as possible.

The Study Monitor performed a closeout visit at the time when all eCRFs were completed, all queries answered, and all open issues at site properly resolved.

9.6.1.3. Audits and Inspections

Inspections were conducted at two sites in Argentina (Site nos. 894 and 941). A brief summary of these inspections is provided below.

- Argentina:
    - Jurisdictional Authority of Mendoza (DICYT) - Site 894 (15th and 17th January 2024) and Site 941 (20th March 2024)

- Comite Independiente de Etica (CIE) - Site 941 and 894 (15th March 2024), ethical monitoring of the sites.

No critical findings were identified in any of the inspections. None of the sites were requested to put activities or screening on hold. All corrective and preventive actions (CAPAs) were implemented.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

The statistical analysis of the data obtained from this study was the responsibility of CliniRx Tangent Research India Pvt Ltd. Full details of the statistical methods are outlined separately in the Statistical Analysis Plan (SAP) located in Appendix 16.1.9 of this CSR. The SAP was finalized and approved before the clinical database lock.

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

Table, Listing and Figure (TLF) shells were provided separately. Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM) data were used to create the subject TLFs.

The SDTM data followed SDTM version 1.7 together with SDTM Implementation Guide version 3.3 and the SDTM Controlled Terminology version 2023-09-29. ADaM data followed ADaM version 2.1 together with ADaM Implementation Guide version 1.1/ ADaM Controlled Terminology version 2023-06-30. Both SDTM and ADaM data were validated using Pinnacle 21 version 4.1.0. Any discrepancies in the validation were noted in reviewer's guides accompanying the final data transfers.

9.7.1. Statistical and Analytical Plans

9.7.1.1. *Analysis Populations*

The following populations were defined for analysis purposes:

Rolled Over Population

The "Rolled Over" Population consisted of those subjects who were randomized and completed the prior Study 008A, met all selection criteria for this open-label extension study, and signed the ICF for this extension study (Study 020).

Safety Population

The Safety population consisted of those subjects who took at least one dose of study medication in this extension study. All safety and tolerability analyses were based on the Safety population.

Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population comprised those subjects who had an OL Baseline *(Day 29 of double-blind Study 008A/Day 0 of Study 020)* efficacy assessment, received at least one dose of the study medication in this extension study and had at least one post-OL-Baseline efficacy assessment for the PANSS.

All efficacy endpoints analyses were performed using the mITT population.

Retrieved Dropout (RDO)

The retrieved dropout population (RDO) was defined as subjects who discontinued treatment, but agreed to continue in the study, and returned for assessment at applicable scheduled visits for selected efficacy parameters (PANSS, CGI-S and CGI-C) including the final assessment at Week 52. There were no subjects in the RDO population in this study.

9.7.1.2. *General Considerations*

All data collected in this study were documented using patient data listings, summary tables, and figures, as applicable.

Summary tables included data for the Initial 52-Week Treatment Period only. Efficacy and safety data collected beyond Week 52, i.e. in the Additional 52-Week Treatment Period, were listed but not utilized for analysis, due to the limited sample size.

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 frequencies and percentages. The percentages were derived based on the total number of subjects in the treatment group within the specified population.

The mean and median were reported to an additional 1 decimal place, and the 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 point; except the percentage was not presented when the count was zero or 100%, which were presented as an integer. The values were rounded to the specified decimal places as above.

Long Text Handling: Data fields of long texts were not retained in listings due to page size limitations. However, the full texts were included in the study datasets.

Baseline(s) determination for efficacy and safety

Two Baselines were considered for the analyses: the double-blind Baseline of core Study 008A (Study 008A Day 0, referred to as "DB Baseline") and the open-label Baseline of the extension Study 020 (Study 008A Day 29/Study 020 Day 0, referred to as "OL Baseline"). The open-label Baseline of Study 020 comprises evaluations performed on Day 29 of Study 008A and on Day 0 of Study 020.

Efficacy analyses were repeated using both Baselines, while safety analyses were performed considering a *mixed Baseline* approach, depending on the treatment received in the double-blind Study 008A: the DB Baseline (Study 008A Day 0) was used for subjects randomized to evenamide in Study 008A and continuing treatment with evenamide in Study 020; the OL Baseline (Study 008A Day 29/Study 020 Day 0) was used for subjects randomized to placebo in Study 008A and switched to evenamide in Study 020.

Data Sources:

Some of the data fields from the prior study (Study 008A) were used for the analysis of the extension Study 020. Table 9-10 below describes the data sources with details for the various types of data.

Table 9-10 Data Sources

S. No.	Data (eCRF panel)	008A -Screening	008A - Baseline	008A – Day 29	020 - Baseline	Data Processing rules
1	DM	X (Race, ethnicity, education, marital status, employment and housing status)	Weight[@]		X (age, sex, childbearing potential, height, weight and substance use)	DM CRF annotation was related to 020 study only.
2	ICF				X	
3	Inclusion/Exclusion				X	
4	Disease Characteristics	X				
5	Medical History	X				
6	Psychiatric History	X				
7	Prior Antipsychotic medication	X				
8	Vital Sign		X		X (other than WC)	WC not included.

S. No.	Data (eCRF panel)	008A -Screening	008A - Baseline	008A – Day 29	020 - Baseline	Data Processing rules
9	Physical Examination				X	
10	Neurological Examination				X	
11	Standard Eye Examination				X	
12	C-SSRS				X	
13	ESRS-A				X	
14	Laboratory evaluations			X		Borrowed from CDISC SDTM 008A Day29.
15	ECG				X	Due to Post 2hrs assessment in Study 020 which was not available in prior study.
16	AE					Not applicable
17	CM/CPM					Not applicable
18	PANSS		X		X	
19	CGI-S/C		X		X	
20	LOF/MSQ		X		X	
21	GAF		X		X	New panel
22	CLZ blood monitoring				X	Not applicable
23	Substance use assessment				X	
24	Urine drug screen				X	
25	Sample collection				X	
26	Urinalysis				X	
27	Serum prolactin				X	

@ For subjects treated with evenamide in Study 008A and Study 020 (EVN-EVN), the Study 008A Baseline was used.
WC = Waist Circumference.

First Dose Date of Study 020 (Day 1): First dose date of Study 020 (Day 1) was considered as the starting point for determining the *treatment compliance*. The treatment start date was taken from the Study 020 Day 1 visit date, when the first IMP kit was dispensed in this extension study.

Last Dose Date: Last dose date available in the Study Completion/Termination form in the eCRF was considered, as applicable.

Week 52/ Early Termination visit **-** All Week 52 evaluations were to be performed when a subject discontinued from the study prematurely before completing the 52-week treatment period. Early withdrawal efficacy data were shown with the closest scheduled visit in the SAS listings and tables; data were grouped with the next scheduled visit if the prior visit was completed as planned. Safety data of early withdrawal subjects was not allocated to the closest visit and was shown as reported in eCRF.

Study Completion and Discontinuation: The study completion date of any patient was the Initial Week 52 or the Additional Week 52, as applicable, irrespective of whether the subject attended the Safety Follow-up (SFUP) visits or not.

The date of discontinuation was the date captured in the Week 52 visit(s), regardless of the date on which the last dose of study medication was administered.

Unscheduled Visits: All unscheduled visit data was listed. For the efficacy analysis, the closest unscheduled assessment data were utilized in case scheduled visit data were not available. In case of duplicates (both sets of data are available), unscheduled visit data were ignored from the analysis.

Missing Safety Data Dates: Partial or completely missing dates for any medications were imputed using the guidance in Appendix 5 of the SAP document presented in the Appendix 16.1.9.

9.7.1.3. *Missing Data Imputation*

No imputation of efficacy data was performed.

9.7.1.4. *Rescue and Prohibited Medications*

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

If a new antipsychotic or other psychotropic medication was initiated to treat the exacerbation, with a start date after Baseline, this would be considered "rescue medication" and should have an indication of "worsening psychosis" or "worsening of schizophrenia symptoms".

A table was provided to summarize the names of rescue medications taken during the study. A subject data listing of the rescue medication details was also presented for the safety population.

The following rules were applied to subjects who received rescue medication, as applicable:

- Efficacy data collected post rescue medication will be flagged in the listings and a footnote added to explain, if applicable.

Clozapine was not permitted as a rescue medication but was allowed as a current antipsychotic medication.

9.7.1.5. *Stratification Factor*

Not applicable as no randomization was performed.

9.7.1.6. *Center Effects*

Patients were enrolled from a total of 8 sites: 2 sites in Italy and 6 sites in Argentina. As this was a small-size, single-arm study, no site (center) effects were evaluated. However, summary statistics might be generated as per site or country, if required.

9.7.1.7. *Adjustments for Multiplicity*

Not applicable.

9.7.1.8. *Analysis Visits*

Analysis visit is only applicable for efficacy analyses for the initial 52-week treatment period. Scheduled visits were designated as analysis visits.

'Analysis visit 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.

9.7.1.9. *Visit Windows*

A window of ± 4 days was allowed on scheduled visits at Weeks 4, 8 and 12, and on the telephone contacts at Weeks 2 and 6. A window of 3 to 14 days after the final dose was permitted for performing the safety follow-up visit (approximately 7 days after last dose). A window of ± 7 days was allowed on scheduled visits at Weeks 20, 28, 36, 44 and 52. A window of ± 12 days was allowed on scheduled visits at Weeks 13, 26, 39 and 52, and on the telephone contacts at Weeks 6, 19, 32, and 45, in the additional treatment period. Sufficient additional study medication was dispensed at each visit to cover the extra days of dosing, according to the allowed visit windows, in case a visit was delayed. If a visit was delayed outside the specified window, additional medication could have been prescribed and delivered to the patient, if feasible.

9.7.1.10. *Subject Disposition*

The number and proportion of subjects in each analysis population (Safety and mITT populations), and disposition category (completed study, discontinued, or early withdrawal with a breakdown of the reasons for early discontinuation) were displayed by Initial 52-Week and Additional 52-Week treatment periods. The number of subjects was shown by randomized

group assignment in the prior Study 008A, i.e. evenamide in the core study and continued evenamide in the extension study (EVN-EVN), and placebo in the core study and switched to evenamide in the extension (PLC-EVN), along with the overall number of subjects in the study.

9.7.1.11. *Protocol Deviations*

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

9.7.1.12. *Demographic and Baseline Characteristics*

The demographic characteristics and Baseline characteristics (age, sex, childbearing potential, height, weight, race, ethnicity, education, marital status, employment, housing status, substance use) collected at Baseline(s) were summarized by EVN-EVN, PLC-EVN, and overall, for the Safety and mITT populations.

Race, ethnicity, education, marital status, employment and housing status data have been taken from Study 008A. Age, sex, childbearing potential and height data have been taken from Study 020. Weight data has been taken from Study 008A for EVN-EVN subjects and from Study 020 for PLC-EVN subjects.

Demographics and baseline characteristics were presented in individual subject data listings for the Safety Population.

9.7.1.13. *Disease Characteristics*

The disease characteristics, including duration of illness, duration of current episode, number of psychiatric hospitalizations, and family history of schizophrenia, 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 was calculated as:

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

9.7.1.14. *Inclusion/Exclusion Criteria*

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

9.7.1.15. *Medical History*

Medical history was coded using the latest Medical Dictionary for Regulatory Activities (MedDRA v24.0). Summaries were presented for the Safety Population by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages. Each subject was counted only once in each SOC or SOC/PT summary. An individual subject listing was provided with all levels of MedDRA hierarchy for all subjects.

9.7.1.16. *Psychiatric History*

The count and percentage of subjects in each of the reported psychiatric history categories were provided for the Safety Population. Subject level data listings were provided for psychiatric history of schizophrenia and other psychiatric disorders.

9.7.1.17. *Prior and Concomitant Medication*

Prior medications were considered as those medications that have a start date and end date before ICF signature (Study 020 ICF date).

Concomitant medications were considered as those medications taken at any time during the Study 020, irrespective of the start date.

Prior and concomitant medications were coded using the WHO Drug Dictionary B3 Mar2021. Medications were presented for the Safety Population by Anatomical Therapeutic Chemical (ATC) level 4 and Preferred Name (PN) with counts and percentages. 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, if applicable.

9.7.1.18. *Prior and Current Antipsychotic Medication*

Data on prior antipsychotic medications were taken from the antecedent Study 008A and included prior antipsychotic medications stopped before the ICF date of Study 008A, as well

as the current antipsychotic medications of Study 008A, which were stopped before the ICF date of Study 020.

Current antipsychotic medications of Study 020 are those antipsychotic medications taken by subjects during this extension study, irrespective of the start date, and collected in the CRF under "Current Psychotropic Medication".

The prior and current antipsychotic medications were summarized by evenamide 30 mg *BID* treated group for the Safety population.

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

ANC levels measured during routine clozapine blood monitoring were listed.

9.7.1.19. *Concomitant Procedures*

Listing and summary counts of concomitant procedures were presented.

9.7.1.20. *Study Drug Accountability*

Study drug accountability data was presented as an individual data listing by patient.

9.7.1.21. *Safety and Tolerability Analyses*

9.7.1.21.1. Exposure and Treatment compliance

A drug exposure table summarizes the duration of exposure and treatment compliance in the extension Study 020 for the Safety Population. The duration of exposure was calculated as the number of days from treatment start date (from Study 020 Day 1) to treatment end date (Study 020 Week 52 or early discontinuation).

Dosing compliance (% compliance) was assessed by calculating the number of capsules consumed and comparing that to the number of capsules expected to be consumed as follows:

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

  Where, number of capsules consumed = Sum of the number of capsules consumed per kit.

- Number of capsules consumed per kit calculated as number of dispensed capsules in the kit – number of returned/lost capsules in the kit, if available.

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.

The number of capsules expected to be consumed per kit was estimated as 2* (Last dose date – First dose date +1).

Compliance was summarized overall.

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, were provided. Note that more than one reason per subject could be provided for dose adjustment, kit replacement and 'other', 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.

9.7.1.21.2. Adverse Events

Adverse events were coded according to the MedDRA version 24.0.

Treatment-emergent AEs (TEAEs) are adverse events that are newly occurring or worsened in severity, compared to pre-existing condition, after the first administration of the study medication in Study 020. The following criteria were used to define treatment emergence for AEs with missing start or stop dates/time (if available):

- 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 falls after the first dose date, then the event was considered treatment-emergent,
- If the start date was the same as the first dose date, then based on time (after dose) that event was considered treatment-emergent. In case of a missing onset time and start date was same as first dosing date, the AE was also considered as 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 system organ class (SOC) and preferred term (PT).

AE summary tables included the following:

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

Treatment-related TEAEs were the TEAEs which are considered possibly or probably related to the study drug, or the relationship is 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. Any safety information collected during the 7/30-day safety follow-up period was also listed. All the TEAEs reported beyond 30 days after the administration of the last dose of study medication were included in the listing and marked appropriately.

9.7.1.21.3. Vital Signs

Tables presenting descriptive statistics for all the observed vital signs (temperature, respiratory rate, pulse, weight, BMI, systolic blood pressure and diastolic blood pressure) were provided. Changes from Baseline at each post-dose visit/timepoint, as applicable, were presented for the single evenamide 30 mg *BID* group.

Table 9-11 below describes vital signs data collection in the study.

For the change from Baseline calculation, DB Baseline was considered for EVN-EVN subjects and OL Baseline for PLC-EVN subjects.

Based on Appendix 2 of the SAP document presented in Appendix 16.1.9, counts and percentages of subjects meeting the clinically notable abnormalities criteria at each visit were provided.

Listings were presented in three parts: Individual subjects listing with change from Baseline (one subject all parameters), time profile (by parameter all subjects), and newly emergent clinically notable abnormalities.

Unscheduled visit data or 2 hr post-dose data from the Initial 52-Week period, or data from the Additional 52-Week period, were listed but not included in analysis.

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

Table 9-11 Vital Signs database structure and instructions for tables and listings

Visit	Time-point	Weight	Height	BMI	RR	Temperature	Position	Pulse	SBP	DBP
DB Baseline (008A)		Y			Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							Standing 3 min	Y	Y	Y
Initial Week 52 treatment period scheduled visits										
OL Baseline (020/Day 0)	Pre-dose	Y	Y	Y	Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
	2hr post dose	Y	Y	Y	Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
Weeks 4, 8, 12, 20, 28, 36, 44	Any time	Y			Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
Week 52	Any time	Y	Y	Y	Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
Safety Follow-Up-7 Days		Y			Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y

Visit	Time-point	Weight	Height	BMI	RR	Temperature	Position	Pulse	SBP	DBP
Additional Week 52 treatment period scheduled visits										
Weeks 13, 26, 39	Any time	Y			Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
Week 52	Any time	Y	Y	Y	Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y
Safety Follow-Up - 7 Days		Y			Y	Y	Supine 5 min	Y	Y	Y
							Standing 1 min	Y	Y	Y
							standing 3 min	Y	Y	Y

For Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Pulse, Weight, Respiratory rate (RR) and Temperature: Change from Baseline = Post Dose - Avg DB Baseline for EVN-EVN subjects, otherwise Post Dose – Pre-Dose OL Baseline for PLC-EVN subjects.
Post- Dose Body Mass Index (BMI) = Weight (Kg) / [Height (m)]^2. Consider Baseline BMI from 008A SDTM VS data, as required.
Orthostatic Hypotension = Supine 5 min - Standing 1 min or Standing 3 min.

9.7.1.21.4. Clinical Laboratory Evaluation

Two central laboratories, Trilab for sites in Argentina and Medpace for sites in Italy, performed laboratory examinations scheduled at selected post-Baseline visits (Weeks 4, 12, 28 and 52 in the Initial 52-Week period and Weeks 13, 26, 39 and 52 in the Additional 52-Week period).

Q2 lab, the central laboratory used in previous Study 008A, reported OL Baseline laboratory results (collected at Day 29 of core Study 008A) for Italian subjects in SI units and for Argentinian subjects in conventional units.

Trilab data were captured in the eCRF, while the rest of lab data were received as external data transfers (from Q2 Lab and Medpace).

Table 9-12 provides more details on data sources and lab vendors.

Table 9-12 Safety Lab Vendors Details

Data Source	Lab Name	Details
eCRF	Trilab	Study 020 post-Baseline data are captured in eCRF; Argentinian subjects.

External Data Transfer	Q2 Central Lab	Baseline laboratory data (Day 29 of Study 008A)
	Medpace Central Lab	Study 020 post-Baseline data; Italian subjects.

SI unit conversion and Normalization:

Lab values (units and reference range as well) were converted into SI units to determine clinically notables for those labs who have not provided results in SI units. Appendix 4 of the SAP document presented in Appendix 16.1.9 provided details of individual labs' SI units and reference ranges.

After SI unit conversion, normalization was performed to generate summary tables using the formulas presented below.

Trilab has been considered as the standard laboratory for normalization of data from other laboratories involved in the study.

Normalization was performed as follows.

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

1) Location-scale normalization formula

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

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

There is a possibility that a derived value becomes negative when there is only a one-sided reference limit (i.e., ALP, ALT, AST, Bilirubin total, Cholesterol, CPK, Creatinine, GGT, LDH, LDL, Triglycerides, BUN, VLDL, Basophils, Eosinophils, Lymphocytes, Monocytes); in that case, the following scale normalization was used:

2) Scale normalization formula

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

where,

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

x = The original value in SI unit

L_X = Lower limit of normal range for an individual parameter test

U_X = Upper limit of normal range for an individual parameter test

L_S = Lower limit for the selected common standard laboratory

U_S = Upper limit for the selected common standard laboratory.

A separate document 'Lab Data SI Unit Conversion and Normalization' provides more details related to applicable parameters for normalization and determination of clinically notable values (Appendix 16.1.9).

The following Special Diagnostic Tests (Baseline) were listed only without any SI unit conversion and transformation:

- HbA1c (Study 008A Baseline and Study 020 Baseline)
- Urine drug screen (Study 008A Baseline and Study 020 Baseline)
- Serum/urine pregnancy tests (Study 008A Baseline and Study 020 Baseline)
- Serum prolactin (Study 008A Baseline and Study 020 Baseline)

Also, urine parameters were listed without any determination of clinically notables, except for Specific Gravity.

Note that, lab values reported as <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.

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, biochemistry and urinalysis selected parameters were presented for the single evenamide 30 mg *BID* group for the Safety Population. If a subject already had a Baseline (last measurement before randomization and treatment start) clinically notable value, then the subject was not counted in the newly emergent clinically notable table, since the notable value was already present before starting the study medication (Table 9-13).

The summary of changes from Baseline to each post-Baseline visit (Weeks 4, 12, 28 and 52) was provided for hematology and chemistry parameters on normalized values mentioned in Appendix 3 of the SAP document presented in Appendix 16.1.9 for the single evenamide 30

mg *BID* group. The DB Baseline values were used for EVN-EVN subjects, whereas the OL Baseline values were used for PLC-EVN subjects.

Table 9-13 Newly Emergent (NE) Clinically Notable (CN) abnormalities

	OL/DB Baseline	Post-Baseline	NE CN
Clinically Notable	No	No	No
	No	Yes	Yes
	Yes	No	No
	Yes	Yes	No

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

For the Additional 52-Week period, only a listing was provided.

Urinalysis data were listed only along with clinical significance evaluated by the Investigator. Only Specific Gravity has been selected for assessing clinically notable values, as other urine parameters have been evaluated by different laboratories in a mixed pattern.

Cancelled lab tests were excluded from the SAS listings. Dates and times of sample collection were considered from the eCRF and not from the external vendor data. In case of mismatch for visit name and time, eCRF data were considered for the analysis. Note that reference ranges and units of Trilab Total Protein and Specific Gravity have been corrected as per Appendix 7 of the SAP document presented in Appendix 16.1.9 due to an error noted in eCRF. Screening visit data of the core Study 008A were carried forward in case of missing DB Baseline data.

For summary statistics and clinically notable values, only nominal visits (i.e., excluding the unscheduled) data were considered.

ANC monitoring for patients on clozapine: ANC levels measured during routine blood monitoring (at Baseline, and Weeks 2, 4, 6, 8, 12, 20, 28, 36, 44 and 52 in the initial 52-week period, and at Weeks 13, 26, 39 and 52 in the additional 52-week period) were listed as per the eCRF.

Limitations: As laboratory data for each subject have been evaluated by two different labs (i.e. OL Baseline values of all subjects were assessed by Q2 lab and post-Baseline values were assessed by TriLab or Medpace), summary statistics based on the normalization method might be biased.

9.7.1.21.5. Electrocardiogram (ECG)

A summary is provided for the following parameters at each scheduled visit for the Initial 52-Week treatment period for the Safety population:

1) Change from Baseline at each visit/ timepoint and at endpoint (Week 52 or early discontinuation) for ECG parameters (Mean Heart Rate, RR Interval, PR Interval, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval).
2) Treatment-emergent abnormalities as assessed by the Central Reader and Principal Investigator.
3) The number (%) of patients meeting the following categorical criteria were summarized by treatment group:
    a. Change from Baseline in QTc interval: from > 30 msec to ≤ 60 msec, and > 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,
    e. The categorical outliers for Heart Rate parameters were categorized as:
        - HR changes reflecting at least a 25% decrease from Baseline to a HR < 50 beats per minute (bpm)
        - HR changes reflecting a 25% increase from Baseline with a HR > 100 bpm.

For change from Baseline calculations, DB Baseline was considered for EVN-EVN subjects and OL Baseline was considered for PLC-EVN subjects.

The following Baseline considerations were used for calculating change from Baseline or for determining Treatment-Emergent Abnormalities:

Study	**Baseline**	**Comments**
008A (DB)	Average of pre-dose triplicate	-
020 (OL)	Pre-dose	2 hr post-dose data was considered at post-dose timepoint.

ECG listings consisted of individual subject data with findings from the Principal Investigator and Central Reader, treatment-emergent abnormalities as assessed by the Central Reader, and changes from Baseline.

In case of a mismatch in the date and time of the ECG assessment visit between the eCRF and external transfer data, the date and time recorded in the eCRF were used .

9.7.1.21.6. Physical Examinations

Treatment-emergent post-Baseline abnormal findings on any body system in the physical examination were summarized and listed for the single evenamide 30 mg *BID* group for the Safety Population. For determination of treatment emergence, DB Baseline was considered for EVN-EVN subjects and OL Baseline was considered for PLC-EVN subjects. For the Additional 52-Week period, only a subject-wise listing was provided.

9.7.1.21.7. Neurological Examinations

Treatment-emergent post-Baseline abnormal findings on any body system in the neurological examination were summarized and listed for the single evenamide 30 mg *BID* group for the Safety Population. For determination of treatment emergence, DB Baseline was considered for EVN-EVN subjects and OL Baseline was considered for PLC-EVN subjects. For the Additional 52-Week period, only a subject-wise listing was provided.

9.7.1.21.8. Standard Eye Examination

Treatment-emergent post-Baseline abnormal findings on the eye examination, were summarized and listed for the single evenamide 30 mg *BID* group for the Safety Population. For determination of treatment emergence, DB Baseline was considered for EVN-EVN subjects and OL Baseline was considered for the PLC-EVN subjects. For the Additional 52-Week period, only a subject-wise listing was provided.

9.7.1.21.9. *Columbia Suicide Severity Rating Scale (C-SSRS)*

Counts and percentages of subjects who answered “Yes” to at least one of the “suicidal ideation” or “suicidal behavior” questions were summarized at each visit for the evenamide 30 mg *BID* dose group for the Safety Population.

An individual subject listing for the Safety Population was provided separately for the “Since Last Visit” version of the C-SSRS.

For the Additional 52-Week period, only a subject-wise listing was provided.

9.7.1.21.10. *Substance Use Assessment*

A subject-wise listing was provided for the single evenamide 30 mg *BID* group.

9.7.1.21.11. Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)

Ratings of the ESRS-A were summarized by each sub-scale and symptom/body part and by visit for the Safety Population and presented for the single evenamide 30 mg *BID* group. The observed value and mean change from Baseline in the total score and sub-scale scores of the ESRS-A were presented for the evenamide 30 mg *BID* group for the Safety Population. For the change from Baseline calculation, DB Baseline was considered for EVN-EVN subjects and OL Baseline was considered for PLC-EVN subjects.

All the findings were also listed.

For the Additional 52-Week period, only a subject-wise listing was provided.

9.7.1.22. *Analysis of Efficacy Parameters*

9.7.1.22.1. Positive and Negative Syndrome Scale (PANSS)

The effect of evenamide 30 mg *BID* dose on the PANSS Total score measured at each visit was analyzed descriptively. Change from Baseline to endpoint on the observed PANSS Total score was presented by mean, median, and range (min, max) at each post-Baseline timepoint (Weeks 12, 28 and 52). Demonstration of a clinically relevant improvement from Baseline to endpoint (Week 52 or early discontinuation) on the PANSS total score for evenamide 30 mg *BID*, would be considered as preliminary evidence of benefit of evenamide as adjunctive therapy in patients with chronic schizophrenia showing inadequate response to their current antipsychotic medication.

'Responder' analyses were performed by summarizing the proportion of patients with improvement from Baseline(s) to endpoint on the PANSS total score (i.e., PANSS Total score reduction ≥20% and ≥30%, as described by Rosenheck et al., 1997 and Meltzer et al., 2008).

A line graph is presented to show the change from Baseline on the PANSS total score by visit until Week 52.

Efficacy analyses were repeated using both Baselines (as explained in the general considerations) based on the mITT population.

9.7.1.22.2. Clinical Global Impression (CGI)

Changes from Baseline (as explained in the general considerations) at each post-Baseline time point till Initial Week 52 (Weeks 12, 28 and 52) on the CGI-S were summarized with descriptive statistics, along with a line graph. Summary statistics (mean rating) of CGI-C at open-label post-Baseline visits (Weeks 12, 28 and 52) were also be presented, along with a line graph.

'Responder' analyses were performed by summarizing the proportion of patients with different categories of improvement ("any improvement" defined as CGI-C score ≤ 3, and "at least much improved" defined as CGI-C score ≤ 2) from OL Baseline to endpoint on the CGI-C. A bar chart of the responder analyses on the CGI-C (any improvement and at least much improved) was presented.

Efficacy analyses of the CGI-S were repeated using both Baselines (as explained in the general considerations) based on the mITT population. Analysis of the CGI-C was performed on the mITT population.

9.7.1.22.3. Global Assessment of Functioning (GAF) scale

Change from OL Baseline to endpoint on the GAF score was summarized for evenamide 30 mg *BID* at each post-Baseline time point of the Initial 52-Week period (i.e., Weeks 12, 28 and 52) for the mITT population.

A graph depicting the mean (SD) change from OL Baseline by visit was presented.

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

Changes from Baseline to endpoint on the total score and Sub-scale scores of the LOF were summarized at each post-Baseline time point (i.e., Weeks 12, 28 and 52). A graph depicting mean (SD) change from OL Baseline by visit was presented.

Efficacy analyses on LOF scale was performed on the mITT population.

9.7.1.22.5. Patient's Medication Satisfaction Questionnaire (MSQ)

Change from Baseline to endpoint on the MSQ was summarized at each post-Baseline time point of the Initial 52-Week period (i.e., Weeks 12, 28 and 52). A graph depicting mean (SD) change from Baseline by visit was presented. Efficacy analyses on the MSQ were performed on the mITT population.

9.7.1.22.6. Efficacy Estimands

The study enrolled a limited number of subjects, and most of the subjects were discontinued by the Sponsor before the study completion. Therefore, no efficacy estimands or any sensitivity analysis on efficacy were planned or performed.

9.7.1.23. *Analysis of Pharmacokinetic Parameters*

No pharmacokinetic sampling or analysis was planned for this study.

Interim Analysis

Not applicable, since no interim analysis on efficacy data was performed.

9.7.2. Determination of Sample Size

Approximately 500 patients with psychiatric disorders who completed prior studies in which they received evenamide at doses of 7.5, 15 or 30 mg *BID* were expected to be enrolled in this open-label extension study. However, Study 020 was required only by health authorities in Argentina and Italy as an extension of Study 008A, therefore a lower number of patients (52) were included in the study. No *a priori* assumptions on sample size and statistical power were made.

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

9.8.1. Changes in the Conduct of the Study

The original protocol version 1.0 dated 10 May 2021 was amended twice (Amendments 1.0 and 1.1). Copies of the protocol and protocol amendments are provided in Appendix 16.1.1. Brief summaries of the non-administrative changes are outlined below.

Amendment 1.0, Protocol version 2.0, dated 26 October 2021

The primary purpose of this amendment to the protocol for Study NW-3509/020/III/2021 (Study 020) was to modify the protocol in response to the following issues raised by the Agenzia Italiana del Farmaco (AIFA):

1. Please confirm that patients enrolled in the proposed trial are those who completed Study 008A and add this information in the inclusion criteria.

2. If the enrolled patients are carried over only from 008A study, they are supposed to have a diagnosis of schizophrenia in accordance with DSM-5. According to the inclusion criteria, in 008A study other Axis-I disorders may be present only as lifetime diagnoses if they are not relevant to the current episode of schizophrenia. In the proposed protocol, primary and secondary objective/endpoints refer to schizophrenia and bipolar patients. Please clarify and list in the protocol the studies from which patients will be selected.

3. There are some typos in the protocol: some sentences seem to refer to the 008A trial as the current study. Please review and amend the protocol accordingly.

The study design section and the inclusion criteria have been modified to specify the prior evenamide studies, including Study 008A, from which patients could be enrolled into this open-label extension study.

Patients with schizophrenia, as well as those with bipolar disorder, who completed their prior study and met all entry criteria for Study 020, were eligible to continue long-term treatment with evenamide in this study, although ultimately, no such bipolar patients were enrolled.

The Benefit/Risk Assessment for Evenamide (Appendix 5) has been amended to correct errors referencing Study 008A as the "current study", which instead should have referred to Study 020.

Amendment 1.1, Protocol version 2.1, dated 05 April 2022

The primary purpose of this amendment to the protocol for Study NW-3509/020/III/2021 (Study 020) was to allow patients in North America enrolled in studies with evenamide to be able to continue long-term, open label extension treatment in Study 020.

Additionally, the following errors and omissions have been corrected in the protocol:

- The timeline for enrollment of patients in the study has been modified to more accurately reflect the current status of the study.
- The inclusion criteria have been revised to specify that all patients must be adults (at least 18 years of age) to be eligible for enrollment.
- An error has been corrected in Section 10.1.1 related to the labeling of the study medication. Since this is an open-label study, bottles would have the evenamide dosage strength printed on the label and were not to be blinded.
- An error has been corrected in Section 10.4 related to the population of patients who would be eligible for inclusion in the trial.

9.8.2. Changes from Protocol Planned Analysis

The following texts related to the analysis were mentioned in the protocol but not considered in this study.

S. No.	Protocol Text	New Changes	Reason
1	Efficacy analyses will also be performed for the bipolar disorder-related scales (i.e. YMRS, MADRS, CGI-BP-S and CGI-BP-C)	Analysis of efficacy in bipolar disorder (YMRS, MADRS, CGI-BP-S and CGI-BP-C) was not required.	The study did not enroll any patients with bipolar disorder.

S. No.	Protocol Text	New Changes	Reason
2	The last visit of the prior (core) study (Day 29 of Study 008A) will be used as Baseline for Study 020.	Safety analysis was performed using mixed Baseline, i.e. DB Baseline for EVN-EVN subjects and OL Baseline for PLC-EVN subjects. Efficacy analysis was performed using both Baselines, i.e. DB and OL.	Scientifically more appropriate.
3	Paired t-test.	Efficacy analysis was limited to descriptive statistics and inferential analysis.	Due to small sample size and study termination by Sponsor.
4	The distribution of patients by each category of change and the proportion of patients with improvement, no change, or worsening from Baseline to endpoint on the CGI-C will be provided.	Responder analysis on the CGI-C was performed by summarizing the proportion of patients with any improvement and at least much improved.	As per Sponsor's advice.
5	The efficacy analyses will be performed on a population comprising all patients who had a Baseline efficacy assessment in Study 020 (final efficacy assessment of the prior evenamide study), received at least one dose of the study medication in this extension study, and have at least one post-Baseline (Study 020) assessment for the primary efficacy measure, the PANSS	Efficacy analysis will be performed using mITT Population.	For a prematurely terminated study, ITT population may not be appropriate because full exposure has been reduced.
6	Responder analysis on the PANSS Total Score was not mentioned in the protocol.	Responder analysis of PANSS Total Score (i.e., PANSS Total score reduction ≥20% and ≥30%) has been added.	As per Sponsor's advice.

All the above changes were made before database lock. No impact on the conduct of the study was identified.

10. STUDY PATIENTS

10.1. Disposition of Patients

The subject disposition, including details of the number of subjects rolled over from Study 008A, completed, and discontinued, along with the reason for discontinuation, are provided in Table 10-1 and presented in Table 14.1.1 and by subject details in Listing 16.2.1.2.

A total of 52 (100.0%) subjects rolled over into the initial 52-week period of the study and 3 (5.8%) subjects from the initial 52-week period rolled over into the additional 52-week period. The Safety Population consisted of 52 (100.0%) subjects, the Modified Intent-to-Treat (mITT) Population consisted of 51 (98.1%) subjects, and none of the subjects was included in the Retrieved Dropout Population [0 (0.0%)]. Five (9.6%) subjects completed the initial 52-week period, and 0 (0.0%) subjects completed the additional 52-week period. The number (%) of subjects who discontinued prematurely or withdrew early was 47 (90.4%) subjects from the initial 52-week period and 3 (5.8%) subjects from the additional 52-week period. The most common reason for early withdrawal was 'Study termination by Sponsor' in both the initial 52-week period [37 (71.2%) subjects] and in the additional 52-week period [3 (5.8%)] (Table 10-1).

Table 10-1 Subject Disposition – Safety Population

Status	Evenamide 30 mg *BID* (N=52) n (%)
Rolled Over from Study 008A to Study 020	52 (100.0)
Rolled over into the additional 52-week period	3 (5.8)
Safety Population [a]	52 (100.0)
Modified Intent-to-Treat Population [b]	51 (98.1)
Retrieved Dropout Population	0 (0.0)
Evenamide to Evenamide (EVN-EVN) group	23 (44.2)
Placebo to Evenamide (PLC-EVN) group	29 (55.8)
Completed Study at Initial Week 52	5 (9.6)
Discontinuation or Early Withdrawal at Initial Week 52	47 (90.4)
Completed Study at Additional Week 52	0 (0.0)
Discontinuation or Early Withdrawal at Additional Week 52	3 (5.8)
Primary Reason for Early Withdrawal at Initial Week 52	
Study termination by Sponsor	37 (71.2)
Withdrawal of consent	6 (11.5)
Adverse Event#	2 (3.8)
Investigator decision	1 (1.9)
Suicidal Risk (Sponsor Decision)	1 (1.9)
Primary Reason for Early Withdrawal at Additional Week 52	
Study termination by Sponsor	3 (5.8)

Source: *Listing 16.2.1.2*; Adapted from *Table 14.1.1*.
#- One subject died due to sudden death.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
[a] Safety Population: The safety population consists of those subjects who took at least one dose of study medication in this extension study.
[b] Modified Intent-to-Treat Population: The modified Intent-to-Treat (mITT) population comprises those subjects who had an OL baseline efficacy assessment, received at least one dose of the study medication in this extension study and had at least one post-OL-baseline efficacy assessment for the PANSS.
[c] Retrieved Dropout Population: The retrieved dropout population (RDO) consists of subjects who discontinued treatment, but agreed to continue in the study, and returned for assessment at applicable scheduled visits for selected efficacy parameters (PANSS, CGI-S and CGI-C) including the final assessment at Week 52.

10.2. Protocol Deviations

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

No critical protocol deviation was reported in this study. Major protocol deviations were reported in a total of 21 (40.4%) subjects, and all of these were due to deviation in the informed consent.

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

Category	Evenamide 30 mg *BID* (N=52) n (%)
Subjects with Major Protocol Deviation	21 (40.4)
Subjects with Critical Protocol Deviation	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 calculated using the number of subjects in the safety population as denominator (N).

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

Overall, 52 (100%) subjects were allocated to treatment and included in the Rolled over Population (Table 14.1.1). All 52 (100%) subjects received at least one dose of study medication and qualified for inclusion in the Safety Population. A total of 51 (98.1%) subjects had a valid Baseline and at least one post-Baseline efficacy assessment for the PANSS and received at least one dose of the study medication and thereby qualified for the mITT Population.

Details of the subjects involved in the study are presented 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 and mITT Population are presented in Table 14.1.3.1.1 and in Table 14.1.3.1.2, respectively, 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 males [38 (73.1%)], Hispanic or Latino [49 (94.2%)], White [51 (98.1%)], single [34 (65.4%)], not employed [44 (84.6%)], with 9-16 years of education [35 (67.3%)], and living with a family [48 (92.3%)]. The mean (SD) age of the subjects was 43.3 (14.55) years, ranging from 18 to 76 years. The mean (SD) weight and body mass index were 81.3 (16.69) kg and 28.0 (5.06) kg/m^2, respectively.

Table 11-1 Demographics and Baseline Characteristics – Safety Population

Characteristics	Statistic	EVN-EVN (N=23)	PLC-EVN (N=29)	Total (N=52)
Age (years)	n	23	29	52
	Mean (SD)	41.7 (14.16)	44.6 (14.98)	43.3 (14.55)
	Median	44.0	47.0	46.0
	Min, Max	18, 66	20, 76	18, 76
Weight (kg)	n	23	29	52
	Mean (SD)	78.4 (15.73)	83.5 (17.35)	81.3 (16.69)
	Median	75.1	82.3	79.4
	Min, Max	51.0, 110.5	49.1, 112.0	49.1, 112.0
Height (cm)	n	23	29	52
	Mean (SD)	169.9 (7.33)	170.5 (11.71)	170.2 (9.93)
	Median	170.0	173.0	171.0
	Min, Max	156, 184	145, 188	145, 188
BMI (kg/m2)	n	23	29	52
	Mean (SD)	27.1 (4.42)	28.8 (5.48)	28.0 (5.06)
	Median	26.2	30.0	27.1
	Min, Max	20.2, 34.9	16.6, 35.0	16.6, 35.0
Sex				
Male	n (%)	17 (73.9)	21 (72.4)	38 (73.1)
Female	n (%)	6 (26.1)	8 (27.6)	14 (26.9)
Childbearing Potential [a]				
Yes	n (%)	3 (50.0)	2 (25.0)	5 (35.7)
No	n (%)	3 (50.0)	6 (75.0)	9 (64.3)
Race				
White	n (%)	22 (95.7)	29 (100.0)	51 (98.1)
South American Indian-Bolivian	n (%)	1 (4.3)	0 (0.0)	1 (1.9)
Ethnicity				
Hispanic Or Latino	n (%)	22 (95.7)	27 (93.1)	49 (94.2)
Not Hispanic Or Latino	n (%)	1 (4.3)	2 (6.9)	3 (5.8)

Characteristics	Statistic	EVN-EVN (N=23)	PLC-EVN (N=29)	Total (N=52)
Education				
1-8 years	n (%)	4 (17.4)	4 (13.8)	8 (15.4)
9-16 years	n (%)	15 (65.2)	20 (69.0)	35 (67.3)
>16 years	n (%)	4 (17.4)	5 (17.2)	9 (17.3)
Marital Status				
Married	n (%)	6 (26.1)	6 (20.7)	12 (23.1)
Single	n (%)	13 (56.5)	21 (72.4)	34 (65.4)
Stable union	n (%)	1 (4.3)	0 (0.0)	1 (1.9)
Divorced	n (%)	3 (13.0)	2 (6.9)	5 (9.6)
Employment				
Full-Time Employment	n (%)	0 (0.0)	1 (3.4)	1 (1.9)
Part-Time Employment	n (%)	3 (13.0)	4 (13.8)	7 (13.5)
Not employed	n (%)	20 (87.0)	24 (82.8)	44 (84.6)
Housing Status				
Living alone	n (%)	2 (8.7)	1 (3.4)	3 (5.8)
Living with family	n (%)	21 (91.3)	27 (93.1)	48 (92.3)
Living in residential care	n (%)	0 (0.0)	1 (3.4)	1 (1.9)

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,
Double Blind Baseline (008A) [race, ethnicity, education, marital status, employment, housing status and weight], Open label Baseline (Study 020) [age, sex, childbearing potential, height and weight].
Weight has been taken from DB baseline for EVN-EVN subjects, and from OL baseline for PLC-EVN subjects.
Percentages are based on the total number of subjects in each group (N) under Safety Population.
SD = Standard Deviation, Age = Age at baseline of Study 020, Min = Minimum, Max = Maximum.
[a] For Childbearing Potential, percentage is based on number of female subjects enrolled.
EVN-EVN = Subjects randomized to evenamide in the core study continuing with evenamide in this extension study.
PLC-EVN = Subjects randomized to placebo in the core study switched over to evenamide in this extension study.

Demographic and baseline characteristics of the mITT Population did not differ meaningfully from those of the Safety Population presented above.

11.2.2. Disease Characteristics

All subjects had a diagnosis of schizophrenia in accordance with DSM-5. The mean (SD) duration of schizophrenia was 18.4 (13.31) years in the overall evenamide treated group. The mean (SD) duration of the current episode of schizophrenia was 18.2 (29.33) months (Table 11-2). The mean (SD) number of psychiatric hospitalizations was 0.9 (1.04), with a range of 0-4. Most of the subjects [39 (75.0%)] did not have a family history of schizophrenia, but for those who did, it was usually the 1st Degree Relatives [5 (9.6%)]. The number (%) of subjects with other psychiatric disorders was 3 (5.8%).

Disease characteristics data are presented by subject in Listing 16.2.4.3.1, Listing 16.2.4.3.2, and Listing 16.2.17, and summarized in Table 14.1.3.2.

Table 11-2 Disease Characteristics - Safety Population

Characteristics	Statistic	Evenamide 30 mg *BID* (N=52) n (%)
Duration of Illness - Schizophrenia (Years) [a]	n	52
	Mean (SD)	18.4 (13.31)
	Median	17.8
	Min, Max	2, 50
Duration of Current Episode of Schizophrenia (Months) [b]	n	52
	Mean (SD)	18.2 (29.33)
	Median	7.3
	Min, Max	2, 187
Number of Psychiatric Hospitalization	n	52
	Mean (SD)	0.9 (1.04)
	Median	1.0
	Min, Max	0, 4
Family History of Schizophrenia		
None	n (%)	39 (75.0)
1st Degree Relatives [c]	n (%)	5 (9.6)
Mother	n (%)	1 (1.9)
Brother	n (%)	4 (7.7)
Sister	n (%)	1 (1.9)
2nd Degree Relatives [d]	n (%)	1 (1.9)
Paternal Grandmother	n (%)	1 (1.9)
Other	n (%)	7 (13.5)
Number of subjects with other psychiatric disorders	n (%)	3 (5.8)

Source: *Listing 16.2.4.3.1*, *Listing 16.2.4.3.2*, *Listing 16.2.17*; Adapted from *Table 14.1.3.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data,
SD = Standard Deviation, Min = Minimum, Max = Maximum.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
[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.

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, 23 (44.2%) subjects reported having any medical history in the evenamide treated group. Hypothyroidism was the most frequently reported medical condition by 8 (15.4%)

subjects, followed by hypertension by 7 (13.5%) subjects. Headache, tonsillectomy, type 2 diabetes mellitus and insomnia were reported by 2 (3.8%) subjects each in the evenamide 30 mg *BID* treated group.

A summary of other psychiatric history of the Safety Population is reported in Table 14.1.3.3.2 and presented by subject in Listing 16.2.4.3.2.

Overall, 3 (5.8%) subjects reported having any other psychiatric history in the evenamide treated group. The psychiatric conditions other than schizophrenia by preferred term (PT) were 'Impulse-control disorder', 'Insomnia' and 'Social anxiety disorder' reported in 1 (1.9%) subject each in the evenamide treated group.

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. These were generally characteristic of subjects with schizophrenia.

Overall, 4 (7.7%) subjects had a record of prior medications other than antipsychotics (these could include antipsychotic drugs used for indications different than schizophrenia, e.g. insomnia). The used prior medications were delorazepam (ATC class: Benzodiazepine derivatives), olanzapine (ATC class: diazepines, oxazepines, thiazepines and oxepines), fosfomycin (ATC class: Other antimicrobials), nimesulide (Other antiinflammatory and antirheumatic agents, non-Steroids) and ibuprofen (ATC class: Propionic acid derivatives) by 1 (1.9%) subject each (Table 14.1.4.1.1).

A total of 44 (84.6%) subjects had a record of concomitant medications other than antipsychotics (these could include antipsychotic drugs used for indications different than schizophrenia, e.g. insomnia). The most commonly used (>5% of the subjects) concomitant medications were clonazepam (ATC class: Benzodiazepine derivatives) by 17 (32.7%) subjects, levothyroxine (ATC class: Thyroid hormones) by 7 (13.5%) subjects, valproate semisodium (ATC class: Other antipsychotics) by 6 (11.5%) subjects, quetiapine (ATC class: Diazepines, oxazepines, thiazepines and oxepines) by 5 (9.6%) subjects, lorazepam (ATC class: Benzodiazepine derivatives) by 4 (7.7%) subjects, amoxicillin (ATC class: Penicillins with extended spectrum) by 4 (7.7%) subjects, losartan [ATC class: Angiotensin II Receptor Blockers (ARBs), Plain] by 3 (5.8%) subjects, paracetamol (ATC class: Anilides) by 3 (5.8%) subjects, venlafaxine (ATC class: Other antidepressants) by 3 (5.8%) subjects, and ibuprofen (ATC class: Propionic acid derivatives) by 3 (5.8%) subjects. (Table 14.1.4.1.2).

A total of 43 (82.7%) subjects had a record of prior antipsychotic medications. Haloperidol and risperidone were the most commonly taken prior antipsychotic medications, which were

taken by 21 (40.4%) subjects each. Olanzapine was the next most common prior antipsychotic medication, which was taken by 13 (25.0%) subjects. Prior antipsychotic medications taken by 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.

A summary of current antipsychotics taken by patients in the Safety Population during the study is presented in Table 14.1.4.2.2 and by subject details in Listing 16.2.4.4.3.2. Risperidone was the most commonly used current antipsychotic medication, which was used by 24 (46.2%) subjects. Olanzapine was the next most common current antipsychotic medication, which was used by 13 (25.0%) subjects. Other current antipsychotic medications used were clozapine by 7 (13.5%) subjects, paliperidone by 6 (11.5%) subjects, aripiprazole and quetiapine by 2 (3.8%) subjects each, and lurasidone by 1 (1.9%) subject (Table 11-3).

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

Drug Name	**Evenamide 30 mg *BID* (N=52) n (%)**
Risperidone	24 (46.2)
Olanzapine	13 (25.0)
Clozapine	7 (13.5)
Paliperidone	6 (11.5)
Aripiprazole	2 (3.8)
Quetiapine	2 (3.8)
Lurasidone	1 (1.9)

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 calculated using the number of subjects in the safety population as denominator (N).
Subjects counted only once for a Drug Name.
Current antipsychotic medications taken at any time during the study irrespective of the start date and collected in the CRF under “Current Psychotropic Medication”.

11.3.1. Concomitant Procedures

A total of 2 (3.8%) subjects received at least one concomitant procedure during the study. Details of concomitant procedures of the Safety Population are presented by subject in Listing 16.2.4.4.2 and in Table 14.1.4.3.1.

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 (5.8%) subjects in the evenamide treated group. Clozapine, haloperidol, lorazepam, lurasidone and olanzapine were used by 1 (1.9%) subject each in the evenamide treated group.

Subject 895021 received haloperidol and lorazepam to manage a possible Intentional Drug Overdose. Subject 855001 received clozapine and lurasidone to manage Psychotic Exacerbation. Subject 895020 received olanzapine to manage a hypomanic episode.

Rescue medication details of the Safety Population are presented by subject in Listing 16.2.4.4.3.3 and in Table 14.1.4.3.2.

Table 11-4 Summary of Rescue Medications – Safety Population

Rescue Medication Name	Statistic	Evenamide 30 mg *BID* (N=52) n (%)
No. of subjects who received at least one rescue medication	n (%)	3 (5.8)
Clozapine	n (%)	1 (1.9)
Haloperidol	n (%)	1 (1.9)
Lorazepam	n (%)	1 (1.9)
Lurasidone	n (%)	1 (1.9)
Olanzapine	n (%)	1 (1.9)

Source: *Listing 16.2.4.4.3.3*; Adapted from *Table 14.1.4.3.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
Dose adjustments for atypical antipsychotics of 25% or more, upwards, or downwards or any psychotropic administered for Exacerbation of Schizophrenia not temporarily (more than 5 days) in the treatment period due to significant worsening are considered rescue medications. For complete definition refer to Section 9.7.1.4 of this report and Section 9.1.2 of the SAP.

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 9.7.1.21.1.

The mean (SD) overall treatment compliance in the evenamide treated group was 99.7% (3.14%), with a median of 99.7% (range: 94 to 120%). One male subject (895021) was reported to have 119.9% compliance.

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. Efficacy Results

11.5.1. Analysis of Efficacy

11.5.1.1. *Positive and Negative Syndrome Scale Results*

11.5.1.1.1. PANSS Total Score

The mean change from Baseline to endpoint (Week 52) on the PANSS total score of the mITT population is presented in Table 14.2.1.1 and by subject details in Listing 16.2.6.1.2 and Listing 16.2.6.1.2a.

11.5.1.1.1.1. PANSS total score results in mITT Population

A summary of mean value and change from Baselines (DB and OL Baseline) in the PANSS total score by visit for the mITT Population is shown in Table 11-5 and change from Baselines in the PANSS total score by visit for the mITT Population is shown in Figure 11-1.

A steady decrease in the PANSS total score in the mITT Population was observed at all study visits (Weeks 12, 28 and 52) compared to both Baselines in the evenamide treated group, reflecting a continuation of improvement in the symptoms of schizophrenia. The DB Baseline mean (SD) of PANSS total score recorded was 79.3 (3.13), and the OL Baseline mean (SD) of PANSS total score recorded was 72.9 (7.54) in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores of the evenamide treated group decreased to 66.7 (9.98), 62.8 (10.38) and 60.5 (9.61), respectively. The mean (SD) changes from DB Baseline in the PANSS Total score recorded were -12.5 (9.28), -16.5 (9.58) and -18.6 (9.77) at Weeks 12, 28 and 52, respectively. The mean (SD) changes from OL Baseline in the PANSS Total score recorded were -6.1 (6.18), -9.4 (8.22) and -12.3 (9.01) at Weeks 12, 28 and 52, respectively (Table 11-5).

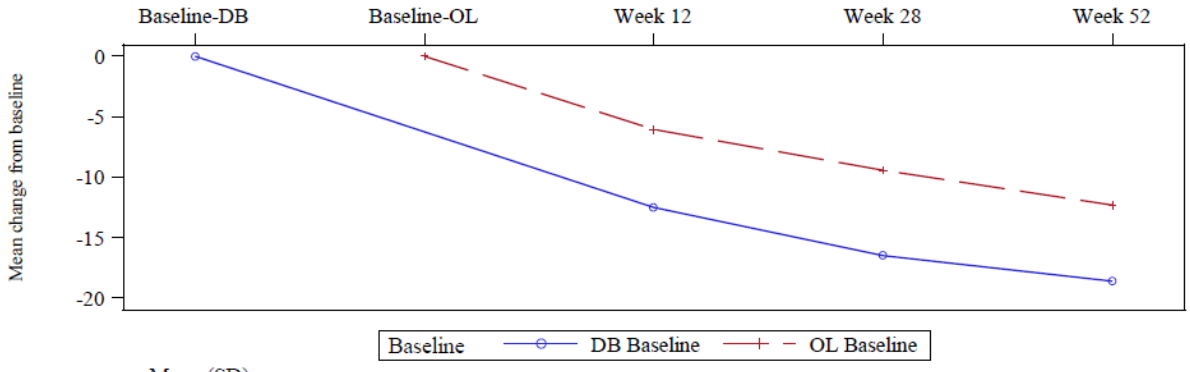
Table 11-5 Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score (Primary Efficacy) - mITT Population

		Evenamide 30 mg *BID* (N=51)		
Visit	**Statistic**	**Observed**	**Change from DB Baseline**	**Change from OL Baseline**
Baseline-DB	n	51		
	Mean (SD)	79.3 (3.13)		
	Median	79.0		
	Min, Max	71, 85		
Baseline-OL	N	51		
	Mean (SD)	72.9 (7.54)		
	Median	73.0		
	Min, Max	56, 93		
Week 12	n	50	50	50
	Mean (SD)	66.7 (9.98)	-12.5 (9.28)	-6.1 (6.18)
	Median	67.0	-13.5	-5.0
	Min, Max	41, 96	-38, 13	-20, 5
Week 28	n	43	43	43
	Mean (SD)	62.8 (10.38)	-16.5 (9.58)	-9.4 (8.22)
	Median	64.0	-17.0	-9.0
	Min, Max	44, 97	-36, 14	-35, 6
Week 52	n	43	43	43
	Mean (SD)	60.5 (9.61)	-18.6 (9.77)	-12.3 (9.01)
	Median	59.0	-19.0	-11.0

	Min, Max	44, 85	-36, 6	-36, 10

Source: *Listing 16.2.6.1.2*, *Listing 16.2.6.1.2a*; Adapted from *Table 14.2.1.1*.
N - Total number of subjects in the mITT Population, n = number of subjects, SD = Standard Deviation, DB = Double blind, OL = Open label, mITT = Modified Intent-to-treat, Min = minimum, Max = maximum, Change = Post Dose – Baseline values.

Figure 11-1 Mean Change from Baseline by Visit in PANSS Total Score – mITT Population



	n, Mean (SD)				
DB Baseline	51		50, -12.5 (9.28)	43, -16.5 (9.58)	43, -18.6 (9.77)
OL Baseline		51	50, -6.1 (6.18)	43, -9.4 (8.22)	43, -12.3 (9.01)

Source: *Listing 16.2.6.1.2*, *Listing 16.2.6.1.2a*, *Table 14.2.1.1*, *Figure 14.2.1.1*

11.5.1.1.1.2. PANSS 'Responder' analyses

The results of a responder analysis by visit for PANSS total score of the mITT Population were presented in Table 14.2.1.10 and by subject details in Listing 16.2.6.1.2 and Listing 16.2.6.1.2a. 'Responders' were defined as patients who improved by at least 20% on the PANSS total score from Baselines (DB Baseline and OL Baseline), which was based on previous studies in TRS patients (Rosenheck et al., 1997; Meltzer et al., 2008). An additional responder category of ≥ 30% improvement from Baselines on the PANSS total score was also analyzed.

Responders with ≥ 20% Improvement in the PANSS Total Score

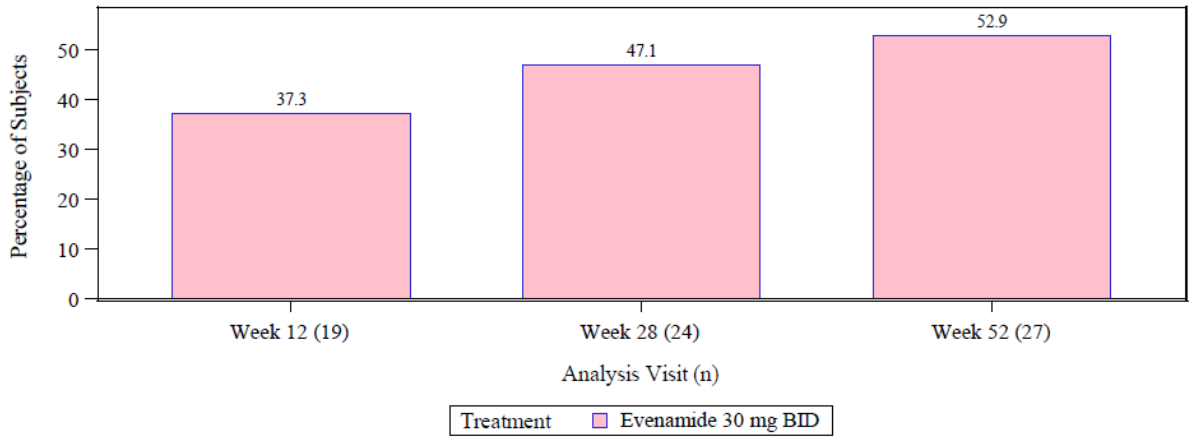
The proportion of responders, based on a ≥ 20% reduction in the PANSS total score from DB Baseline and OL Baseline, increased over time. The number (%) of responders from DB Baseline were 19 (37.3%), 24 (47.1%) and 27 (52.9%) at Weeks 12, 28 and 52, respectively (Table 11-6, Figure 11-2). The number (%) of responders from OL Baseline were 7 (13.7%), 11 (21.6%) and 17 (33.3%) at Weeks 12, 28 and 52, respectively (Table 11-6, Figure 11-3).

Table 11-6 Responder Analysis by Visit- Positive and Negative Syndrome Scale (PANSS) - mITT Population

			Evenamide 30 mg *BID* (N=51)	
Visit	Improvement Category	Statistic	From DB Baseline	From OL Baseline
Week 12	Change >=20%	n (%)	19 (37.3)	7 (13.7)
	Change >=30%	n (%)	5 (9.8)	0 (0.0)
Week 28	Change >=20%	n (%)	24 (47.1)	11 (21.6)
	Change >=30%	n (%)	9 (17.6)	2 (3.9)
Week 52	Change >=20%	n (%)	27 (52.9)	17 (33.3)
	Change >=30%	n (%)	14 (27.5)	4 (7.8)

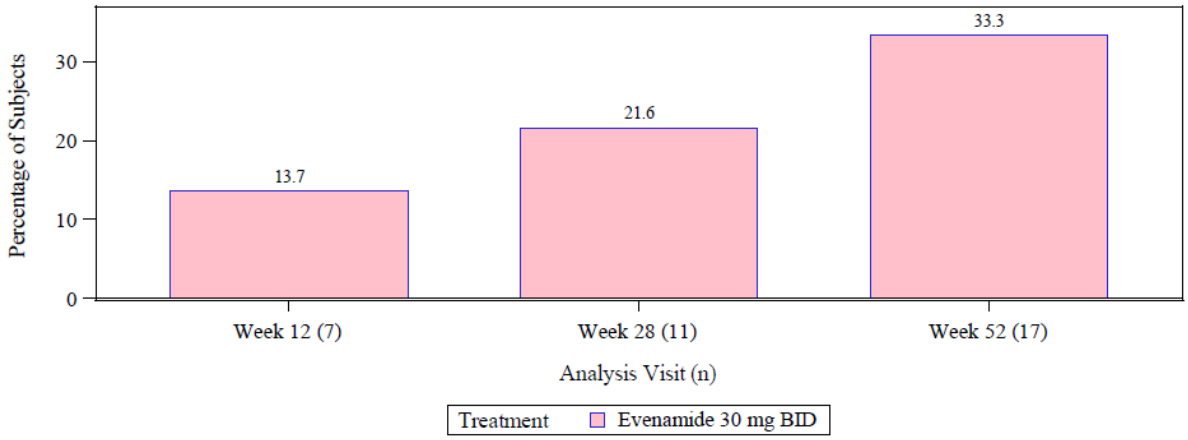
Source: *Listing 16.2.6.1.2*, *Listing 16.2.6.1.2a*; Adapted from *Table 14.2.1.10*.
N - Total number of subjects in the mITT Population, n = number of subjects, mITT = Modified intent-to-treat. DB = Double blind, OL = Open label.
Responder analyses have been performed by summarizing the proportion of patients in different categories of improvement (PANSS score Change >=20% and Change >=30%) from baselines (DB Baseline and OL Baseline) to endpoint on the PANSS total score.
Responders (for Total score): Patients with >=20% and >=30% Improvement from Baselines in PANSS Score
Percentages are based on the total number of subjects in the mITT population as denominator (N).

Figure 11-2 Bar Chart for Positive and Negative Syndrome Scale (PANSS) Total Score Responder Analysis ≥ 20% Improvement from DB Baseline by visit: mITT Population



Source: *Listing 16.2.6.1.2, Listing 16.2.6.1.2a*, *Table 14.2.1.10, Figure 14.2.1.10*.

Figure 11-3 Bar Chart for Positive and Negative Syndrome Scale (PANSS) Total Score Responder Analysis ≥ 20% Improvement from OL Baseline by visit: mITT Population

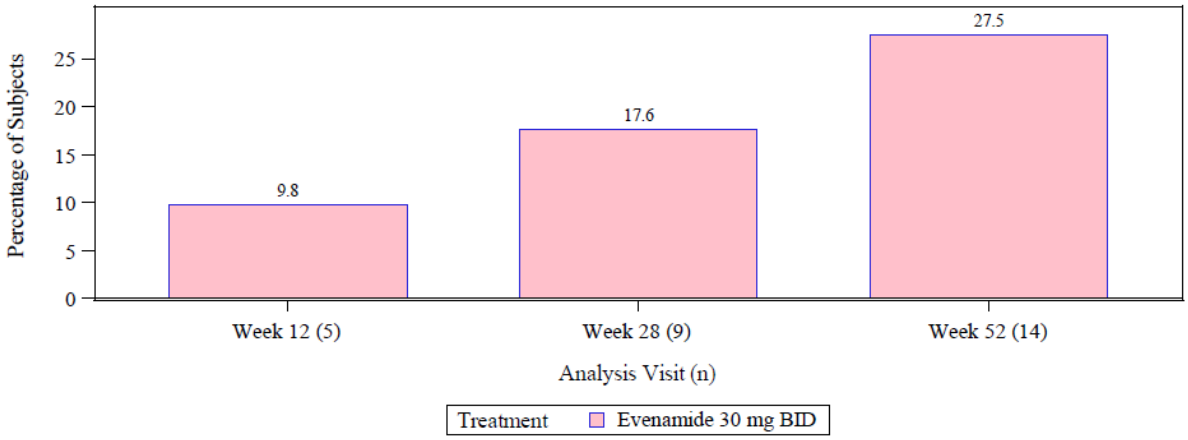


Source: *Listing 16.2.6.1.2, Listing 16.2.6.1.2a*, *Table 14.2.1.10, Figure 14.2.1.10*.

Responders with ≥ 30% Improvement in the PANSS Total Score

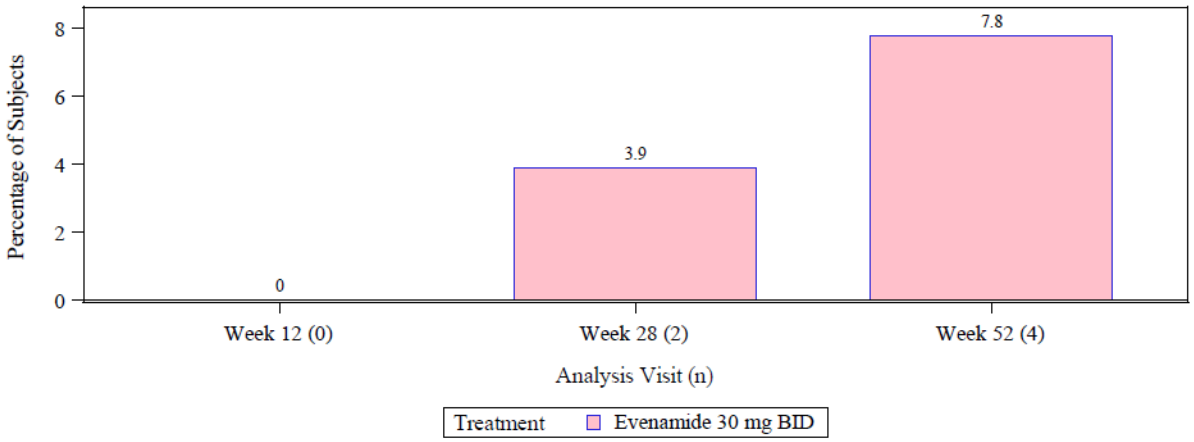
The proportion of responders, based on a ≥ 30% reduction in the PANSS total score from DB Baseline and OL Baseline, increased over time. The number (%) of responders from DB Baseline were 5 (9.8%), 9 (17.6%) and 14 (27.5%) at Weeks 12, 28 and 52, respectively (Table 11-6, Figure 11-4). The number (%) of responders from OL Baseline were 0 (0.0%), 2 (3.9%) and 4 (7.8%) at Weeks 12, 28 and 52, respectively (Table 11-6, Figure 11-5).

Figure 11-4 Bar Chart for Positive and Negative Syndrome Scale (PANSS) Total Score Responder Analysis ≥ 30% Improvement from DB Baseline by visit: mITT Population



Source: *Listing 16.2.6.1.2, Listing 16.2.6.1.2a*, *Table 14.2.1.10*, *Figure 14.2.1.10*.

Figure 11-5 Bar Chart for Positive and Negative Syndrome Scale (PANSS) Total Score Responder Analysis ≥ 30% Improvement from OL Baseline by visit: mITT Population



Source: *Listing 16.2.6.1.2, Listing 16.2.6.1.2a*, *Table 14.2.1.10*, *Figure 14.2.1.10*.

11.5.1.2. *Clinical Global Impression Results*

The Clinical Global Impression (CGI) has two components, the CGI-Severity (CGI-S), which measures the global severity of illness at a given point in time, and the CGI-Change (CGI C) which measures the change from the Baseline state at each post-Baseline visit. In Study 020, the CGI-C was assessed comparing the patient's condition with the OL Baseline status. The CGI rating scale permits a global evaluation of the subject's improvement over time.

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

The results of CGI-S by visit for the mITT population is presented in Table 14.2.2.1 and by subject details in Listing 16.2.6.2.1 and Listing 16.2.6.2.1a.

11.5.1.2.1.1. Clinical Global Impression - Severity of Illness (CGI-S) by Visit – mITT Population

The mean scores of CGI-S in the mITT Population decreased over time compared to both Baselines at each visit till Week 52 in the evenamide treated group.

The DB Baseline mean (SD) of CGI-S score recorded was 4.8 (0.53) and the OL Baseline mean (SD) of CGI-S score recorded was 4.4 (0.57) in the evenamide treated group, indicating moderate to severe symptoms. At Weeks 12, 28 and 52, the mean (SD) scores of the evenamide treated group decreased to 3.8 (0.70), 3.3 (0.68) and 3.3 (0.74), respectively. The mean (SD) changes from DB Baseline in the CGI-S score recorded were -1.0 (0.67), -1.5 (0.70) and -1.5 (0.83) at Weeks 12, 28 and 52, respectively. The mean (SD) changes from OL Baseline in the

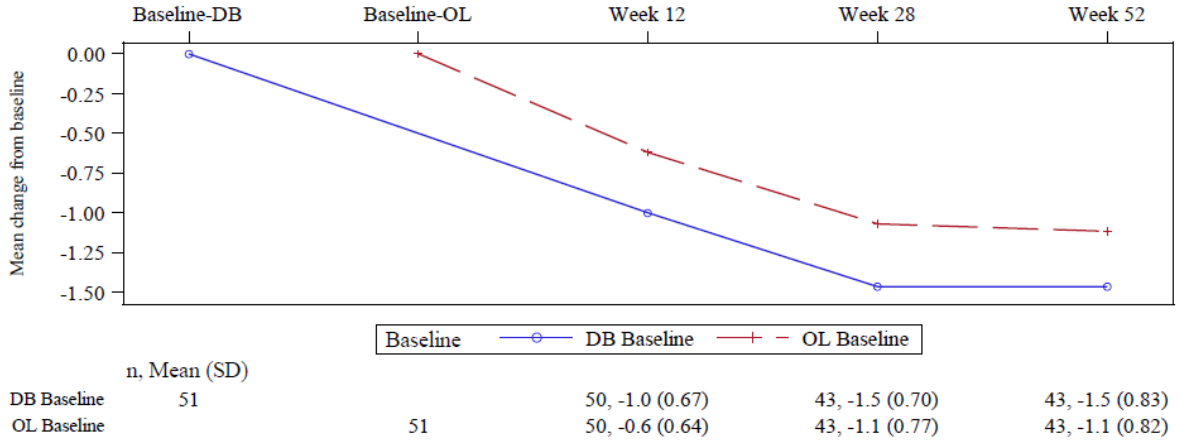
CGI-S score recorded were -0.6 (0.64), -1.1 (0.77) and -1.1 (0.82) at Weeks 12, 28 and 52, respectively (Table 11-7 and Figure 11-6).

Table 11-7 Change from Baseline in Clinical Global Impression - Severity of Illness (CGI-S) – mITT Population

		Evenamide 30 mg *BID* (N=51)		
Visit	**Statistic**	**Observed**	**Change from DB Baseline**	**Change from OL Baseline**
Baseline-DB	n	51		
	Mean (SD)	4.8 (0.53)		
	Median	5.0		
	Min, Max	4, 6		
Baseline-OL	n	51		
	Mean (SD)	4.4 (0.57)		
	Median	4.0		
	Min, Max	3, 6		
Week 12	N	50	50	50
	Mean (SD)	3.8 (0.70)	-1.0 (0.67)	-0.6 (0.64)
	Median	4.0	-1.0	-1.0
	Min, Max	2, 6	-3, 0	-2, 0
Week 28	N	43	43	43
	Mean (SD)	3.3 (0.68)	-1.5 (0.70)	-1.1 (0.77)
	Median	3.0	-1.0	-1.0
	Min, Max	2, 5	-3, 0	-3, 0
Week 52	n	43	43	43
	Mean (SD)	3.3 (0.74)	-1.5 (0.83)	-1.1 (0.82)
	Median	3.0	-1.0	-1.0
	Min, Max	2, 5	-3, 0	-3, 0

Source: *Listing 16.2.6.2.1*, *Listing 16.2.6.2.1a*, Adapted from *Table 14.2.2.1*.
N - Total number of subjects in the mITT Population, n = number of subjects, SD = Standard Deviation, Min = Minimum, Max = Maximum, DB = Double blind, OL = Open label, mITT = Modified Intent-to-treat. Change = Post Dose – Baseline values.

Figure 11-6 Mean Change from Baseline by Visit in Clinical Global Impression - Severity of Illness (CGI-S) - mITT Population



Source: *Listing 16.2.6.2.1*, *Listing 16.2.6.2.1a*, *Table 14.2.2.1*, *Figure 14.2.2.1*.

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

The Clinical Global Impression – Change from Baseline (CGI-C) scores for the mITT Population are presented in Table 14.2.3.1 and by subject details in Listing 16.2.6.3.

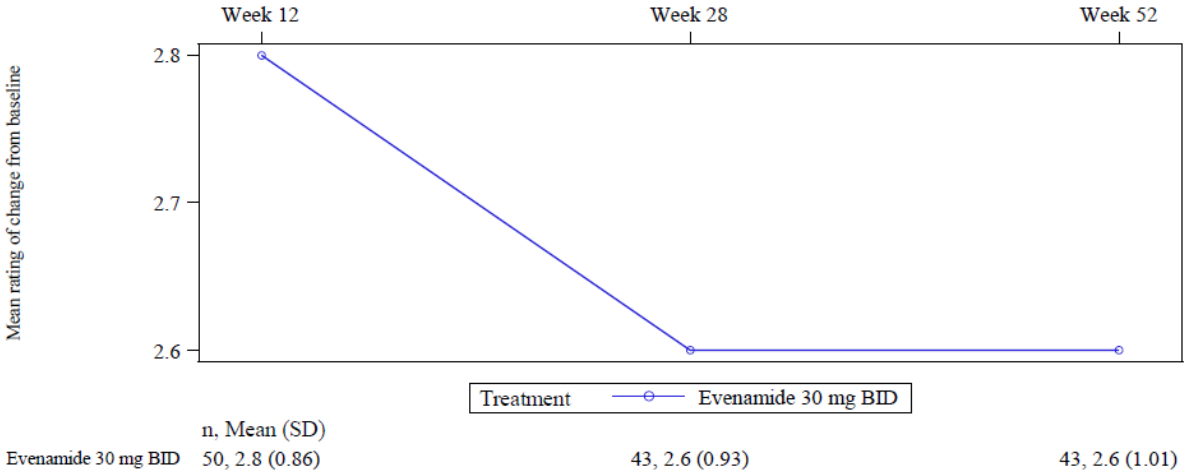
The mean (SD) CGI-C ratings recorded in the evenamide treated groups were 2.8 (0.86), 2.6 (0.93) and 2.6 (1.01) at Weeks 12, 28, and 52, respectively (Table 11-8), indicating improvement from Baseline at all the visits (Figure 11-7).

Table 11-8 Clinical Global Impression - Change from Baseline (CGI-C) – mITT Population

Visit	Statistic	Evenamide 30 mg *BID* (N=51)
Week 12	N	50
	Mean (SD)	2.8 (0.86)
	Median	3.0
	Min, Max	1, 5
Week 28	N	43
	Mean (SD)	2.6 (0.93)
	Median	2.0
	Min, Max	1, 5
Week 52	n	43
	Mean (SD)	2.6 (1.01)
	Median	2.0
	Min, Max	1, 5

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.
The patient's condition at the time of OL baseline (Study 020) was considered when assessing the CGI-C.

Figure 11-7 Clinical Global Impression – Change from Baseline (CGI-C) - mITT Population



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

Responder Analysis - CGI-C score change ≤3

A responder analysis assessing the proportion of patients rated as improved on the CGI-C at each visit was performed by considering different categories of change from Baseline (CGI-C score ≤ 3 [any improvement from Baseline] and CGI-C score >3 [no change or worsening from Baseline]) as dependent variable. Results of the responder analysis are presented in Table 14.2.3.2 for the mITT Population. Data by subject details are presented in Listing 16.2.6.3. A summary of the results is provided in Table 11-9.

Table 11-9 Responder analysis - Clinical Global Impression - Change from Baseline (CGI-C) - mITT Population

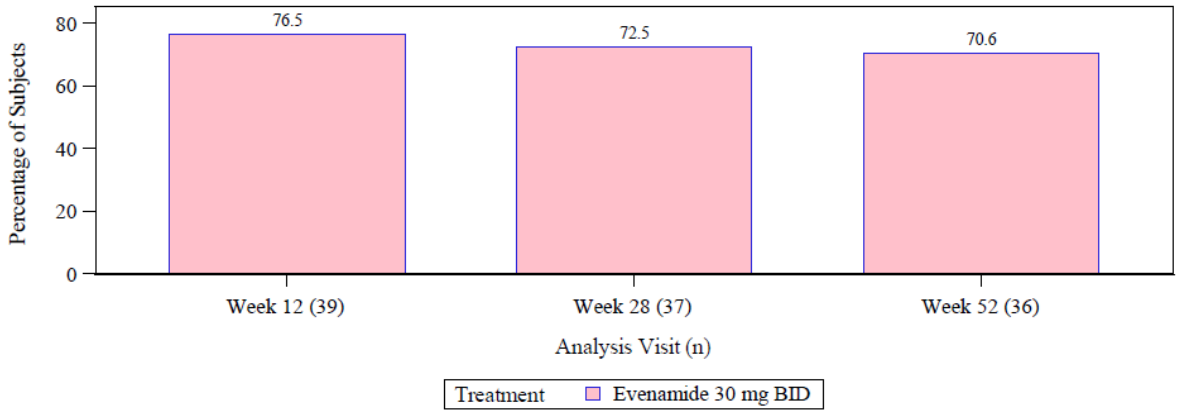
Visit	Improvement Category	Statistic	Evenamide 30 mg *BID* (N=51)
Week 12	CGI-C score <=3	n (%)	39 (76.5)
	CGI-C score >3	n (%)	11 (21.6)
	CGI-C score <=2	n (%)	22 (43.1)
	CGI-C score >2	n (%)	28 (54.9)
Week 28	CGI-C score <=3	n (%)	37 (72.5)
	CGI-C score >3	n (%)	6 (11.8)
	CGI-C score <=2	n (%)	24 (47.1)
	CGI-C score >2	n (%)	19 (37.3)
Week 52	CGI-C score <=3	n (%)	36 (70.6)
	CGI-C score >3	n (%)	7 (13.7)
	CGI-C score <=2	n (%)	23 (45.1)
	CGI-C score >2	n (%)	20 (39.2)

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 subjects, mITT = Modified intent-to-treat.

Responder analysis is performed by summarizing the proportion of patients with different categories of improvement ("any improvement" defined as CGI-C score <= 3, and "at least much improved" defined as CGI-C score <= 2) from OL Baseline to endpoint of the initial 52-Week period on the CGI-C.
Responders: Patients with <= 3 or <= 2 CGI-C Score. Percentages are calculated using the number of subjects in the mITT population as denominator (N).

The number (%) of patients rated as improved (score ≤ 3) on the CGI-C in the evenamide treated group was greater than 70% at all post-baseline visits [n(%): 39 (76.5%), 37 (72.5%) and 36 (70.6%) at Weeks 12, 28 and 52, respectively] (Figure 11-8).

Figure 11-8 Bar Chart for Clinical Global Impression - Change from Baseline (CGI-C) Responder Analysis CGI-C ≤ 3 - mITT Population

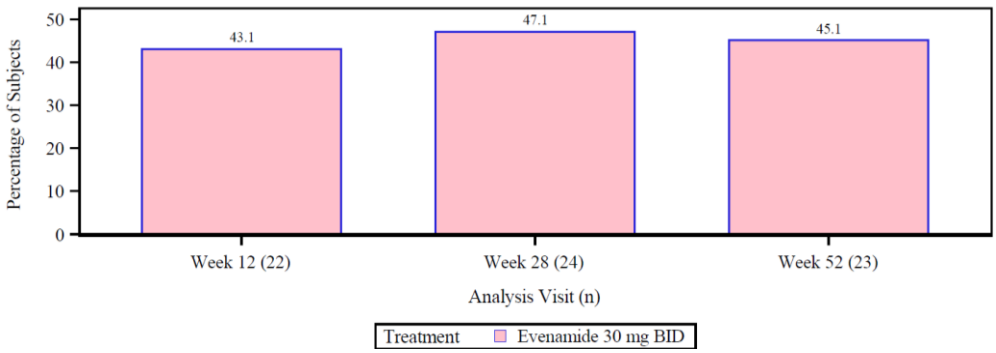


Source: *Listing 16.2.6.3*, *Table 14.2.3.2*, *Figure 14.2.3.2*.

Responder Analysis - CGI-C score change ≤ 2

The number (%) of patients rated as at least "much improved" (score ≤ 2) in the evenamide treated group was greater than 40% at all post-baseline visits [n(%): 22 (43.1%), 24 (47.1%) and 23 (45.1%) at Weeks 12, 28 and 52, respectively] (Figure 11-9).

Figure 11-9 Bar Chart for Clinical Global Impression - Change from Baseline (CGI-C) Responder Analysis CGI-C ≤ 2 - mITT Population



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

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

Mean (SD) of observed values and mean (SD) of change from Baseline in the Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-Scales and Total Score at Weeks 12, 28 and 52 (Endpoint) in the mITT Population are presented in Table 14.2.4.1 and by subject details in Listing 16.2.6.4 and Listing 16.2.6.4a.

LOF Total Score

The mean (SD) LOF Total Scores at DB Baseline and OL Baseline were 17.0 (6.82) and 16.8 (6.77), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores improved to 19.1 (6.65), 19.7 (6.06) and 19.8 (6.29), respectively, with mean (SD) changes from DB Baseline of 2.1 (5.38), 2.7 (5.13) and 2.5 (5.13), respectively, and from OL Baseline of 2.3 (4.89), 2.8 (5.65) and 2.7 (5.95), respectively in the evenamide treated group (Table 11-10, Figure 11-10).

Table 11-10 Change from Baseline in Strauss-Carpenter - Level of Functioning Scale (LOF) Sub-Scale and Total Score by Visit - mITT Population

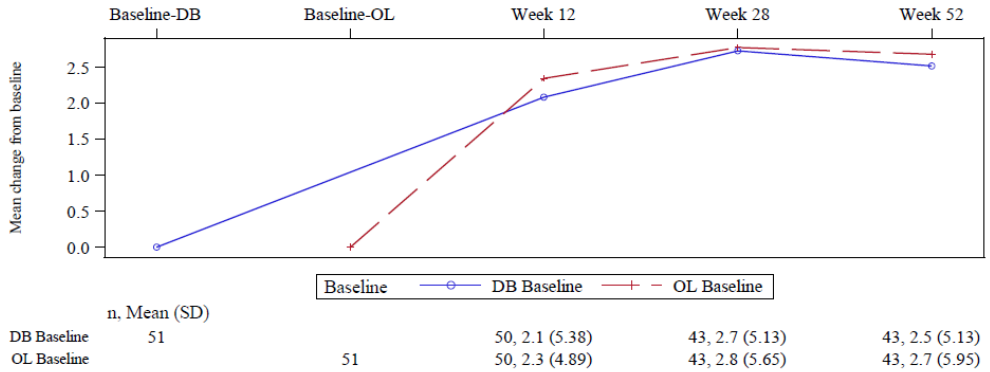
			Evenamide 30 mg *BID* (N=51)		
Sub-scale	**Visit**	**Statistic**	**Observed**	**Change from DB Baseline**	**Change from OL Baseline**
Social Contact	Baseline-DB	N	51		
		Mean (SD)	1.4 (1.12)		
		Median	1.5		
		Min, Max	0, 4		
	Baseline-OL	n	51		
		Mean (SD)	1.5 (1.23)		
		Median	1.5		
		Min, Max	0, 4		
	Week 12	n	50	50	50
		Mean (SD)	1.7 (1.14)	0.4 (0.96)	0.2 (0.80)
		Median	1.5	0.0	0.0
		Min, Max	0, 4	-2.5, 3	-1.5, 3
	Week 28	n	43	43	43
		Mean (SD)	1.7 (1.23)	0.3 (1.10)	0.2 (1.24)
		Median	2.0	0.0	0.0
		Min, Max	0, 4	-3, 3.5	-2.5, 3.5
	Week 52	n	43	43	43
		Mean (SD)	1.8 (1.35)	0.4 (1.08)	0.3 (1.23)
		Median	2.0	0.0	0.0
		Min, Max	0, 4	-1.5, 4	-2.5, 4
Work	Baseline-DB	n	51		
		Mean (SD)	1.2 (1.10)		
		Median	1.0		
		Min, Max	0, 3		
	Baseline-OL	n	51		

		Mean (SD)	1.1 (1.14)		
		Median	1.0		
		Min, Max	0, 4		
	Week 12	n	50	50	50
		Mean (SD)	1.5 (1.15)	0.3 (0.86)	0.4 (0.81)
		Median	2.0	0.0	0.0
		Min, Max	0, 4	-2, 2	-1, 3
	Week 28	n	43	43	43
		Mean (SD)	1.4 (1.05)	0.2 (0.77)	0.3 (0.90)
		Median	2.0	0.0	0.0
		Min, Max	0, 4	-1, 2	-2, 2
	Week 52	n	43	43	43
		Mean (SD)	1.3 (1.09)	0.2 (0.90)	0.2 (1.04)
		Median	2.0	0.0	0.0
		Min, Max	0, 3	-3, 3	-3, 3
Symptomatology	Baseline-DB	n	51		
		Mean (SD)	2.7 (0.88)		
		Median	3.0		
		Min, Max	0, 4		
	Baseline-OL	n	51		
		Mean (SD)	2.8 (0.71)		
		Median	3.0		
		Min, Max	1, 4		
	Week 12	n	50	50	50
		Mean (SD)	3.1 (0.59)	0.4 (0.95)	0.3 (0.56)
		Median	3.0	0.0	0.0
		Min, Max	1, 4	-2, 3.5	-0.5, 2
	Week 28	n	43	43	43
		Mean (SD)	3.2 (0.69)	0.5 (0.97)	0.3 (0.56)
		Median	3.5	0.5	0.0
		Min, Max	1, 4	-2, 3.5	-0.5, 2.5
	Week 52	n	43	43	43
		Mean (SD)	3.2 (0.65)	0.5 (0.96)	0.3 (0.63)
		Median	3.5	0.5	0.0
		Min, Max	1, 4	-2, 3	-0.5, 2.5
Function	Baseline-DB	n	51		
		Mean (SD)	2.1 (0.68)		
		Median	2.0		
		Min, Max	1, 4		
	Baseline-OL	n	51		
		Mean (SD)	2.0 (0.90)		
		Median	2.0		
		Min, Max	0, 4		
	Week 12	n	50	50	50
		Mean (SD)	2.2 (0.86)	0.1 (0.67)	0.2 (0.79)
		Median	2.0	0.0	0.0
		Min, Max	0, 4	-2, 1.4	-2.7, 2
	Week 28	n	43	43	43
		Mean (SD)	2.4 (0.72)	0.3 (0.71)	0.4 (0.87)

		Median	2.7	0.0	0.0
		Min, Max	1, 4	-2, 2	-2.7, 2
	Week 52	n	43	43	43
		Mean (SD)	2.4 (0.67)	0.2 (0.76)	0.3 (0.94)
		Median	2.7	0.0	0.0
		Min, Max	1, 4	-1.3, 2	-1.3, 2.7
Total Score	Baseline-DB	n	51		
		Mean (SD)	17.0 (6.82)		
		Median	19.0		
		Min, Max	2, 31		
	Baseline-OL	n	51		
		Mean (SD)	16.8 (6.77)		
		Median	17.0		
		Min, Max	4, 33		
	Week 12	n	50	50	50
		Mean (SD)	19.1 (6.65)	2.1 (5.38)	2.3 (4.89)
		Median	20.0	0.5	0.5
		Min, Max	5, 35	-12, 13	-12, 16
	Week 28	n	43	43	43
		Mean (SD)	19.7 (6.06)	2.7 (5.13)	2.8 (5.65)
		Median	20.0	2.0	2.0
		Min, Max	7, 32	-7, 19	-12, 18
	Week 52	n	43	43	43
		Mean (SD)	19.8 (6.29)	2.5 (5.13)	2.7 (5.95)
		Median	20.0	1.0	0.0
		Min, Max	8, 31	-8, 16	-12, 16

Source: Source: *Listing 16.2.6.4, Listing 16.2.6.4a*; Adapted from *Table 14.2.4.1*.
N - Total number of subjects in the mITT Population, n = number of subjects, SD = Standard Deviation, Min = Minimum, Max = Maximum, DB = Double blind, OL = Open label, mITT = Modified Intent-to-treat.
Total score is calculated as the sum of scores of the nine items in LOF.
Change = Post Dose – Baseline values.

Figure 11-10 Mean Change from Baseline by Visit in Strauss-Carpenter-Level of Functioning Scale (LOF) Total Score – mITT Population



Source: *Listing 16.2.6.4*, *Listing 16.2.6.4a*, *Table 14.2.4.1*, *Figure 14.2.4.1*.

LOF Social Contact Subscale Score

The mean (SD) LOF Social Contact Subscale Scores at DB Baseline and OL Baseline were 1.4 (1.12) and 1.5 (1.23), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores improved to 1.7 (1.14), 1.7 (1.23) and 1.8 (1.35), respectively, with mean (SD) changes from DB Baseline of 0.4 (0.96), 0.3 (1.10) and 0.4 (1.08), respectively, and from OL Baseline of 0.2 (0.80), 0.2 (1.24) and 0.3 (1.23), respectively in the evenamide treated group (Table 11-10).

LOF Work Subscale Score

The mean (SD) LOF Work Subscale Scores at DB Baseline and OL Baseline were 1.2 (1.10) and 1.1 (1.14), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores improved to 1.5 (1.15), 1.4 (1.05) and 1.3 (1.09), respectively, with mean (SD) changes from DB Baseline of 0.3 (0.86), 0.2 (0.77) and 0.2 (0.90), respectively, and from OL Baseline of 0.4 (0.81), 0.3 (0.90) and 0.2 (1.04), respectively in the evenamide treated group (Table 11-10).

LOF Symptomatology Subscale Score

The mean (SD) LOF Symptomatology Subscale Scores at DB Baseline and OL Baseline were 2.7 (0.88) and 2.8 (0.71), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores improved to 3.1 (0.59), 3.2 (0.69) and 3.2 (0.65), respectively, with mean (SD) changes from DB Baseline of 0.4 (0.95), 0.5 (0.97) and 0.5 (0.96), respectively, and from OL Baseline of 0.3 (0.56), 0.3 (0.56) and 0.3 (0.63), respectively in the evenamide treated group (Table 11-10).

LOF Function Subscale Score

The mean (SD) LOF Function Subscale Scores at DB Baseline and OL Baseline were 2.1 (0.68) and 2.0 (0.90), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores improved to 2.2 (0.86), 2.4 (0.72) and 2.4 (0.67), respectively, with mean (SD) changes from DB Baseline of 0.1 (0.67), 0.3 (0.71) and 0.2 (0.76), respectively, and from OL Baseline of 0.2 (0.79), 0.4 (0.87) and 0.3 (0.94), respectively in the evenamide treated group (Table 11-10).

11.5.1.4. *Patient's Medication Satisfaction Questionnaire (MSQ)*

The results of the MSQ are presented in Table 14.2.5.1 for change from Baselines at Weeks 12, 28 and 52 (endpoint). A summary of the results in the mITT Population is shown in Table 11-11. MSQ data by subject details are presented in Listing 16.2.6.5 and Listing 16.2.6.5a. The mean change from Baselines by visit in the mITT Population is shown in Figure 11-11.

Table 11-11 Change from Baseline in Medication Satisfaction Questionnaire (MSQ) by visit - mITT Population

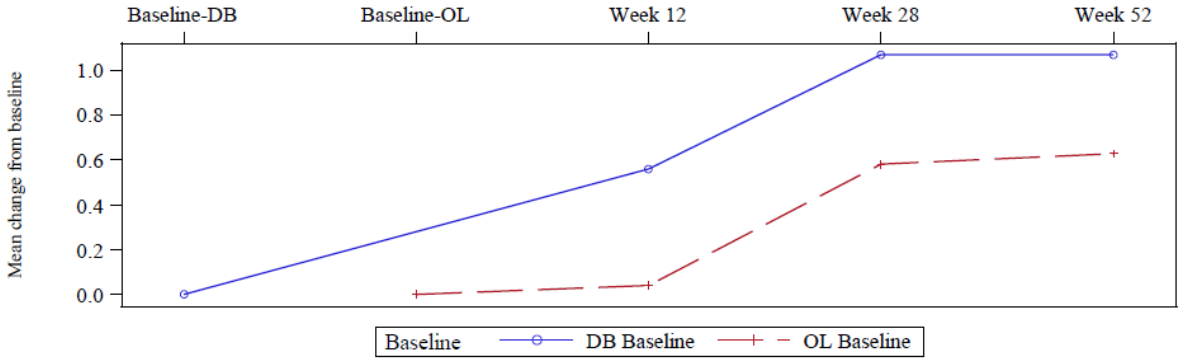
		Evenamide 30 mg *BID* (N=51)		
Visit	**Statistic**	**Observed**	**Change from DB Baseline**	**Change from OL Baseline**
Baseline-DB	n	51		
	Mean (SD)	4.6 (0.98)		
	Median	4.0		
	Min, Max	2, 7		
Baseline-OL	n	51		
	Mean (SD)	5.2 (1.07)		
	Median	5.0		
	Min, Max	2, 7		
Week 12	n	50	50	50
	Mean (SD)	5.2 (1.50)	0.6 (1.59)	0.0 (1.65)
	Median	5.0	1.0	0.0
	Min, Max	1, 7	-4, 3	-6, 4
Week 28	N	43	43	43
	Mean (SD)	5.8 (0.82)	1.1 (1.03)	0.6 (1.24)
	Median	6.0	1.0	1.0
	Min, Max	2, 7	-2, 3	-2, 4
Week 52	N	43	43	43
	Mean (SD)	5.8 (0.87)	1.1 (1.18)	0.6 (1.20)
	Median	6.0	1.0	1.0
	Min, Max	4, 7	-2, 3	-2, 3

Source: Listing 16.2.6.5, Listing 16.2.6.5a; Adapted from *Table 14.2.5.1*.
N - Total number of subjects in the mITT Population, n = number of subjects, SD = Standard Deviation, Min = Minimum, Max = Maximum, DB = Double blind, OL = Open label, mITT = Modified Intent-to-treat.
Change = Post Dose – Baseline values.

The MSQ mean (SD) scores at DB Baseline and OL Baseline were 4.6 (0.98) and 5.2 (1.07), respectively in the evenamide treated group. At Weeks 12, 28 and 52, the mean (SD) scores increased to 5.2 (1.50), 5.8 (0.82) and 5.8 (0.87), respectively, with mean (SD) changes from DB Baseline score of 0.6 (1.59), 1.1 (1.03), and 1.1 (1.18), respectively, and from OL Baseline score of 0.0 (1.65), 0.6 (1.24), and 0.6 (1.20), respectively (Table 11-11).

There was an improvement in the MSQ mean (SD) change from Baselines in the evenamide treated group at each visit from Week 12 till Week 52 as evident from the Figure 11-11.

Figure 11-11 Mean Change from Baseline by Visit in Medication Satisfaction Questionnaire – mITT Population



	n, Mean (SD)				
DB Baseline	51		50, 0.6 (1.59)	43, 1.1 (1.03)	43, 1.1 (1.18)
OL Baseline		51	50, 0.0 (1.65)	43, 0.6 (1.24)	43, 0.6 (1.20)

Source: *Listing 16.2.6.5, Listing 16.2.6.5a, Table 14.2.5.1, Figure 14.2.5.1*.

11.5.1.5. *Global Assessment of Functioning Scale (GAF)*

The results of the GAF ratings on a scale of 1 to 10 (instead of actual GAF values of 0 to 100) are presented in Table 14.2.6.1 for change from Baseline (OL) at Weeks 12, 28 and 52 (endpoint). A summary of the results in the mITT Population is shown in Table 11-12. GAF category data (on a scale of 1 to 10) by subject details are presented in Listing 16.2.6.6. The mean change from Baseline by visit in the mITT Population is shown in Figure 11-12.

Table 11-12 Summary of Global Assessment of Functioning (GAF) by visit - mITT Population

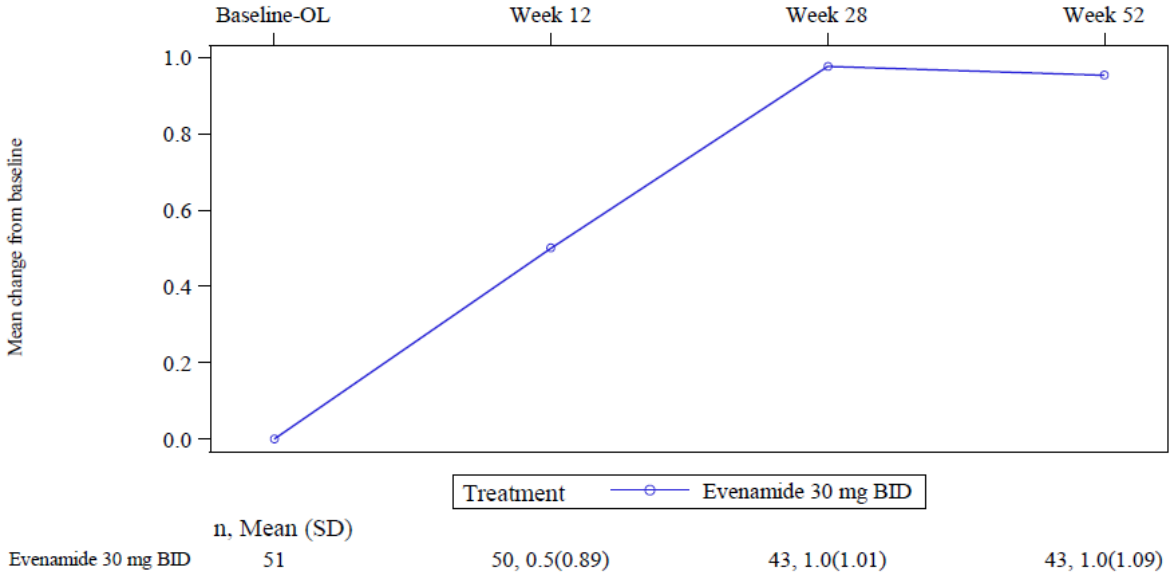
		Evenamide 30 mg *BID* (N=51)	
Visit	**Statistic**	**Observed***	**Change from OL Baseline**
Baseline-OL	n	51	
	Mean (SD)	6.6 (1.18)	
	Median	6.0	
	Min, Max	4, 8	
Week 12	n	50	50
	Mean (SD)	7.1 (1.07)	0.5 (0.89)
	Median	7.0	0.0
	Min, Max	3, 9	-2, 3
Week 28	n	43	43
	Mean (SD)	7.6 (0.91)	1.0 (1.01)
	Median	8.0	1.0
	Min, Max	5, 9	-1, 3
Week 52	N	43	43
	Mean (SD)	7.7 (0.87)	1.0 (1.09)

	Median	8.0	1.0
	Min, Max	6, 9	-1, 3

Source: *Listing 16.2.6.6*; Adapted from *Table 14.2.6.1*.
N - Total number of subjects in the mITT Population, n = number of subjects, SD = Standard Deviation, Min = Minimum, Max = Maximum, OL = Open label, mITT = Modified Intent-to-treat.
Change = Post Dose – Baseline values.
*GAF category data on a scale of 1 to 10 (instead of actual GAF values of 0 to 100).

The GAF category (on a scale of 1 to 10) mean (SD) score at OL Baseline was 6.6 (1.18) in the evenamide treated group, and increased to 7.1 (1.07), 7.6 (0.91) and 7.7 (0.87) at Weeks 12, 28 and 52, respectively, indicating an overall improvement in functioning. The mean (SD) changes from OL Baseline score at Weeks 12, 28 and 52 were 0.5 (0.89), 1.0 (1.01), and 1.0 (1.09), respectively (Table 11-12).

Figure 11-12 Mean Change from Baseline by Visit in Global Assessment of Functioning (GAF) – mITT Population



Source: *Listing 16.2.6.6*, *Table 14.2.6.1*, *Figure 14.2.6.1*.

There was improvement in the GAF category mean (SD) change from Baseline in the evenamide treated group from Week 12 to Week 28, with no further improvement at Week 52, as evident from Figure 11-12.

11.5.2. Statistical/Analytical Issues

Detailed documentation of statistical methods is presented in Section 9.7.1 and in the Statistical Analysis Plan (Appendix 16.1.9). There were no statistical/analytical issues reported.

11.5.2.1. *Handling of Dropouts or Missing Data*

Handling of missing data is described in Section 9.7.1.3.

11.5.2.2. *Interim Analyses and Data Monitoring*

No interim assessments were performed.

11.5.2.3. *Multicenter Studies*

Analyses conducted did not assess possible differences among sites.

11.5.2.4. *Multiple Comparisons/Multiplicity*

Not applicable.

11.5.2.5. *Use of an Efficacy Subset of Subjects*

Not applicable.

11.5.2.6. *Active-Control Studies Intended to Show Equivalence*

Not applicable.

11.5.2.7. *Examination of Subgroups*

Not applicable.

11.5.3. Tabulation of Individual Response Data

Individual efficacy response data are provided in Section 16.2.6.

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

Not applicable.

11.5.5. Drug-Drug and Drug-Disease Interactions

Not applicable.

11.5.6. By-Subject Displays

Not applicable.

11.6. Efficacy Conclusions

The primary efficacy objective of the study was to evaluate the long-term efficacy of evenamide 30 mg *BID*, based on improvement in symptoms of psychosis, as assessed by the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the total score on the Positive and Negative Syndrome Scale (PANSS) in patients with schizophrenia. Secondary efficacy objectives of the study were to evaluate the

long-term efficacy of evenamide, based on the rating of the Clinical Global Impression - Change from Baseline (CGI-C) at endpoint (Week 52 or early discontinuation) and mean change from Baseline(s) to endpoint on the CGI - Severity of illness (CGI-S). Other secondary efficacy objectives were to determine the long-term effect of evenamide on general functioning, based on the change from Baseline to endpoint (Week 52 or early discontinuation) on the Global Assessment of Functioning (GAF) scale; daily functioning based on the change from Baseline(s) (Study 008A and Study 020) to endpoint (Week 52 or early discontinuation) on the Strauss-Carpenter Levels of Functioning (LOF) scale, and patients' satisfaction with the study medication using the Patient's Medication Satisfaction Questionnaire (MSQ).

Positive and Negative Syndrome Scale (PANSS)

Patients treated with evenamide 30 mg *BID* experienced an improvement of symptoms of schizophrenia, as assessed by the change from Baseline on the PANSS Total score, which was steadily decreasing (indicating improvement) visit by visit through Week 52.

PANSS Responder analysis

Treatment with evenamide 30 mg *BID* resulted in a clinically meaningful benefit, defined as ≥20% improvement from Baseline. This level of response was achieved by an increasing proportion of patients at each visit, with more than 50% of patients meeting this criterion at Week 52, compared to the DB Baseline. Similarly, an increasing proportion of patients achieved an even greater improvement of ≥30% from Baseline at each visit, with 27.5% of patients meeting this criterion at Week 52, compared to the DB Baseline.

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

In the analysis of the secondary efficacy measures, evenamide 30 mg *BID* treatment was associated with a decrease from Baseline in the mean CGI-S score over time at each visit, indicating the efficacy of add-on treatment with evenamide in reducing the overall severity of illness in patients with chronic schizophrenia.

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

The CGI-C mean rating at post-baseline visits indicated that patients treated with evenamide 30 mg *BID* were considered, on average, minimally to much improved. More than 70% of patients at each visit were considered as responders based on CGI-C rating [score ≤ 3 (any improvement from Baseline)], with more than 40% of patients at each visit considered to be "at least much improved" (score ≤ 2).

Strauss-Carpenter - Level of Functioning Scale (LOF)

The evenamide 30 mg *BID* treatment was associated with an improvement from Baseline OL and DB) on the LOF Total score and LOF sub-scale scores (Social Contact, Symptomatology, Work, and Function) at all visits.

Patient's Medication Satisfaction Questionnaire (MSQ)

The MSQ scores at post-baseline visits indicated an increased satisfaction with treatment compared to baseline, except at Week 12, which remained unchanged compared to the OL Baseline. An improvement in the MSQ mean change from Baseline(s) was observed in the evenamide 30 mg *BID* treatment group from Week 12 to Week 28, whereas no further reduction was noted from Week 28 to Week 52.

Global Assessment of Functioning Scale (GAF)

A steady improvement in the GAF category mean (SD) scores (on a scale of 1 to 10) was noted at each visit from Baseline (OL) till Week 52.

Efficacy Summary

The long-term efficacy of evenamide 30 mg *BID* was demonstrated by improvement in the symptoms of schizophrenia assessed by the PANSS Total Score, a decrease in the disease severity assessed by the CGI-S score, and improvement in overall severity of illness assessed by the CGI-C. In addition, evenamide enhanced functionality of patients as evident from improvements in the LOF Total score and subscale scores, and improvement in the individual's social, occupational, and psychological functioning as assessed by the Global Assessment of Functioning (GAF) scale. An increase in patient's satisfaction with their medication, as assessed by the Patient's Medication Satisfaction Questionnaire (MSQ), was also noted. In addition, the proportion of patients with clinically meaningful improvement, defined based on responder criteria for the PANSS total score and CGI-C, increased through 52 weeks of treatment. These long-term beneficial effects of evenamide treatment, which increased over time, were observed in patients with chronic schizophrenia who have been symptomatic on their current single SGA medication.

12. SAFETY EVALUATION

12.1. Extent of Exposure

In the Safety Population, the mean (SD) duration of exposure to study drug was 279.8 (81.73) days, ranging from 33 to 408 days, in the overall evenamide treated group (Table 12-1).

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

Table 12-1 Study Drug Exposure - Safety Population

Characteristics	Statistic	Evenamide 30 mg *BID* (N=52)
Duration of Exposure (days) [a]	n	52
	Mean (SD)	279.8 (81.73)
	Median	295.5
	Min, Max	33, 408
Overall Treatment Compliance (%) [b]	n	52
	Mean (SD)	99.7 (3.14)
	Median	99.7
	Min, Max	94, 120

Source: *Listing 16.2.5.2*; Adapted from *Table 14.3.0.1*.
N - Total number of subjects in the Safety Population, n = number of patients, SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a] Duration of exposure (days) = [Treatment end date - Treatment start date + 1].
[b] Treatment compliance is computed as 100*[#Capsules consumed / #Capsules expected to be consumed].
#Capsules consumed per kit calculated as #dispensed capsules in the kit – #returned/lost capsules in the kits.
#Capsules expected to be consumed = 2 * [(Last dose date – First dose date) + 1].

12.2. Dose Adjustments or Kit Replacement

A summary of Dose Adjustments or Kit Replacement in the Safety Population is presented in Table 14.3.0.2 and by subject details in Listing 16.2.5.3.

Only 1 (1.9%) subject in the evenamide treated group had a dose adjustments or kit replacement; this was a dose adjustment (dose was decreased) because of the start of an adverse event.

12.3. Adverse Events

The primary safety objective of the study was to evaluate the long-term safety and tolerability of an oral dose of evenamide of 30 mg *BID* [60 mg/day], achieved after a 4-week titration starting with 15 mg *BID* in patients with schizophrenia.

12.3.1. Brief Summary of Adverse Events

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

At least one TEAE was reported in 22 (42.3%) subjects, at least one serious TEAE was reported in 4 (7.7%) subjects, at least one Treatment-Related TEAE was reported in 4 (7.7%) subjects, ‘any TEAE leading to study drug discontinuation’ was reported in 3 (5.8%) subjects and ‘any TEAE resulting in death’ was reported in 2 subjects. One of the 2 TEAEs resulting in death occurred more than 30 days after the last dose of study medication. There were no reports of ‘any serious and treatment-related TEAE’ (Table 12-2).

Among the 22 subjects who reported at least one TEAE in the study, 10 (19.2%) subjects had a TEAE that was mild in severity, 8 (15.4%) subjects had a TEAE that was moderate in severity, and 4 (7.7%) subjects had a TEAE that was severe in nature (Table 12-2).

Among the 4 (7.7%) subjects who reported at least one treatment-related TEAE in the study, 3 (5.8%) subjects had a TEAE that was mild in severity, 1 (1.9%) subject had a TEAE that was moderate in severity, and no subjects had a TEAE that was severe in nature (Table 12-2).

Table 12-2 Overall Summary of Treatment-Emergent Adverse Events – Safety Population

Category	Evenamide 30 mg *BID* (N=52) n (%)
No. of Subjects with at least one TEAE	22 (42.3)
No. of Subjects with at least one Serious TEAE	4 (7.7)
No. of Subjects with at least one Treatment-Related TEAE [a]	4 (7.7)
No. of Subjects with Any Serious and Treatment-related TEAE	0 (0.0)
No. of Subjects with Any TEAE Leading to Study Drug Discontinuation	3 (5.8)
No. of Subjects with Any TEAE Resulting in Death @	2 (3.8)
No. of Subjects with Any TEAE by Severity	
Mild	10 (19.2)
Moderate	8 (15.4)
Severe	4 (7.7)
No. of Subjects with Any Treatment-related TEAE by Severity	
Mild	3 (5.8)
Moderate	1 (1.9)
Severe	0 (0.0)

Source: *Listing 16.2.7.1*, *Listing 16.2.7.2*, *Listing 16.2.7.3*; 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 calculated using the number of subjects in the safety population as denominator (N).
@ = One of the 2 AEs resulting death occurred more than 30 days after the last dose of study medication.
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 open label extension Study 020.
Unique terms within subjects are considered by counting each TEAE only once within each subject. Subjects 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 of unknown relationship (not reported).

12.3.2. 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.

The most frequently reported TEAEs by SOCs with ≥5% incidence were:

- Infections and infestations [19.2% (10/52)], Gastrointestinal disorders [7.7% (4/52)], Nervous system disorders [7.7% (4/52)], Blood and lymphatic system disorders [5.8% (3/52)], and Investigations [5.8% (3/52)] (Table 12-3).

The most frequently reported TEAEs by PTs with ≥2% incidence were:

- Nasopharyngitis [5.8% (3/52)], Influenza [3.8% (2/52)], Tooth infection [3.8% (2/52)], Akathisia [3.8% (2/52)], Headache [3.8% (2/52)], and Anaemia [3.8% (2/52)] (Table 12-3).

A summary of treatment-emergent serious adverse events by SOC and PT for the Safety Population is presented in Table 14.3.1.3 and by subject details in Listing 16.2.7.2.

Four (7.7%) subjects experienced serious TEAEs, with cellulitis, pneumonia, femur fracture, intentional overdose, acute myocardial infarction, and sudden death reported in 1 (1.9%) subject each in the evenamide treated group. Of these, pneumonia and acute myocardial infarction occurred more than 30 days after the last dose of study medication.

A summary of treatment-related TEAEs by SOC and PT for the Safety Population is presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1.

The reported treatment-related TEAEs by SOC were 'Nervous system disorders' with PTs 'Akathisia' in 1 (1.9%) subject and 'Headache' in 1 (1.9%) subject. The PT 'Dry mouth' under the SOC 'Gastrointestinal disorders' was reported in 1 (1.9%) subject and the PT 'Psychotic disorder' under the SOC 'Psychiatric disorders' was reported in 1 (1.9%) subject.

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

Three (5.8%) subjects in the evenamide treated group had a TEAE leading to study drug discontinuation, with the PTs of 'Cellulitis', 'Intentional overdose', and 'Psychotic disorder' reported in 1 (1.9%) subject each.

12.3.3. Analysis of Adverse Events

12.3.3.1. *Overall Incidence of Treatment-Emergent Adverse Events*

The number of subjects who reported any TEAE was 22 (42.3%) subjects.

A summary of TEAEs that occurred with a ≥1% incidence (by SOC) in the evenamide treated group by SOC and PT is presented in Table 12-3, and by subject details in Listing 16.2.7.1.

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

Table 12-3 Summary of Treatment-Emergent Adverse Events by System Organ Class (SOC) and Preferred Term (PT) - Safety Population

System Organ Class Preferred Term	Evenamide 30 mg *BID* (N=52) n (%)
Number of subjects with any TEAE	22 (42.3)
Infections and infestations	10 (19.2)
Cellulitis	1 (1.9)
Gastroenteritis	1 (1.9)
Influenza	2 (3.8)
Nasopharyngitis	3 (5.8)
Pharyngitis	1 (1.9)
Pneumonia@	1 (1.9)
Tooth infection	2 (3.8)
Urinary tract infection	1 (1.9)
Gastrointestinal disorders	4 (7.7)
Abdominal pain	1 (1.9)
Constipation@	1 (1.9)
Dry mouth	1 (1.9)
Toothache	1 (1.9)
Nervous system disorders	4 (7.7)
Akathisia	2 (3.8)
Headache	2 (3.8)
Blood and lymphatic system disorders	3 (5.8)
Anaemia	2 (3.8)
Leukopenia	1 (1.9)
Investigations	3 (5.8)
Blood prolactin increased	1 (1.9)
Blood triglycerides increased	1 (1.9)
Weight decreased	1 (1.9)
Cardiac disorders	2 (3.8)
Acute myocardial infarction@	1 (1.9)
Sinus tachycardia	1 (1.9)
Injury, poisoning and procedural complications	2 (3.8)
Fall	1 (1.9)
Femur fracture	1 (1.9)
Intentional overdose	1 (1.9)
Musculoskeletal and connective tissue disorders	2 (3.8)
Back pain	1 (1.9)
Exostosis	1 (1.9)
Psychiatric disorders	2 (3.8)
Hypomania	1 (1.9)
Insomnia	1 (1.9)
Psychotic disorder	1 (1.9)
Eye disorders	1 (1.9)
Cataract	1 (1.9)

General disorders and administration site conditions	1 (1.9)
Sudden death	1 (1.9)
Renal and urinary disorders	1 (1.9)
Dysuria	1 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (1.9)
Bronchospasm	1 (1.9)

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 calculated using the number of subjects in the safety population as denominator (N).
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 open label extension Study 020.
@ = Adverse event started 30 days after the last dose of study medication.
Adverse events are coded with MedDRA Version 24.0.
Subjects are counted only once per system organ class and per preferred term.

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

A summary of treatment-related TEAEs by SOC and PT for the Safety Population is presented in Table 14.3.1.4 and by subject details in Listing 16.2.7.1.

Overall, a total of 4 (7.7%) subjects reported at least one treatment-related TEAE (Table 12-4).

The most frequently reported treatment-related TEAEs (> 1% incidence in the treated group) by PT were ‘Akathisia’, ‘Headache’, ‘Dry Mouth’ and Psychotic disorder’ in 1 (1.9%) subject each. No other treatment-related TEAEs reported in the treated group (Table 12-4).

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

Table 12-4 Summary of Treatment-Related Treatment-Emergent Adverse Events by SOC and Preferred Term - Safety Population

System Organ Class Preferred Term	**Evenamide 30 mg *BID* (N=52) n (%)**
Number of subjects with any Treatment-Related TEAE	4 (7.7)
Nervous system disorders	2 (3.8)
Akathisia	1 (1.9)
Headache	1 (1.9)
Gastrointestinal disorders	1 (1.9)
Dry mouth	1 (1.9)
Psychiatric disorders	1 (1.9)
Psychotic disorder	1 (1.9)

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 calculated using the number of subjects in the safety population as denominator (N).
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 open label extension Study 020.

Treatment related TEAEs are the TEAEs which are possibly or probably related to study drug, or of unknown relationship (not reported). Adverse events are coded with MedDRA Version 24.0.
Subjects are counted only once per system organ class and per preferred term.

12.3.3.3. *Incidence of Treatment-Emergent Adverse Events by Severity*

All TEAEs by maximum severity by SOC and Preferred Term are presented in Table 14.3.1.6 and a by subject listing is included in Listing 16.2.7.1. The overall incidence of most frequent (> 1% incidence in any group) TEAEs by severity is summarized in Table 12-5.

The majority of subjects had TEAEs of mild or moderate intensity [18 (34.6%)] and 4 (7.7%) subjects had severe TEAEs, including Tooth infection, Femur fracture, Intentional overdose, Acute myocardial infarction (occurring more than 30 days after the last dose of study medication), and Sudden death. Detailed narrative of these severe TEAEs are provided in Section 14.

Of the 18 (34.6%) subjects with TEAEs of mild or moderate intensity, 10 (19.2%) subjects were of mild intensity and 8 (15.4%) subjects were of moderate intensity.

Table 12-5 Summary of Treatment-Emergent Adverse Events by Maximum Severity by SOC and Preferred Term - Safety Population

System Organ Class Preferred Term	Severity	Evenamide 30 mg *BID* (N=52) n (%)
Number of subjects with any TEAE	Mild	10 (19.2)
	Moderate	8 (15.4)
	Severe	4 (7.7)
Infections and infestations	Mild	6 (11.5)
	Moderate	3 (5.8)
	Severe	**1 (1.9)**
Cellulitis	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Gastroenteritis	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Influenza	Mild	0 (0.0)
	Moderate	2 (3.8)
	Severe	0 (0.0)
Nasopharyngitis	Mild	3 (5.8)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Pharyngitis	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Pneumonia@	Mild	0 (0.0)
	Moderate	1 (1.9)

System Organ Class Preferred Term	Severity	Evenamide 30 mg *BID* (N=52) n (%)
	Severe	0 (0.0)
Tooth infection	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Urinary tract infection	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Blood and lymphatic system disorders	Mild	3 (5.8)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Anaemia	Mild	2 (3.8)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Leukopenia	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Gastrointestinal disorders	Mild	3 (5.8)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Abdominal pain	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Constipation@	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Dry mouth	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Toothache	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Nervous system disorders	Mild	3 (5.8)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Akathisia	Mild	1 (1.9)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Headache	Mild	2 (3.8)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Injury, poisoning and procedural complications	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**2 (3.8)**
Fall	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)

System Organ Class Preferred Term	Severity	Evenamide 30 mg *BID* (N=52) n (%)
Femur fracture	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Intentional overdose	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Investigations	Mild	1 (1.9)
	Moderate	2 (3.8)
	Severe	0 (0.0)
Blood prolactin increased	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Blood triglycerides increased	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Weight decreased	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Cardiac disorders	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Acute myocardial infarction@	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Sinus tachycardia	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Eye disorders	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Cataract	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
General disorders and administration site conditions	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Sudden death	Mild	0 (0.0)
	Moderate	0 (0.0)
	Severe	**1 (1.9)**
Musculoskeletal and connective tissue disorders	Mild	1 (1.9)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Back pain	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)

System Organ Class Preferred Term	Severity	Evenamide 30 mg *BID* (N=52) n (%)
Exostosis	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Psychiatric disorders	Mild	1 (1.9)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Hypomania	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Insomnia	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Psychotic disorder	Mild	0 (0.0)
	Moderate	1 (1.9)
	Severe	0 (0.0)
Renal and urinary disorders	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Dysuria	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	0 (0.0)
Bronchospasm	Mild	1 (1.9)
	Moderate	0 (0.0)
	Severe	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 calculated using the number of subjects in the safety population as denominator (N).
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 open label extension Study 020.
@ = Adverse event started more than 30 days after the last dose of study medication.
Adverse events are coded with MedDRA Version 24.0.
A subject with multiple occurrences of the same AE or a continuing AE is counted only once under the highest reported severity or relationship.

12.3.4. Listing of Adverse Events by Subject

All AEs for each subject are listed in Listing 16.2.7.1.

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

Two deaths (one occurred more than 30 days after the last dose of study medication) were reported in this study and are presented in Table 12-6 and in Listing 16.2.7.4.

Other serious adverse events reported in this study are presented in Table 12-7 and in Listing 16.2.7.2.

Other significant adverse events leading to study drug discontinuation are presented in Table 12-8 and in Listing 16.2.7.3.

The brief narratives of all the SAEs, including the death cases and other significant adverse events leading to study drug discontinuation are described in Section 12.4.2. The Expanded Narratives of deaths, SAEs, and AEs leading to study drug discontinuation are provided in Section 14.

12.4.1. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.4.1.1. *Deaths*

A 66-year-old female subject (number 892018) was found dead by her family member and the death was determined to be due to cardiorespiratory arrest. A 76-year-old male subject (number 895015) died due to acute myocardial infarction more than 30 days after the last dose of study medication (Table 12-6). Brief narratives of these two serious adverse events are presented in Section 12.4.2.1.

Table 12-6 Adverse Events with Fatal Outcome - Safety Population

Subject Number Age/Sex	Date of First Dose and Time /Last Dose (Day)	Reported Term	Preferred Term/ System Organ Class	Date of Death (Day)	Brief Description of Event
892018 66/F	31OCT2023/12:27/ 25APR2024 (178)	Sudden Death	Sudden death/ General disorders and administration site conditions	26APR2024 (179)	Patient was found dead by family member. Cardiorespiratory arrest
895015 76/M	25OCT2023/12:10/ 26NOV2023 (33)	Acute Myocardial Infarction@	Acute myocardial infarction/ Cardiac disorders	10FEB2024 (109)	Acute myocardial infarction that led to death.

Source: Adapted from *Listing 16.2.7.4*.
F = Female, M = Male, Y = Yes, N = No, Age = Age at baseline of Study 020.
@ = Adverse event started more than 30 days after the last dose of study medication.
Day = Date of last dose of investigational product - Date of first dose of investigational product + 1 if last dose is on or after the date of the first dose. Else Date of last dose - Date of first dose.
Day of Death/Autopsy = Date of Death/Autopsy - Date of first dose of investigational product + 1 if Death/Autopsy date is on or after the date of the first dose of investigational product.

12.4.1.2. *Other 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 by subject details in Listing 16.2.7.2.

A total of 4 (7.7%) subjects experienced a serious TEAE. Serious adverse events other than death under the SOC 'Infections and infestations' were reported in 2 (3.8%) subjects ['Cellulitis' in 1 subject (892007) and 'Pneumonia' in 1 subject (895015 - occurring more than 30 days after the last dose of study medication)] and 'Injury, poisoning and procedural complications' were reported in 2 (3.8%) subjects ['Femur fracture' in 1 subject (895015) and 'Intentional overdose' in 1 subject (895021)] (Table 12-7). Brief narratives of these events are provided in Section 12.4.2.

Table 12-7 Summary of Treatment-Emergent Serious Adverse Events by SOC and Preferred Term - Safety Population

System Organ Class Preferred Term	Evenamide 30 mg *BID* (N=52) n (%)
Number of subjects with any Serious TEAE	4 (7.7)
Infections and infestations	2 (3.8)
Cellulitis	1 (1.9)
Pneumonia@	1 (1.9)
Injury, poisoning and procedural complications	2 (3.8)
Femur fracture	1 (1.9)
Intentional overdose	1 (1.9)
Cardiac disorders	1 (1.9)
Acute myocardial infarction@	1 (1.9)
General disorders and administration site conditions	1 (1.9)
Sudden death	1 (1.9)

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 calculated using the number of subjects in the safety population as denominator (N).
@ = Adverse event started more than 30 days after the last dose of study medication.
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 open label extension Study 020. Adverse events are coded with MedDRA Version 24.0. Subjects are counted only once per system organ class and per preferred term.

12.4.1.3. *Other Significant Adverse Events (TEAEs) leading to Study Drug Discontinuation*

A summary of TEAEs leading to study drug discontinuation by SOC and PT for the Safety Population is presented in Table 12-8 and by subject details in Listing 16.2.7.3.

A total of 3 (5.8%) subjects reported TEAEs leading to study drug discontinuation in the evenamide treated group.

The TEAEs leading to study drug discontinuation, by SOC, were 'Infections and infestations' (PT: Cellulitis) [subject 892007] considered as mild and not related to the study medication;

'Injury, poisoning and procedural complications' (PT: Intentional overdose) [subject 895021] considered as severe and not related to the study medication, and 'Psychiatric disorders' (PT: Psychotic disorder) [subject 855001] considered not-serious, of moderate intensity and possibly related to the study medication. Brief narratives of these TEAEs leading to study drug discontinuation are given in Section 12.4.2.2.

Table 12-8 Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation - Safety Population

System Organ Class Preferred Term	Evenamide 30 mg *BID* (N=52) n (%)
Number of subjects with any TEAE Leading to Study Drug Discontinuation	3 (5.8)
Infections and infestations	1 (1.9)
Cellulitis	1 (1.9)
Injury, poisoning and procedural complications	1 (1.9)
Intentional overdose	1 (1.9)
Psychiatric disorders	1 (1.9)
Psychotic disorder	1 (1.9)

Source: *Listing 16.2.7.3*; Adapted from *Table 14.3.1.5*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
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 open label extension Study 020.
Adverse events are coded with MedDRA Version 24.0.
Subjects are counted only once per system organ class and per preferred term.

12.4.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

All expanded narratives are presented in the CSR Section 14. Short narratives of Serious Adverse Events, including Death, in Section 12.4.2.1, and short narratives of TEAEs leading to Study Drug Discontinuation in Section 12.4.2.2 are presented below.

12.4.2.1. Narratives of Serious Adverse Events including Death

Four subjects experienced a total of 6 serious TEAEs. Three serious TEAEs, i.e., Pneumonia, Femur fracture, and Acute myocardial infarction occurred in a single subject, with pneumonia and infarction occurring more than 30 days after the last dose of study medication. The other 3 serious TEAEs, i.e., Cellulitis, Intentional overdose, and Sudden death were reported in 1 subject each. These SAEs are summarized in Table 12-9.

Table 12-9 Summary of Serious Adverse Events - Safety Population

Subject Number Age/Sex	Date of onset (Day on treatment) Reported term [Preferred Term]
892007 37M	17NOV2023 (100) Cellulitis [Cellulitis]
892018 66/F	26APR2024 (179) Sudden Death [Sudden death]
895015 76/M	18DEC2023 (55) Left Femoral Head Fracture [Femur fracture]
895015 76/M	30JAN2024 (98) Pneumonia@ [Pneumonia]
895015 76/M	10FEB2024 (109) Acute Myocardial Infarction@ [Acute myocardial infarction]
895021 25/M	02MAY2024 (177) Possible Intentional Drug Overdose [Intentional overdose]

Source: Adapted from *Listing 16.2.7.2*
F = Female, M = Male, Age = Age at baseline of Study 020, TEAE = Treatment Emergent Adverse Event, Y = Yes, N = No.
@ = Adverse event started more than 30 days after the last dose of study medication.
Day = Date of last dose of investigational product - Date of first dose of investigational product + 1 if last dose is on or after the date of the first dose of investigational product. Else Date of last dose - Date of first dose.
Day of AE Start/End = AE start/end date - Date of first dose of investigational product + 1 if the AE start/end date is on or after the date of the first dose of investigational product. Adverse events are coded with MedDRA Version 24.0.

A brief summary of each of the above SAEs is provided below. The Expanded Narratives are provided in Section 14.

Subject Number: 892018 ("Sudden death")

This 67-year-old female subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history, concurrent conditions and past drugs were not reported. Relevant concomitant medication included clozapine for schizophrenia. The subject's physical examination was normal for all body systems. On 31-Oct-2023, the subject started the treatment with oral evenamide (capsule, 15 mg) twice daily. On 28-Nov-2023, the dose of study medication was increased to 30 mg twice daily till 25-Apr-2024 for the psychiatric disorder.

On 26-Apr-2024, at 17:00 hours, 5 months and 26 days after administering the first dose of study medication, the subject died due to possible cardiorespiratory arrest (severity: severe).

As per the report, the subject's daughter called an ambulance and informed the site that she found the subject asleep and on trying to wake her up, she did not respond and was declared dead.

The investigator considered the event as not related to study medication. On 10 October 2024 the investigator changes the definition of SAE with Sudden death.

Subject Number: 895015 (Death due to "Acute myocardial infarction")

This 76-year-old male subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history and past drugs were not reported. Relevant concurrent conditions included hypothyroidism (since 2013). Relevant concomitant medication included olanzapine for schizophrenia and levothyroxine for hypothyroidism. On 25-Oct-2023, the subject started the treatment with oral evenamide at a dose of 15 mg *BID*, which was up-titrated to 30 mg *BID* on 22-Nov-23. On 26-Nov-2023, the subject received the last dose of evenamide due to alert of hyperkalemia, which turned out to be false after re-test. On 18-Dec-2023, the subject fell from his own height after tripping over a piece of furniture leg, due to which he was transferred to the hospital and was diagnosed with left femoral head fracture (severity: severe) and recovered on 22-Dec-2023. On 25-Jan-2024, it was confirmed that the subject had withdrawn his informed consent form (ICF) as decided by family.

On 30-Jan-2024, the subject was hospitalized due to pneumonia (severity: moderate) and recovered on 09-Feb-2024. On 10-Feb-2024, at 13:45 hours, 2 months and 15 days after the administration of the last dose of study medication, the subject died at home due to an acute myocardial infarction. As a treatment, he had received oxygen and cardiopulmonary resuscitation, available on the nursing cart. No lab test or ECG was performed for the SAE. Additionally, he had no previous cardiac conditions that could have contributed to the SAE.

The investigator considered the SAE as not related to study medication.

Subject Number: 892007 (Cellulitis)

This 37-year-old male subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history, concurrent conditions and past drugs were not reported. Relevant concomitant medication included clozapine for schizophrenia. The subject's physical examination was normal for all body systems. On 10-Aug-2023, the subject started the treatment with oral evenamide 15 mg *BID*, which was up-titrated to 30 mg *BID* on 07-Sep-23.

On 17-Nov-2023, 3 months and 7 days after starting treatment with the study medication, the subject's mother informed the site that in the afternoon the subject had accidentally hit his

ankle. At 21:00 hours, the subject was presented to the ward as he had pain, swelling and blisters on his left ankle and was diagnosed with cellulitis (severity: mild) and was kept under observation in the ward. The next day, he was treated with intravenous (IV) penicillin sodium, ciprofloxacin and clindamycin at an unknown dose and frequency till 13-Dec-2023. On 21-Nov-2023, the subject underwent venous doppler ultrasound of right lower limb revealing the absence of deep vein thrombosis (DVT)/superficial venous thrombosis (SVT). On the next day, chest computed tomography (CT) showed no signs of pulmonary thromboembolism (PTE) in major arterial branches. 04-Dec-2023, abdominal ultrasound showed normal results for abdominal aorta, superior vena cava, and retroperitoneum. Later, on 13-Dec-2023, the subject was stable, recovered from the SAE and was discharged. The same day, the subject was withdrawn from the study drug treatment so that he could repose and prepare for possible surgeries.

The investigator considered the event as not related to study medication.

Subject Number: 895015 (Pneumonia)

This 76-year-old male subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history and past drugs were not reported. Relevant concurrent conditions included hypothyroidism (since 2013). Relevant concomitant medication included olanzapine for schizophrenia and levothyroxine for hypothyroidism. On 25-Oct-2023, the subject started the treatment with oral evenamide at a dose of 15 mg *BID*, which was up-titrated to 30 mg *BID* on 22-Nov-2023. On 26-Nov-2023, the subject received the last dose of evenamide due to alert of hyperkalemia, which turned out to be false after re-test. On 25-Jan-2024, it was confirmed that the subject had withdrawn his informed consent form (ICF) as decided by family.

On 29-Jan-2024, the subject's vitals included blood pressure (BP) as 80/50 mmHg, oxygen saturation (SaO2) was 91%, temperature (T) was 36.5 ºC and functional capacity (FC) was 97 lpm (normal range was unknown). On 30-Jan-2024, 2 months and 4 days after receiving the last dose of the study medication, the subject was hospitalized due to pneumonia (severity: moderate). Reportedly, the subject appeared pale, had a coated tongue, refused to eat and was vomiting, and his vital signs were as follows - BP was 100/70 mmHg, SaO2 was 91%, temperature was 38º C and FC was 101 lpm. No chest X-ray or CT scan was performed for the SAE. As a corrective treatment, he was administered unknown antibiotics of broad spectrum for the SAE pneumonia. On 09-Feb-2024, the subject recovered from the SAE of pneumonia and was subsequently discharged from the hospital. Later, on 16-Feb-2024, the subject's sister informed the site that the subject died on 10-Feb-2024 due to an acute myocardial infarction.

The investigator considered the SAE as not related to study medication.

Subject Number: 895015 (Femur fracture)

This 76-year-old male subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history was not reported. Relevant concurrent conditions included hypothyroidism (since 2013). The subject's past drugs were not reported. Relevant concomitant medication included olanzapine for schizophrenia and levothyroxine for hypothyroidism. On 25-Oct-2023, the subject started the treatment with oral evenamide at a dose of 15 mg *BID*, which was up-titrated to 30 mg *BID* on 22-Nov-23. On 26-Nov-2023, the subject received the last dose of evenamide due to alert of hyperkalemia, which turned to be false after re-test.

On 18-Dec-2023, at around 07:00 pm, 22 days after receiving the last dose of the study medication, the subject's sister reported to the site that the subject fell from his own height after tripping over a piece of furniture leg. On the same day, he was transferred to the hospital and was diagnosed with left femoral head fracture. On 20-Dec-2023, the subject received oral anti-coagulants and antibiotics (names and dose were unknown). The next day, the subject's sister informed the site that a day prior at 04:30 PM, the subject underwent a successful hip replacement surgery, after which he was stable, and no complications were observed. On 22-Dec-2023, at 12:30 pm, the subject recovered from the SAE and was discharged from the hospital. Reportedly, the subject was doing physiotherapy rehabilitation sessions.

On 25-Jan-2024, it was confirmed that the subject had withdrawn his informed consent form (ICF) as decided by family. Later, on 16-Feb-2024, the subject's sister informed the site that the subject died on 10-Feb-2024 due to an acute myocardial infarction. It was confirmed that an autopsy was not performed. Reportedly, the PI stated that SAE pneumonia might be a complication of the fracture.

The investigator considered the SAE as not related to study medication.

Subject Number: 895021 (Intentional overdose)

This 26-year-old male subject (Ethnicity: Hispanic/Latino) with a psychiatric disorder met all the eligibility criteria and signed the informed consent form. The subject's medical history was not reported. Relevant concurrent conditions included myopia (since 2021) and schizophrenia (since 2020). The subject's past drugs included risperidone (2015). Relevant concomitant medications included risperidone for schizophrenia, sertraline for negative symptoms of schizophrenia and bromazepam for anxiety. The subject's physical examination was normal for all body systems. On 08-Nov-2023, the subject started the treatment with oral evenamide at a dose of 15 mg twice day till 04-Dec-2023 for the psychiatric disorder. On 05-Dec-2023, the dose of study medication was increased to 30 mg (capsule, 30 mg) twice daily. On 27-Apr-2024, the subject's mother observed her son's behavior as scattered, nervous and irritable. He

was not hallucinating, but presented with strange behavior. He also suffered from terminal insomnia and discontinuous sleep. On 01-May-2024, the subject received the most recent dose of evenamide prior to the SAE.

On 02-May-2024, by 09:00 am, the subject's mother found him lying unconscious on his bed with the pills. She confirmed that the evenamide medication boxes were opened and he had taken at least 10 capsules of evenamide, and other medications like bromazepam, risperidone and sertraline were also there. After finding him unconscious, she called an ambulance, and the subject was admitted to the intensive care unit (ICU) with low oxygen saturation (70%) due to possible intentional drug overdose (severity: severe). As a lifesaving procedure, he was provided with mechanical ventilatory assistance. The next day, the subject was transferred to another hospital to address the worsening respiratory function. Later, the subject regained consciousness but remained confused. From 04-May-2024, the subject was breathing on his own without respiratory assistance and was being administered haloperidol and risperidone.

On 08-May-2024, the subject was transferred to the crisis care unit (CCU) and was administered oral lorazepam and haloperidol at a dose of 4 mg and 5 mg, respectively, at every 8 hours for possible intentional drug overdose. On 09-May-2024, he showed a reticent attitude, clear consciousness, was oriented to person and partially to place and time. He was restless, responded to specific questions, had a dysphoric mood, with bradypsychia, hypobulia and impaired judgement. No pathological, delusional or suicidal ideation was reported. He lacked awareness of the situation and had partial awareness of the illness. On 13-May-2024, the PI interviewed the subject's family and was informed that the subject ingested approximately 100 tablets including risperidone, olanzapine, evenamide, bromazepam, and sertraline with the intention of falling asleep, not to commit suicide, likely due to interpersonal conflict with his brother. At the time of the interview, he did not express suicidal ideation. Both the mother and the subject expressed their intention of continuing treatment with evenamide. On the same day, at 11:30 pm, the subject was transferred to his reference hospital along with the referral reports and remains hospitalized in the mental health service. On 16-May-2024, the subject recovered from the SAE and subsequently was discharged from the hospital and was taken home.

The investigator considered the SAE as not related to study medication.

12.4.2.2.Narratives of TEAEs leading to Study Drug Discontinuation

A total of 3 (5.8%) subjects experienced TEAE leading to discontinuation of the study medication. Table 12-10 below summarizes the TEAEs that led to treatment discontinuation.

Table 12-10 Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation – Safety Population

System Organ Class Preferred Term	Evenamide 30 mg *BID* (N=52) n (%)
Number of subjects with any TEAE Leading to Study Drug Discontinuation	3 (5.8)
Infections and infestations	1 (1.9)
Cellulitis	1 (1.9)
Injury, poisoning and procedural complications	1 (1.9)
Intentional overdose	1 (1.9)
Psychiatric disorders	1 (1.9)
Psychotic disorder	1 (1.9)

Source: *Listing 16.2.7.3*; Adapted from *Table 14.3.1.5*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
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 open label extension Study 020.
Adverse events are coded with MedDRA Version 24.0.
Subjects are counted only once per system organ class and per preferred term.

A brief summary of adverse events leading to treatment discontinuation (excluding SAE cases, i.e., cellulitis and intentional overdose, which are described in Section 12.4.2.1 above), is provided below. The Expanded Narratives are provided in Section 14.

Subject Number: 855001 (Psychotic disorder)

This 46-year-old schizophrenic male was screened in the study NW-3509/008A/II/2020 on 17 Jan 2023. Subsequently, after completing the NW-3509/008A/II/2020 study, he received the first dose of investigational drug (evenamide) for study NW-3509/020/III/2021 on date 23 March 2023. At the baseline evaluation (NW-3509/020/III/2021) on 16 March 2023, vital signs measurements were blood pressure of 130/95 mmHg, temperature 36.8°C, pulse rate 89 beats per minute (bpm), and respiratory rate 24 resp/min, and the ECG was normal. The patient developed an adverse event of Psychotic Exacerbation [Psychiatric disorders], on Day 57 (18-May-2023). The investigator assessed the adverse event of Psychotic Exacerbation [Psychiatric disorders] as being of moderate intensity and possibly related to the study medication. This adverse event led to study medication dose discontinuation on 16 June 2023 and withdrawal from the study on 18-Sept-2023, considering the lack of improvement and the concomitant worsening of symptoms as reasoned by Principal Investigator.

12.5. Clinical Laboratory Evaluation

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

Results of the laboratory measurements are presented in Table 14.3.4.1 (hematology) and Table 14.3.4.2 (blood chemistry), and by subject details 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.

Results of the clinical laboratory continuous and categorical special diagnostic tests for the Safety Population are presented in Listing 16.2.8.4 and Listing 16.2.8.5, respectively.

12.5.2. Evaluation of Each Laboratory Parameter

12.5.2.1. Hematology

12.5.2.1.1. Laboratory Values over Time

Summary statistics for change from Baseline by visit are presented for hematology parameters in Table 14.3.4.1 (observed values and change from Baseline). There were no clinically meaningful changes in mean values from Baseline for hematology parameters in the treated group.

12.5.2.1.2. Individual Subject Changes

A summary of newly emergent clinically notable abnormal findings in laboratory hematology parameters at any post-Baseline in the Safety Population is presented in Table 14.3.4.3. There were no clinically meaningful trends for notable abnormalities observed in the evenamide treated group over the time points (Table 12-11).

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

Test (Unit)	Visit	Notable Criteria	Evenamide 30 mg *BID* (N=52) n (%)
Hemoglobin (g/L)	Week 4	<=0.85 x LLN	1 (1.9)
	Week 12	<=0.85 x LLN	1 (1.9)
Leukocytes (10^9/L)	Week 12	<= 3.0	1 (1.9)
	Week 28	<= 3.0	2 (3.8)
	Week 4	>=15.0	1 (1.9)
	Week 52	>=15.0	1 (1.9)

Platelets (10^9/L)	Week 28	>=600	1 (1.9)

Source: *Listing 16.2.8.1*; Adapted from *Table 14.3.4.3*.
N = Total number of subjects in the Safety Population, n = number of subjects with available data.
Percentages are calculated by considering Male/Female count (38/14) whenever the criterion is specific for Male/Female.

ANC monitoring for patients on clozapine: ANC levels measured during routine blood monitoring in the Safety Population are provided in the Listing 16.2.4.4.4. ANC level of one subject (895020) was in the Mild Neutropenia range (1000 to 1499/µL) only at Week 36 and Week 52. All other subjects for whom the ANC levels were monitored at specified visits, were in the normal range.

12.5.2.2. Blood Chemistry

12.5.2.2.1. Laboratory Values over Time

Summary statistics of change from Baseline by visit are presented for blood chemistry parameters in Table 14.3.4.2 (observed values and changes from Baseline). There were no clinically meaningful changes in mean values from Baseline for blood chemistry parameters in the treated group.

12.5.2.2.2. Individual Subject Changes

A summary of clinically notable abnormalities by visit is presented for blood chemistry parameters in Table 14.3.4.4. There were no clinically meaningful trends for notable abnormalities observed in the evenamide treated group (Table 12-12).

The blood chemistry parameter with the maximum number of newly emergent clinically notable abnormal findings was potassium (≥ 6.0 mmol/L) seen in 6 (11.5%) subjects at Week 4 and in 3 (5.8%) subjects at Week 52, followed by LDL cholesterol (≥ 4.1 mmol/L) seen in 5 (9.6%) subjects at Week 12 and in 4 (7.7%) subjects each at Week 28 and Week 52, and HDL cholesterol (≤ 0.8 mmol/L) seen in 4 (7.7%) subjects at Week 4 (Table 12-12).

Table 12-12 Laboratory Chemistry: Newly Emergent Clinically Notable Abnormal Findings at any Post-Baseline Visit - Safety Population

Test (Unit)	Visit	Notable Criteria	Evenamide 30 mg *BID* (N=52) n (%)
Bicarbonate (mmol/L)	Week 4	<= 18	1 (1.9)
	Week 12	<= 18	2 (3.8)
Bilirubin (umol/L)	Week 4	>= 34	1 (1.9)
Calcium (mmol/L)	Week 28	>= 2.7	1 (1.9)
Cholesterol (mmol/L)	Week 4	>= 7.25	2 (3.8)
	Week 12	>= 7.25	2 (3.8)
Creatine Kinase (U/L)	Week 4	>=400	1 (1.9)
	Week 12	>=400	2 (3.8)

	Week 52	>=400	1 (1.9)
HDL Cholesterol (mmol/L)	Week 4	<= 0.8	4 (7.7)
	Week 12	<= 0.8	2 (3.8)
	Week 28	<= 0.8	2 (3.8)
	Week 52	<= 0.8	2 (3.8)
LDL Cholesterol (mmol/L)	Week 4	>= 4.1	2 (3.8)
	Week 12	>= 4.1	5 (9.6)
	Week 28	>= 4.1	4 (7.7)
	Week 52	>= 4.1	4 (7.7)
Lactate Dehydrogenase (U/L)	Week 4	>= 500	1 (1.9)
Potassium (mmol/L)	Week 4	>= 6.0	6 (11.5)
	Week 12	>= 6.0	2 (3.8)
	Week 28	>= 6.0	2 (3.8)
	Week 52	>= 6.0	3 (5.8)
Triglycerides (mmol/L)	Week 4	>= 4.5	2 (3.8)
	Week 12	>= 4.5	1 (1.9)

Source: *Listing 16.2.8.2*; Adapted from *Table 14.3.4.4*.
N = Total number of subjects in the Safety Population, n = number of subjects with available data.
Percentages are calculated by considering Male/Female count (38/14) whenever the criterion is specific for Male/Female.

12.5.2.3. Urinalysis

Urinalysis data are listed (Listing 16.2.8.3) only, along with clinical significance as evaluated by the Investigator.

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

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

12.6.1. Vital Signs

Vital sign measurements (mean values and changes from Baseline) for the Safety Population are presented in Table 14.3.6.1, and by subject details in Listing 16.2.9.1 and Listing 16.2.9.2. Vital signs values at each of the scheduled timepoints are presented in Listing 16.2.9a, and newly emergent clinically notable abnormalities are presented in Table 14.3.6.2, with by subject details in Listing 16.2.9b. The criteria for clinically notable vital signs abnormalities are displayed in Appendix 2 of the protocol presented in Appendix 16.1.1.

12.6.1.1. *Vital Signs over Time*

Summary statistics of change from Baseline by visit are presented for vital signs in Table 14.3.6.1 (observed values and changes from Baseline). There were no clinically meaningful changes in mean values from Baseline for vital signs in the evenamide treated group.

12.6.1.2. *Individual Clinically Notable Abnormalities – Vital Signs*

A summary of incidence of newly emergent clinically notable abnormalities for vital signs is presented in Table 14.3.6.2, 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 (Table 14.3.6.2).

The percentage of subjects with a clinically notable value in blood pressure (systolic/ diastolic), and/or pulse rate (change from Baseline and/or orthostatic change) at any time post Baseline, including Week 52, was low [1.9% (1 of 52) of subjects]. Data for subjects with at least one post Baseline clinically notable finding for blood pressure (systolic/ diastolic), pulse rate change from Baseline or orthostatic changes are displayed in Table 12-13.

Table 12-13 Incidence of Newly Emergent Clinically Notable Abnormalities for Vital Signs – Safety Population

Vital Signs	Visit	Timepoint	Criteria	Evenamide 30 mg *BID* (N=52) n (%)
Diastolic BP-Standing (1 minutes) (mmHg)	Week 8	Any Time	Value >= 105 and >= 15 increase from Baseline	1 (1.9)
Orthostatic Hypotension-SBP (1 minute) (mmHg)	Week 36	Any Time	Decrease in SBP/DBP from Supine to Standing position > 30 mmHg	1 (1.9)
Orthostatic Hypotension-SBP (3 minutes) (mmHg)	Week 36	Any Time	Decrease in SBP/DBP from Supine to Standing position > 30 mmHg	1 (1.9)
Pulse Rate-Standing (3 minutes) (beats/min)	Week 36	Any Time	Value > = 120 and > = 15 increase from Baseline	1 (1.9)
Pulse Rate-Supine (5 minutes) (beats/min)	Week 8	Any Time	Value <= 50 and >= 15 decrease from Baseline	1 (1.9)
Systolic BP-Standing (1 minutes) (mmHg)	Week 8	Any Time	Value <= 90 and >= 20 decrease from Baseline	1 (1.9)
	Week 12	Any Time	Value <= 90 and >= 20 decrease from Baseline	1 (1.9)
	Week 20	Any Time	Value <= 90 and >= 20 decrease from Baseline	1 (1.9)
Weight (kg)	Week 4		>=7% increase from Baseline	2 (3.8)
	Week 8		>= 7% decrease from Baseline	2 (3.8)
	Week 8		>=7% increase from Baseline	3 (5.8)
	Week 12		>= 7% decrease from Baseline	4 (7.7)
	Week 12		>=7% increase from Baseline	1 (1.9)
	Week 20		>= 7% decrease from Baseline	4 (7.7)

Vital Signs	Visit	Timepoint	Criteria	Evenamide 30 mg *BID* (N=52) n (%)
	Week 20		>=7% increase from Baseline	2 (3.8)
	Week 28		>= 7% decrease from Baseline	2 (3.8)
	Week 28		>=7% increase from Baseline	1 (1.9)
	Week 36		>= 7% decrease from Baseline	3 (5.8)
	Week 36		>=7% increase from Baseline	3 (5.8)
	Week 44		>= 7% decrease from Baseline	4 (7.7)
	Week 44		>=7% increase from Baseline	1 (1.9)
	Week 52		>= 7% decrease from Baseline	6 (11.5)
	Week 52		>=7% increase from Baseline	3 (5.8)
	Safety follow-up - Day 7		>= 7% decrease from Baseline	6 (11.5)
	Safety follow-up - Day 7		>=7% increase from Baseline	5 (9.6)

Source: *Listing 16.2.9b*; Adapted from *Table 14.3.6.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
For EVN-EVN Subjects 008A Baseline and for PLC-EVN Subjects 020 Baseline is considered.

The percentage of subjects with a clinically notable increase in weight (defined as ≥ 7% increase from Baseline) at any time post Baseline was 9.6% (5 of 52) of subjects at Safety follow-up - Day 7, followed by 5.8% (3 of 52) of subjects each at Weeks 8, 36, and 52. The percentage of subjects with a clinically notable increase in weight (defined as ≥ 7% increase from Baseline) at the other visits (Weeks 4, 12, 20, 28, and 44) was lower than 5% (1 or 2 of 52) of subjects.

The percentage of subjects with a clinically notable decrease in weight (defined as ≥ 7% decrease from Baseline) at any time post Baseline was 11.5% (6 of 52) of subjects each at Safety follow-up - Day 7 and at Week 52, followed by 7.7% (4 of 52) of subjects each at Weeks 12, 20, and 44, followed by 5.8% (3 of 52) of subjects at Week 36. The percentage of subjects with a clinically notable decrease in weight (defined as ≥ 7% decrease from Baseline) at the other visits (Weeks 8 and 28) was lower than 5% (2 of 52) of subjects.

12.6.2. Electrocardiogram Findings

A total of 297 ECGs from 52 subjects enrolled in the study were considered for statistical analysis. The change from baseline at each visit and at endpoint (Week 52 or early discontinuation) for ECG parameters (Mean heart rate, RR interval, PR interval, QRS axis, 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 was no significant prolongation of mean baseline QTcF value at any post-dose timepoint in the study. There were no clinically meaningful changes from baseline in mean values for any ECG parameters (Mean Heart Rate,

RR Interval, PR Interval, QRS Axis, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval) among all the subjects evaluated (Table 12-14).

A summary of treatment-emergent abnormalities in ECG, as assessed by the Central reader, in the safety population is presented in Table 14.3.5.2 and by subject details in Listing 16.2.11.2. There were 2 (3.85%) treatment-emergent abnormalities identified, both of which were deemed 'not clinically significant' by the central reader. A summary of treatment-emergent abnormalities in ECG, as assessed by the investigators, in the safety population is presented in Table 14.3.5.3 and by subject details in Listing 16.2.11.4. There were 11 (21.2%) treatment-emergent abnormalities identified, all of which were deemed as 'not clinically significant' by the investigators.

Table 12-14 Summary of Change from Baseline in Electrocardiogram (ECG) Parameters - Safety Population

			Evenamide 30 mg *BID* (N=52)	
Parameter	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
ECG Mean Heart Rate (bpm)	Baseline [a]	n	52	
		Mean (SD)	73.1 (11.71)	
		Median	70.7	
		Min, Max	52, 101	
	Week 4	n	52	52
		Mean (SD)	71.3 (14.57)	-1.8 (9.14)
		Median	68.0	-3.0
		Min, Max	50, 107	-30, 17
	Week 12	n	49	49
		Mean (SD)	73.4 (13.70)	0.5 (11.96)
		Median	72.0	-1.0
		Min, Max	52, 110	-22, 30
	Week 28	n	43	43
		Mean (SD)	75.0 (14.92)	1.8 (11.88)
		Median	71.0	2.7
		Min, Max	50, 115	-17, 39
	Week 52	n	43	43
		Mean (SD)	75.7 (11.64)	2.6 (11.03)
		Median	73.0	3.0
		Min, Max	59, 104	-18, 33
PR Interval, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	160.1 (17.24)	
		Median	160.3	
		Min, Max	123, 207	
	Week 4	n	52	52
		Mean (SD)	158.3 (14.97)	-1.7 (10.67)
		Median	155.5	-2.5

			Evenamide 30 mg *BID* (N=52)	
Parameter	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
		Min, Max	123, 186	-25, 25
	Week 12	n	49	49
		Mean (SD)	155.6 (15.85)	-4.3 (10.96)
		Median	155.0	-3.7
		Min, Max	124, 194	-32, 18
	Week 28	n	43	43
		Mean (SD)	155.5 (17.12)	-4.4 (8.93)
		Median	156.0	-3.0
		Min, Max	125, 186	-26, 12
	Week 52	n	43	43
		Mean (SD)	156.3 (15.98)	-2.0 (13.35)
		Median	156.0	0.7
		Min, Max	129, 191	-26, 27
QRS Axis (deg)	Baseline [a]	n	51	
		Mean (SD)	34.6 (32.17)	
		Median	35.0	
		Min, Max	-60, 95	
	Week 4	n	52	51
		Mean (SD)	35.4 (34.00)	-0.7 (8.24)
		Median	40.0	0.0
		Min, Max	-50, 110	-30, 18
	Week 12	n	49	48
		Mean (SD)	33.9 (35.21)	-2.4 (7.01)
		Median	30.0	0.0
		Min, Max	-60, 110	-20, 10
	Week 28	n	42	42
		Mean (SD)	32.7 (31.91)	-4.2 (9.44)
		Median	35.0	-2.5
		Min, Max	-30, 95	-25, 25
	Week 52	n	43	42
		Mean (SD)	33.8 (37.06)	-2.6 (11.02)
		Median	40.0	0.0
		Min, Max	-50, 95	-25, 20
QRS Duration, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	94.4 (7.28)	
		Median	94.5	
		Min, Max	82, 115	
	Week 4	n	52	52
		Mean (SD)	95.6 (7.69)	1.2 (5.08)
		Median	96.0	1.8
		Min, Max	74, 114	-11, 12
	Week 12	n	49	49
		Mean (SD)	95.9 (7.22)	1.4 (5.13)
		Median	95.0	1.0

			Evenamide 30 mg *BID* (N=52)	
Parameter	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
		Min, Max	83, 115	-9, 13
	Week 28	n	43	43
		Mean (SD)	95.0 (8.43)	0.5 (6.69)
		Median	95.0	0.0
		Min, Max	73, 108	-17, 19
	Week 52	n	43	43
		Mean (SD)	96.5 (6.15)	1.7 (4.77)
		Median	96.0	1.0
		Min, Max	82, 106	-9, 10
QT Interval, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	381.5 (27.28)	
		Median	381.5	
		Min, Max	326, 442	
	Week 4	n	51	51
		Mean (SD)	383.1 (31.03)	2.1 (19.40)
		Median	386.0	2.0
		Min, Max	323, 451	-42, 40
	Week 12	n	49	49
		Mean (SD)	385.2 (27.03)	2.0 (20.50)
		Median	386.0	4.0
		Min, Max	324, 438	-57, 42
	Week 28	n	43	43
		Mean (SD)	379.6 (30.85)	-3.3 (22.54)
		Median	385.0	-2.0
		Min, Max	320, 442	-72, 44
	Week 52	n	43	43
		Mean (SD)	376.8 (23.95)	-6.8 (20.51)
		Median	377.0	-10.0
		Min, Max	316, 426	-56, 39
QTcB Interval, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	417.8 (22.15)	
		Median	419.8	
		Min, Max	352, 460	
	Week 4	n	51	51
		Mean (SD)	413.4 (20.79)	-4.5 (16.96)
		Median	415.0	-1.7
		Min, Max	369, 454	-44, 28
	Week 12	n	49	49
		Mean (SD)	422.2 (23.82)	3.3 (19.41)
		Median	422.0	7.0
		Min, Max	365, 482	-33, 39
	Week 28	n	43	43
		Mean (SD)	420.0 (23.20)	0.5 (20.02)
		Median	420.0	4.0

			Evenamide 30 mg *BID* (N=52)	
Parameter	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
		Min, Max	363, 466	-43, 35
	Week 52	n	43	43
		Mean (SD)	420.3 (18.86)	0.6 (17.02)
		Median	422.0	-1.7
		Min, Max	371, 468	-25, 27
QTcF Interval, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	405.1 (18.87)	
		Median	404.5	
		Min, Max	351, 447	
	Week 4	n	51	51
		Mean (SD)	402.6 (16.86)	-2.4 (13.25)
		Median	401.0	1.0
		Min, Max	366, 447	-41, 19
	Week 12	n	49	49
		Mean (SD)	409.1 (18.14)	2.7 (12.35)
		Median	410.0	4.0
		Min, Max	363, 448	-24, 27
	Week 28	n	43	43
		Mean (SD)	405.6 (19.35)	-1.0 (15.11)
		Median	404.0	0.3
		Min, Max	355, 448	-31, 30
	Week 52	n	43	43
		Mean (SD)	405.0 (15.30)	-2.0 (11.39)
		Median	408.0	-3.0
		Min, Max	356, 437	-26, 18
RR Interval, Aggregate (ms)	Baseline [a]	n	52	
		Mean (SD)	843.2 (133.09)	
		Median	857.3	
		Min, Max	592, 1158	
	Week 4	N	52	52
		Mean (SD)	874.8 (168.20)	31.6 (115.02)
		Median	882.0	33.5
		Min, Max	560, 1193	-195, 363
	Week 12	N	49	49
		Mean (SD)	843.8 (149.23)	-2.2 (140.96)
		Median	838.0	14.0
		Min, Max	545, 1158	-315, 294
	Week 28	N	43	43
		Mean (SD)	828.3 (151.07)	-15.4 (128.61)
		Median	843.0	-26.0
		Min, Max	523, 1205	-377, 218
	Week 52	N	43	43
		Mean (SD)	810.6 (118.02)	-35.1 (128.77)
		Median	823.0	-17.0

			Evenamide 30 mg *BID* (N=52)	
Parameter	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
		Min, Max	575, 1019	-324, 204

Source: *Listing 16.2.11.1*; Adapted from *Table 14.3.5.1*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
[a]: For 008A Evenamide to 020 Evenamide Subjects 008A Baseline has been considered and for 008A Placebo to 020 Evenamide switchover Subjects 020 Baseline has been considered.

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.

In the categorical analysis of ECG parameters (Table 14.3.5.4; Table 12-15), there were 2 subjects (3.85%) with a 25% increase in heart rate from baseline at Week 28, along with a HR > 100 bpm; both were EVN-EVN subjects. In EVN-EVN subjects, there was 1 subject (1.92%) with QTcB interval aggregate >480 and ≤ 500 ms at Week 12. One subject (1.92%) at Week 4, 2 subjects (3.85%) at Week 12, 2 subjects (3.85%) at Week 28, and 1 subject (1.92%) at Week 52 had a QTcB interval aggregate >450 and ≤480 ms. Two subjects (3.85%) at Week 12 and 1 subject (1.92%) at Week 28 had a change from baseline in QTc interval: > 30 msec and ≤ 60 msec. In PLC-EVN subjects, there were 2 subjects (3.85%) at Baseline-2 hours post dose visit, 2 subjects (3.85%) at Week 28, and 1 subject (1.92%) at Week 52 who had a QTcB interval aggregate >450 and ≤480 ms. Two subjects (3.85%) each at Baseline-2 hours post dose visit, Week 12 and Week 28 had a change from baseline in QTc interval: > 30 msec and ≤ 60 msec.

In the categorical analysis of ECG parameters, an Aggregate (ms) of > 450 and ≤ 480 ms in QTcB Interval was noted in one subject at Week 52 (PLC-EVN subject), and no significant abnormal QTcF interval aggregate or an abnormal change from baseline in QTcF values were noted. When considered in alignment with the antecedent study, Fridericia correction method for QT (QTcF) is more relevant for data in this study, and therefore more importance should be given to QTcF values than QTcB when interpreting the results.

Table 12-15 Electrocardiogram (ECG) Treatment-Emergent Parameters Categorical Analysis - Safety Population

Treatment: Evenamide 30 mg *BID* (Evenamide to Evenamide)				
Parameter	**Visit**	**Criteria**	**Category**	**Evenamide 30 mg *BID* (N=52) n (%)**
ECG Mean Heart Rate (bpm)	Week 28	Change From Baseline value	EGHRMN % CHANGE FROM BASELINE >=25 to a HR > 100 bpm	2 (3.85)
QTcB Interval, Aggregate (ms)	Week 4	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	1 (1.92)
	Week 12	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	2 (3.85)
	Week 12	Absolute Value	QTc ABSOLUTE INTERVAL > 480 AND <= 500	1 (1.92)
	Week 12	Change From Baseline value	QTc CHANGE FROM BASELINE > 30 AND <= 60	2 (3.85)
	Week 28	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	2 (3.85)
	Week 28	Change From Baseline value	QTc CHANGE FROM BASELINE > 30 AND <= 60	1 (1.92)
	Week 52	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	1 (1.92)
Treatment: Evenamide 30 mg *BID* (Placebo to Evenamide)				
QTcB Interval, Aggregate (ms)	Baseline-2 hours Post Dose	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	2 (3.85)
	Baseline-2 hours Post Dose	Change From Baseline value	QTc CHANGE FROM BASELINE > 30 AND <= 60	2 (3.85)
	Week 12	Change From Baseline value	QTc CHANGE FROM BASELINE > 30 AND <= 60	2 (3.85)
	Week 28	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	2 (3.85)
	Week 28	Change From Baseline value	QTc CHANGE FROM BASELINE > 30 AND <= 60	2 (3.85)
	Week 52	Absolute Value	QTc ABSOLUTE INTERVAL > 450 AND <= 480	1 (1.92)

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.
EGHRMN: ECG Mean Heart Rate

12.6.3. Physical and Neurological Findings

12.6.3.1. *Physical and Neurological Examination individual subject changes*

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

Summaries for physical and neurological examination findings by visit are presented in Table 14.3.7 and Table 14.3.9, respectively. The proportion of patients in the evenamide 30 mg *BID* treated group with treatment-emergent abnormal findings on the physical examinations and neurological examinations are presented in Table 12-16 and Table 12-17, respectively.

Table 12-16 Physical Examination: Treatment Emergent Abnormalities – Safety Population

Result	Evenamide 30 mg *BID* (N=52) n (%)
Abnormal, NCS	0 (0.0)
Abnormal, CS	0 (0.0)

Source: *Listing 16.2.10*; Adapted from *Table 14.3.7*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
For EVN-EVN Subjects 008A Baseline and for PLC-EVN Subjects 020 Baseline is considered.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any body system are counted only once.

Table 12-17 Neurological Examination: Treatment Emergent Abnormalities - Safety Population

Result	Evenamide 30 mg *BID* (N=52) n (%)
Abnormal, NCS	0 (0.0)
Abnormal, CS	0 (0.0)

Source: *Listing 16.2.13*; Adapted from *Table 14.3.9*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
For EVN-EVN Subjects 008A Baseline and for PLC-EVN Subjects 020 baseline is considered.
Percentages are calculated using the number of subjects in the safety population as denominator (N). CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any neurological system are counted only once.

No significant abnormalities were identified during physical examinations and neurological examinations in the evenamide treated group.

12.6.4. Columbia-Suicide Severity Rating Scale Findings

A summary of the Columbia Suicide Severity Rating Scale (C-SSRS) 'Since Last Visit' - Suicidal Ideation, Intensity of Most Severe Suicidal Ideation and Suicidal Behavior for the Safety Population is presented in Table 14.3.11.1.1, Table 14.3.11.1.2 and Table 14.3.11.2,

respectively. By subject details are presented in Listing 16.2.15.1 and Listing 16.2.15.2 for Ideation and Intensity, and Suicidal Behavior, respectively.

The number of subjects with newly emergent suicidal ideation since the last visit for the Safety Population is shown in Table 12-18. At Week 4, 'Non-Specific Suicidal thought' and 'Wish to be Dead' were reported by 1 subject each. Also at Week 8, 'Non-Specific Suicidal Thought' and 'Wish to be Dead' were reported by 1 subject each. At Weeks 12, 20 and 28, the Suicidal Ideation 'Wish to be Dead' was reported by 1 (1.9%), 1 (1.9%) and 2 (3.8%) subjects, respectively.

Table 12-18 Summary of Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit - Suicidal Ideation - Safety Population

Visit	Suicidal Ideation	Evenamide 30 mg *BID* (N=52) n (%)
Week 4	Non-Specific Suicidal Thought	1 (1.9)
	Wish to be Dead	1 (1.9)
Week 8	Non-Specific Suicidal Thought	1 (1.9)
	Wish to be Dead	1 (1.9)
Week 12	Wish to be Dead	1 (1.9)
Week 20	Wish to be Dead	1 (1.9)
Week 28	Wish to be Dead	2 (3.8)

Source: *Listing 16.2.15.1*; Adapted from *Table 14.3.11.1.1*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data. Percentages are calculated using the number of subjects in the safety population as denominator (N).

The maximum number of subjects with the most severe suicidal ideation 'Wish to be dead' was 2 (3.8%) subjects, and they had a 'controllability' score of 1. A maximum of 1 (1.9%) subject had the most severe suicidal ideation 'Non-specific active suicidal thoughts' with a maximum intensity score of 4 for 'Reasons for Ideation' (Table 14.3.11.1.2).

'Non-suicidal Self-injurious Behaviour' was reported in 1 (1.9%) subject each at Week 28 and Week 52 (Table 14.3.11.2).

12.6.5. 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 14.3.10 and listed by subjects details for the Safety Population in Listing 16.2.14.

A clinically significant treatment-emergent post-Baseline abnormal finding on the eye examination was noted in 1 (1.9%) subject (852005) (with a score of 2/10 in the visual acuity of the right eye and abnormality in the overall status of the left and right eye). Clinically non-

significant treatment-emergent post-Baseline abnormal findings on the eye examination were noted in 8 (15.4%) subjects (Table 12-19).

Table 12-19 Standard Eye Examination: Treatment Emergent Abnormalities - Safety Population

Result	Evenamide 30 mg *BID* (N=52) n (%)
Abnormal, NCS	8 (15.4)
Abnormal, CS	1 (1.9)

Source: *Listing 16.2.14*; Adapted from *Table 14.3.10*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
For EVN-EVN Subjects 008A Baseline and for PLC-EVN Subjects 020 Baseline is considered.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
CS = Clinically Significant, NCS = Not Clinically Significant.
Treatment emergent abnormality is the change from Normal or Abnormal NCS at baseline to Abnormal or Abnormal CS, respectively, at any post baseline visit.
Subjects with multiple abnormal post-baseline findings on any body system are counted only once.

12.6.6. 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, Week 12, Week 28 and Week 52 is presented in Table 14.3.12.1. 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 14.3.12.2. 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 14.3.12.3. ESRS-A results are presented by subject details in Listing 16.2.16.

The majority of patients did not show extrapyramidal symptoms in any of the ESRS-A subscales (parkinsonism, dystonia, dyskinesia, akathisia), and few had symptoms rated as “minimal” or “mild” in severity. The incidence of extrapyramidal symptoms with a rating of “moderate” was 1.9% (1 subject each) for ‘Postural instability’ in the subscale Parkinsonism at Week 12, and ‘Objective’ and ‘Subjective’ symptoms in the subscale Akathisia at Week 12, Week 28, and Week 52 (Table 14.3.12.1).

The observed values of the ESRS-A Total Score decreased steadily from the Baseline mean (SD) of 3.0 (4.86) to 2.5 (4.38), 2.0 (3.85), and 1.8 (3.75) respectively at Weeks 12, 28 and 52. Similarly, the observed values of ESRS-A Parkinsonism subscale decreased steadily from the Baseline mean (SD) of 2.2 (3.59) to 1.6 (3.19), 1.2 (2.83), and 1.1 (2.72) respectively at Weeks 12, 28 and 52. There were no notable deteriorations in the other subscale symptom scores (Table 12-20).

Table 12-20 Change from Baseline in Sub-Scale Total and Total Score of Extrapyramidal Symptom Rating Scale - Abbreviated Version (ESRS-A) Safety Population

			Evenamide 30 mg *BID* (N=52)	
Scale Category	**Visit**	**Statistic**	**Observed**	**Change from Baseline**
Parkinsonism	Baseline [a]	n	52	
		Mean (SD)	2.2 (3.59)	
		Median	0.0	
		Min, Max	0, 14	
	Week 12	n	49	49
		Mean (SD)	1.6 (3.19)	-1.5 (2.77)
		Median	0.0	0.0
		Min, Max	0, 10	-12, 3
	Week 28	n	43	43
		Mean (SD)	1.2 (2.83)	-1.7 (3.78)
		Median	0.0	0.0
		Min, Max	0, 10	-18, 3
	Week 52	N	44	44
		Mean (SD)	1.1 (2.72)	-1.7 (3.78)
		Median	0.0	0.0
		Min, Max	0, 10	-18, 3
Dystonia	Baseline [a]	n	52	
		Mean (SD)	0.2 (0.50)	
		Median	0.0	
		Min, Max	0, 2	
	Week 12	n	49	49
		Mean (SD)	0.2 (0.69)	-2.9 (4.66)
		Median	0.0	0.0
		Min, Max	0, 4	-17, 0
	Week 28	n	43	43
		Mean (SD)	0.1 (0.41)	-2.8 (4.85)
		Median	0.0	0.0
		Min, Max	0, 2	-18, 0
	Week 52	n	44	44
		Mean (SD)	0.1 (0.41)	-2.7 (4.70)
		Median	0.0	0.0
		Min, Max	0, 2	-18, 0
Dyskinesia	Baseline [a]	n	52	
		Mean (SD)	0.3 (0.66)	
		Median	0.0	
		Min, Max	0, 3	
	Week 12	n	49	49
		Mean (SD)	0.2 (0.55)	-2.9 (4.74)
		Median	0.0	0.0
		Min, Max	0, 2	-18, 0

	Week 28	n	43	43
		Mean (SD)	0.2 (0.48)	-2.8 (4.86)
		Median	0.0	0.0
		Min, Max	0, 2	-18, 0
	Week 52	n	44	44
		Mean (SD)	0.2 (0.43)	-2.6 (4.72)
		Median	0.0	0.0
		Min, Max	0, 2	-18, 0
Akathisia	Baseline [a]	n	52	
		Mean (SD)	0.4 (0.82)	
		Median	0.0	
		Min, Max	0, 3	
	Week 12	n	49	49
		Mean (SD)	0.4 (1.06)	-2.7 (4.74)
		Median	0.0	0.0
		Min, Max	0, 6	-18, 6
	Week 28	N	43	43
		Mean (SD)	0.5 (1.12)	-2.4 (4.73)
		Median	0.0	0.0
		Min, Max	0, 6	-18, 6
	Week 52	n	44	44
		Mean (SD)	0.5 (1.09)	-2.3 (4.63)
		Median	0.0	0.0
		Min, Max	0, 6	-18, 6
Total Score	Baseline [a]	n	52	
		Mean (SD)	3.0 (4.86)	
		Median	0.0	
		Min, Max	0, 18	
	Week 12	n	49	49
		Mean (SD)	2.5 (4.38)	-0.6 (2.64)
		Median	0.0	0.0
		Min, Max	0, 16	-11, 6
	Week 28	n	43	43
		Mean (SD)	2.0 (3.85)	-0.9 (3.73)
		Median	0.0	0.0
		Min, Max	0, 13	-18, 7
	Week 52	n	44	44
		Mean (SD)	1.8 (3.75)	-1.0 (3.80)
		Median	0.0	0.0
		Min, Max	0, 13	-18, 7

Source: *Listing 16.2.16*; Adapted from *Table 14.3.12.2*.
N - Total number of subjects in the Safety Population, n - number of subjects with available data.
Percentages are calculated using the number of subjects in the safety population as denominator (N).
SD = Standard Deviation, Min = Minimum, Max = Maximum.
The scores in individual categories are added to obtain the scores in each sub-scale and total score.
[a]: 008A baseline has been considered for Evenamide to Evenamide subjects and for Placebo to Evenamide subjects, 020 Baseline has been considered.

On the CGI of Movement Severity, all patients had ratings of “absent”, “minimal”, or “mild” on all the subscales, except for one (1.9%) subject with a rating of “moderate” on Akathisia at Week 12 and 28. No subjects in the evenamide treated group had ratings of “moderate”, “severe”, or “extreme” on the CGI for Parkinsonism, Dyskinesia, or Dystonia at any visit (Table 14.3.12.3).

12.7. Safety Conclusions

The primary safety objective of the study was to evaluate the long-term safety and tolerability of an oral dose of evenamide of 30 mg *BID* [60 mg/day] in patients with schizophrenia.

A total of 22 (42.3%) subjects reported at least one TEAE. The most common TEAEs (incidence by PT ≥2%) were nasopharyngitis [5.8% (3/52)], influenza [3.8% (2/52)], tooth infection [3.8% (2/52)], akathisia [3.8% (2/52)], headache [3.8% (2/52)], and anemia [3.8% (2/52)].

Treatment-related TEAEs were reported in 4 (7.7%) subjects, and the same proportion experienced at least one serious TEAE, although two of these events occurred more than 30 days after the last dose of study medication. None of the reported serious TEAEs were considered related to the study medication.

The number of subjects with any TEAE leading to study drug discontinuation was 3 (5.8%), with cellulitis, intentional overdose, and psychotic disorder reported in 1 (1.9%) subject each. Cellulitis and intentional overdose were considered serious TEAEs not related to the study medication, and both recovered; whereas psychotic disorder did not resolve and was deemed as possibly related to the study drug.

Two (3.8%) subjects had a TEAE resulting in death. One subject died due to cardiorespiratory arrest, and the other subject died due to acute myocardial infarction 2 months and 15 days after the administration of the last dose of study medication. The Investigator considered both of these events as not related to study medication.

The majority of TEAEs reported were of mild [10 (19.2%)] or moderate [8 (15.4%)] intensity, and only 4 (7.7%) subjects had severe TEAEs, including Tooth infection, Femur fracture, Intentional overdose, Acute myocardial infarction, and Sudden death.

Very few clinical laboratory test results were deemed clinically significant by the Principal Investigator, and no notable trends in the occurrence of laboratory abnormalities were noted in the evenamide 30 mg *BID* treated subjects.

Vital signs data did not indicate any clinically significant effects of evenamide 30 mg *BID*, with the number of treatment-emergent clinically notable abnormalities being very low. At endpoint (Week 52) clinically notable weight gain was reported in only 3 (5.8%) of subjects.

In the analysis of data from the ECGs, there was no significant increase in mean QTcF value from baseline at any post-dose timepoint in the study. There were no clinically meaningful changes from baseline in mean values for any ECG parameters (Mean Heart Rate, RR Interval, PR Interval, QRS Axis, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval) among all the subjects evaluated. In the categorical analysis of ECG parameters, QTcB Interval, Aggregate (ms) of >450 and ≤ 480 ms was noted in 1 subject at Week 52 (PLC-EVN subject), but no significant abnormal QTcF interval aggregate or an abnormal change from baseline in QTcF values were noted. These findings are consistent with data available from previous studies, which are further corroborated in this 52-week open-label extension study.

No safety concerns were noted on the physical or neurological examinations and standard eye examinations. On the ESRS-A, the vast majority of patients either did not show any EPS, or showed "minimal"/"mild" symptoms, with very few exceptions in which a "moderate" symptom was reported, and there was no evidence of worsening of EPS with evenamide treatment. On the C-SSRS, the Suicidal Ideation categories 'Non-Specific Suicidal Thought' and 'Wish to be Dead' were reported in a small number of patients, and only one reported a 'Non-suicidal Self-injurious Behaviour'.

Overall, the results from all safety parameters indicated that evenamide 30 mg *BID* as add-on treatment in patients with chronic schizophrenia who have been symptomatic on their current single SGA medication was well tolerated when taken orally concomitantly with the patients' background SGA for up to 52 weeks.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

13.1.1. Study Overview

This was a 52-week, multi-center, open-label, extension study designed to determine the long-term safety, tolerability, and efficacy of evenamide (NW-3509) in patients with psychiatric disorders who participated in prior studies with evenamide. However, only Study NW-3509/008A/II/2020 (Study 008A), a 4-week, randomized, double-blind, placebo-controlled trial evaluating a dose of evenamide of 30 mg *BID* in patients with schizophrenia not responding adequately to their current single SGA, enrolled patients into this open-label extension study. This study was designed for an initial duration of 52 weeks, followed by another 52-week extension; however, the study was prematurely discontinued by the Sponsor. The primary reasons for this discontinuation were non-compliance and protocol deviations identified at the sites in Argentina during the study, along with administrative reasons for a site in Italy. However, it is important to note that no pattern of safety abnormalities was identified during the course of Study 020.

Two-hundred and eighty (280) subjects completed the core Study 008A, and a total of 52 subjects from sites in Argentina and Italy were enrolled in the initial 52-week period of the open-label extension Study 020. Among these 52 subjects, 29 subjects from the placebo arm of Study 008A started treatment with evenamide 30 mg *BID* in Study 020, and the remaining 23 subjects from the evenamide arm of Study 008A continued treatment with evenamide 30 mg *BID* in Study 020, after starting at 15 mg *BID* during an initial 4-week titration period. Three subjects from the initial 52-week period rolled over into the additional 52-week period. The number (%) of subjects who discontinued prematurely or withdrew early was 47 (90.4%) subjects from the initial 52-week period and 3 (5.8%) subjects from the additional 52-week period. The major reason for discontinuation or early withdrawals in both treatment periods was 'Study Termination by Sponsor' [37 (71%) subjects in the initial 52-week period, and all 3 subjects in the additional 52-week period].

The objective of the study was to evaluate the long-term safety, tolerability and efficacy of an oral dose of evenamide 30 mg *BID* (60 mg/day) in patients with schizophrenia who were being treated with stable doses of antipsychotic medication. The primary and secondary efficacy objectives were based on improvements in symptoms of schizophrenia, as assessed by the PANSS total score, and improvement in overall severity of the disease, as assessed by the CGI-C and CGI-S. Other secondary objectives were based on improvements in patient's function as assessed by the GAF and LOF, and their satisfaction with the medication as assessed by the MSQ.

13.1.2. Efficacy

Treatment with evenamide 30 mg *BID* for up to 52 weeks in this long-term extension study was associated with improvement over time in the symptoms of schizophrenia assessed by the PANSS Total Score, a decrease in the disease severity assessed by the CGI-S score, improvement in overall severity of illness assessed by the CGI-C, enhancement in functionality of patients assessed by the LOF Total score and LOF subscale scores, improvement in the patient's satisfaction with the medication as assessed by the MSQ, and improvement in the individual's social, occupational, and psychological functioning as assessed by the GAF scale. 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; or ≥ 30% improvement from baseline) at each visit increased over time. Moreover, >70% of patients at each visit were considered as responders based on CGI-C rating [score ≤ 3 (any improvement from Baseline)], and >40% of patients at each visit were considered "at least much improved" (score ≤ 2). These beneficial effects of evenamide treatment, which

increased over time, were observed in patients with chronic schizophrenia who were symptomatic on their current single SGA medication.

The limitations of the efficacy results in this study need to be considered to justify the acceptability of the efficacy data for this extension period. 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 or more. Furthermore, the pattern of improvement from baseline is consistent across all efficacy measures, although the magnitude of the benefit varied among the PANSS, CGI-S, CGI-C, LOF, MSQ and GAF.

In addition, a relatively small number of patients (52) were enrolled in Study 020 (out of the 280 patients who completed treatment in Study 008A), and all of them were from only two countries (Argentina and Italy), raising the possibility that local practices may preclude the generalizability of these results to a global patient population. Moreover, a majority of the patients could not complete this extension study due to premature termination of the same by the Sponsor, which is also a limiting factor for making any firm conclusions from the efficacy results.

13.1.3. Safety

The primary safety objective of the study was to evaluate the long-term safety and tolerability of an oral dose of evenamide of 30 mg *BID* [60 mg/day], achieved after a 4-week titration starting with 15 mg *BID*, in patients with schizophrenia. Standard safety assessments were performed, including ECGs, vital signs, laboratory tests, and physical, neurological, and standard eye examinations. Review of the data from ECGs, vital signs, and laboratory tests did not detect any meaningful changes from baseline or a significant increase in the number of patients with clinically significant or notable abnormalities. No safety concerns were noted with regard to EPS (assessed by ESRS-A) or suicidality (assessed by the C-SSRS). Also, most adverse events were assessed as mild or moderate in intensity, and there were no severe or serious adverse events suggestive of involvement of evenamide. Only 3 (5.8%) subjects experienced a TEAE leading to study drug discontinuation. Two deaths were reported in the study, one due to cardiorespiratory arrest, and the other due to acute myocardial infarction that occurred 2 months and 15 days after the last dose of study medication; the investigators considered both of these events as not related to study medication.

Overall, the results from all safety parameters collected during the 52-week period in this study indicated that evenamide 30 mg *BID* as add-on treatment in patients with chronic schizophrenia who are symptomatic on their current single SGA medication was well tolerated, and no safety

issues were observed that would preclude long-term administration of this dose to patients with schizophrenia.

13.2. Overall Conclusions

The results of this study confirm previous clinical evidence and suggest that evenamide at a dose of 30 mg *BID* for 52 weeks as add-on treatment in moderately to severely ill patients with schizophrenia, who were experiencing worsening symptoms of psychosis and demonstrating inadequate response to their current SGA medication, is well tolerated, based on the data from multiple safety assessments, including vital signs, laboratory tests, ECGs, and incidence of TEAEs, with no patterns of safety abnormalities detected. Furthermore, there were no Serious and Treatment-Related TEAEs reported in this study. Treatment with evenamide at a dose of 30 mg *BID* given as add-on to SGAs (including clozapine) in patients with schizophrenia for 52 weeks was associated with a sustained improvement and clinically relevant benefits 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)

A total of 6 SAEs were reported in 4 subjects during the study, with 3 SAEs reported in a single subject. The short narratives for the same are presented in Section 12.4.2. The expanded narratives for each of these events are provided below.

Deaths

Subjects Number: 895015 (Acute myocardial infarction)

Country of Origin : Argentina

Type of Narrative : Serious Adverse Event

Subject Number : 895015

MFR Case ID : 2024NEW000003

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term] : Acute myocardial infarction [Acute myocardial infarction]

This 76-year-old male subject with chronic schizophrenia after completing the prior study 008A on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he received evenamide (15-30 mg *BID*). On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID*. On 10 February 2024 (Day 109) 77 days after receiving the last dose of the study medication, the subject died due to an acute myocardial infarction.

This patient experienced other SAEs requiring hospitalization: Fall and Femur Fracture (MFR Case ID 2023NEW000006), and Pneumonia (MFR Case ID 2024NEW000002)

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 020.*

This 76-year-old male subject with chronic schizophrenia completed the prior study 008A on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he started evenamide at the dose of 15 mg *BID* that was increased to 30 mg *BID* after 4-weeks.

On 12 Oct 2023 (in study 008A) the subject experienced somnolence (strong desire for sleep) that was considered mild in intensity and probably related to study medication by the Investigator. The dose of study medication was reduced (placebo) from 19 Oct 2023. On 25

Oct 2023 (Day 1) he started evenamide at 15 mg *BID* in study 020. The dose was increased at 30 mg *BID* from 22 Nov 2023 (Day 29).

On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID* due to a false alert of hypokalemia. The last dose was taken on 26 Nov 2023 (Day 33).

On 18 Dec 2023, 23 days after receiving the last dose of the study medication, the subject fell from his own height after tripping over a piece of furniture. Subject did not have any episode of loss of consciousness blurring of vision or dizziness before the fall. The subject did not experience any head injury or loss of consciousness after the accidental fall. On the same day, he was transferred to the hospital and was diagnosed with left femoral head fracture and on 20 Dec 2023 (Day 57) the subject underwent successful hip replacement surgery. The postoperative course was uneventful, and treatment included antibiotics and anticoagulants (name, dose, frequency, and duration not known).

On 22 Dec 2023 (Day 59) subject was diagnosed with anemia (lab value not available) as complication of hip replacement surgery for left femoral fracture. Treatment of post-operative anemia included intramuscular administration of iron.

On 30 January 2024 (Day 98) 66 days after receiving the last dose of the study medication, the subject was diagnosed with pneumonia, and treated with a broad-spectrum antibiotic. On 08 Feb 2024 he developed constipation that required treatment with a murphy enema and the event resolved the same day. On 09 Feb 2024 he recovered without sequelae and was discharged from the hospital.

On 10 February 2024 (Day 109) 77 days after receiving the last dose of the study medication, the subject died due to acute myocardial infarction. No autopsy was performed.

Medical History and Concomitant Medication:

The subject’s medical history included schizophrenia since 2003 (~20 years) and hypothyroidism since 2013. The subject’s current antipsychotic medications included olanzapine ongoing since 2008 (the actual dose of 15 mg daily was started on March 2018). Other concomitant medication included levothyroxine 50 µg for hyperthyroidism since 2013.

Investigator Assessment:

The investigator considered the serious adverse event of “Acute myocardial infarction”, severe in intensity and not related with the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

The Sponsor agrees with the investigator's assessment that the serious adverse event, that occurred 77 days after receiving the last dose of the study medication, is not related to the study

medication (evenamide 30 mg *BID*). The event of "Acute myocardial infarction" causing death is assessed as serious with the seriousness criteria of fatality and is unexpected as per current Investigator's Brochure.

Pertinent Positives and Negatives:

This 76-year-old male subject with history of chronic schizophrenia (~20 years), treated with olanzapine, received the last dose of evenamide 26 Nov 2023 (Day 33). On 20 Dec 2023 twenty-five days after receiving the last dose of evenamide, the subject experienced an accidental fall (tripping over a piece of furniture), was hospitalized, and was diagnosed with left femoral head fracture. For this reason, the subject underwent successful hip replacement surgery. On 30 January 2024 the subject was hospitalized for 10 days due to pneumonia that resolved, after treatment with broad-spectrum antibiotic. On 10 February 2024 approximately 2.5 months after receiving the last dose of the study medication, the subject died due to acute myocardial infarction. No autopsy was performed.

Patients with schizophrenia have a higher mortality rate than the general population, as well as they also have a higher risk of physical illness and poor outcomes. Schizophrenia and advanced age are contributory factors for the development of pneumonia that is frequently associated with complication and may result in death. Evenamide has a short half-life (approximately 2-3 hour), does not lead to accumulation, and the subject had been off the study medication (evenamide 30 mg *BID*) for 77 days (since 26 Nov 2023) before the event of acute myocardial infarction and died. A temporal relationship between evenamide and the events can be excluded, therefore, the events are not related to evenamide 30 mg *BID*.

Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry. 2000;177:212–217.

Subjects Number: 892018 (Sudden death)

Country of Origin : Argentina

Type of Narrative : Serious Adverse Event

Subject Number : 892018

MFR Case ID : 2024NEW000004

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term]: Sudden death [Sudden death]

This 67-year-old female subject with chronic schizophrenia after completing the prior study 008A on placebo; on 31 Oct 2023 (Day 1) she entered the study 020 (open label extension of study 008A) where she received evenamide. On 26 Apr 2024 (Day 179) the subject was found

dead in her bed. The reported cause of death is a possible cardiorespiratory arrest. No autopsy was performed.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 020.*

This 67-year-old female subject with chronic schizophrenia completed uneventfully the prior study 008A on placebo; on 31 Oct 2023 (Day 1) she entered the study 020 (open label extension of study 008A) where she started evenamide at the dose of 15 mg *BID* that was increased to 30 mg *BID* after 4-weeks.

On 12 Sep 2023 (during the screening period), the subject showed an alkaline phosphatase (ALP) high.

On 28 Nov 2023 (Day 29) the subject completed the study week 4 visit: laboratory findings included elevated alkaline phosphatase (ALP) 317 U/L (normal range 0-240U/L) and total bilirubin 1.31 (0.1-1.0 mg/dL). All other safety parameters were unremarkable with normal ECGs, hematology, vital signs, neurological and physical examination.

On 23 Jan 2024 (Day 85) the subject completed the study week 12 visit: except for elevated lactate dehydrogenase (LDH) 270 U/L (normal range 117-250UI/L), ALP 279 U/L (normal range 0-240U/L) and total bilirubin 1.13 (0.1-1.0 mg/dL) all other safety parameters were normal (ECGs, vital signs, neurological and physical examination).

On 19 Mar 2024 (Day 141) the subject completed the study week 20 visit, and her physical exam was unremarkable with normal vital signs and no adverse events reported.

On 26 Apr 2024 (Day 179), at around 5:00 pm, the subject's daughter returned home and found the mother in bed, she did not respond to any attempt to wake her up. The subject was declared dead.

The investigator reported a possible cardiorespiratory arrest as cause of death. No autopsy was performed.

On 10 October 2024 the investigator changed the definition of SAE with Sudden death.

Medical History and Concomitant Medication:

The subject's medical history included schizophrenia since 1980 (~40 years), 3 psychiatric hospitalizations and the current psychotic episode started on 10 May 2023. The subject received haloperidol oral 10 mg/day from 1980 to 9 May 2022; then treatment with clozapine was initiated. The subject's current antipsychotic medications included clozapine 150 mg *BID* ongoing since 10 May 2022. No other concomitant condition or medication is reported.

Investigator Assessment:

The investigator considered the serious adverse event of "possible cardiorespiratory arrest", severe in intensity and not related to the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

No autopsy was performed. The sponsor concurs with the investigator that the event is not related to study medication. The event of "possible cardiorespiratory arrest" causing death is assessed as serious with the seriousness criteria of fatality and is unexpected as per current Investigator's Brochure.

Pertinent Positives and Negatives:

This 67-year-old female subject with history of chronic schizophrenia (~40 years), treated with clozapine, received the last dose of evenamide on 25 Apr 2024 (Day 178). On 26 Apr 2024, approximately 6 months on evenamide 30 mg *BID*, she was found dead in her bed. The investigator reported a "possible cardiorespiratory arrest" as cause of death. No autopsy was performed.

Patients with schizophrenia have a higher mortality rate than the general population, as well as they also have a higher risk of physical illness and poor outcomes. Long history of schizophrenia (~40 years) and advanced age are contributory factors for frequently associated to complication and including sudden death. The patient was receiving treatment with clozapine, that has been associated with sudden death. The sponsor concurs with the investigator that the event is not related to evenamide.

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Other Serious Adverse Events

Subject Number: 892007 (Cellulitis)

Subject Number	: 892007
Country of Origin	: Argentina
Type of Narrative	: Serious Adverse Event
MFR Case ID	: 2023NEW000005

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term]: Cellulitis [Cellulitis]

This 37-year-old male subject with chronic schizophrenia after completing the previous study 008A on 10 Aug 2023 (Day 1) entered into the study 020 (open label extension of study 008A) where he received evenamide (15-30 mg *BID*). On 17 Nov 2023 (Day 100), the subject accidentally hurt his ankle; this was accompanied by persistent pain, swelling and blisters on his left ankle. He was hospitalized on the same day with the diagnosis of cellulitis and the study medication was discontinued.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 020.*

This 37-year-old male subject with chronic schizophrenia completed the previous study 008A on 09 Aug 2023 where he was randomized to receive evenamide 30 mg *BID* or placebo. On 10 Aug 2023 (Day 1) the subjects entered in the study 020 (open label extension of study 008A) and received evenamide at the initial dose of 15 mg *BID* for 4-week that was then increased at 30 mg *BID*.

On 17 Nov 2023 (Day 100), the subject's mother contacted the site via telephone and informed that in the afternoon the subject had accidentally hit his ankle. On the same day at 21:00 hours, the subject presented with pain, swelling and blisters on his left ankle and was diagnosed with cellulitis that was considered mild in severity. The subject was hospitalized and kept under observation in the ward. The study medication (evenamide 30 mg *BID*) was discontinued. The last dose of study medication (evenamide 30 mg *BID*) was administered on 16 Nov 2023 (Day 99).

On 18 Nov 2023 (Day 101) the subject started corrective treatment with intravenous (iv) antibiotics penicillin, ciprofloxacin and clindamycin (dose, frequency, and duration not known).

Further, on 21-Nov-2023, the subject underwent venous doppler ultrasound of right lower limb revealing the absence of deep vein thrombosis (DVT)/superficial venous thrombosis (SVT). On 22-Nov-2023, chest computed tomography (CT) showed no signs of pulmonary thromboembolism (PTE) in major arterial branches. On 24-Nov-2023, ultrasound of left lower extremity showed edema of the integuments of the entire lower limb, with a tendency to collect in the anterior-internal region of the left ankle and instep. This edema involved the skin, the subcutaneous tissue (SCT), and minimally the superficial muscle plane. On 04-Dec-2023, abdominal ultrasound showed normal results for the abdominal aorta, superior vena cava, and retroperitoneum.

On 11-Dec-2023 (Day 124), laboratory tests included red blood cell (RBC) count 3.82 10^6/uL (normal range: 4.50-6.50 10^6/uL), hemoglobin (Hb) 11.2 g/dl (normal range: 13.0-17.0 g/dl), hematocrit 32% (normal range: 42-52 %), segmented neutrophils 52.7 % (normal range: 55.0-75.0 %) and eosinophils 0.2 % (normal range: 1.0-4.0 %).

On 13 Dec 2023 (Day 126) the subject recovered from the event of cellulitis and was discharged from the hospital.

Medical History and Concomitant Medication:

The subject's current antipsychotic medications included clozapine 150 mg oral twice a day since 27 Feb 2023. Neither the subject's past medical history nor other concomitant medications were reported.

Investigator Assessment:

The investigator considered the serious event of "cellulitis", mild in intensity and not related with the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

The Sponsor concurs with the investigator's assessment that the serious adverse event is not related to the study medication (evenamide 30 mg *BID*). The event of cellulitis is assessed as serious with the seriousness criteria of hospitalization, and is unexpected as per the current Investigator's Brochure.

Pertinent Positives and Negatives:

This 37-year-old male subject with chronic schizophrenia (~10 years) on clozapine received the first dose of study medication in study 020 on 10 Aug 2023 and approximately after 3 months on evenamide 30 mg *BID* on 17 Nov 2023 (Day 100) accidentally hurt his ankle. He was hospitalized and diagnosed with cellulitis, that was considered mild in intensity. This led to the discontinuation of the study drug (evenamide). The event was treated with intravenous antibiotics (penicillin, ciprofloxacin and clindamycin) and on 13 Dec 2023 the event was considered resolved with a complete recovery of the subject. On the same day the subject was discharged from the hospital. The event of cellulitis is not related to evenamide.

Subject Number: 895015 (Femur fracture)

Country of Origin	: Argentina
Type of Narrative	: Serious Adverse Event
Subject Number	: 895015
MFR Case ID	: 2023NEW000006

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term]: Left femoral head fracture (Femur fracture)

This 76-year-old male subject with chronic schizophrenia after completing the prior study 008A and on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he received evenamide (15-30 mg *BID*). On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID*. On 18 Dec 2023 (Day 55) 23 days after receiving the last dose of the study medication, the subject's sister reported to the site that the subject fell from his own height after tripping over a piece of furniture. The subject was hospitalized with the diagnosis of left femoral head fracture. On 20 Dec 2023 (Day 57) the subject underwent successful hip replacement surgery, and the event was considered resolved on 22 Dec 2023 (Day 59).

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 020.*

This 76-year-old male subject with chronic schizophrenia completed the prior study 008A and on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he started evenamide at the dose of 15 mg *BID* that was increased to 30 mg *BID* after 4-weeks.

On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID* due to a false alert of hypokalemia. It was retested and came out within normal range, however the patients decided to stop the study medication. That was never reintroduced. The last dose was taken on 26 Nov 2023 (Day 33).

On 18 Dec 2023, at around 07:00 pm, 23 days after receiving the last dose of the study medication, the subject's sister reported to the site that the subject fell from his own height after tripping over a piece of furniture. Subject did not have any episode of loss of consciousness blurring of vision or dizziness before the fall. The subject did not experience any head injury or loss of consciousness after the accidental fall. On the same day, he was transferred to the hospital and was diagnosed with left femoral head fracture and on 20 Dec 2023 (Day 57) the subject underwent successful hip replacement surgery. The postoperative course was uneventful, and treatment included antibiotics and anticoagulants (name, dose, frequency, and duration not known).

On 22-Dec-2023, he was diagnosed with non-serious AE of anemia for which he received injectable iron, which was still ongoing. At 12:30 pm, the subject recovered from the SAE and was discharged from the hospital. Reportedly, the subject was doing physiotherapy rehabilitation sessions.

Medical History and Concomitant Medication:

The subject's medical history included schizophrenia since 2003 (~20 years) and hypothyroidism since 2013. According to his family, the subject did not suffer from similar episodes of fall in the past. The subject's current antipsychotic medications included olanzapine ongoing since 2008 (the actual dose of 15 mg daily was started on March 2018). Other concomitant medication included levothyroxine 50 µg for hyperthyroidism since 2013.

Investigator Assessment:

The investigator considered the serious adverse event of "left femoral head fracture" after a fall, moderate in intensity and not related with the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

The Sponsor agrees with the investigator's assessment that the serious adverse event, that occurred 23 days after receiving the last dose of the study medication, is not related to the study medication (evenamide 30 mg *BID*). The event of fall causing "left femoral head fracture" is assessed as serious with the seriousness criteria of hospitalization and is unexpected as per current Investigator's Brochure.

Pertinent Positives and Negatives:

This 76-year-old male subject with history of chronic schizophrenia (~20 years), treated with olanzapine, received the first dose of study medication in study 020 on 25Oct 2023 (Day 1) and on 18 Dec 2023 (Day 55) fell after tripping over a piece of furniture and for this reason on the same day he was hospitalized with the diagnosis of left femoral head fracture that was treated with hip replacement surgery. The subject did not have any episode of loss of consciousness, blurring of vision or dizziness before the fall. He did not experience any head injury or loss of consciousness after the accidental fall. The age of this subject could be considered a contributory factor. Evenamide has a short half-life (approximately 2-3 hour), does not lead to accumulation, and the subject had been off the study medication (evenamide 30 mg *BID*) for 23 days (since 26 Nov 2023) before the event of left femoral head fracture due to a fall (tripping over an obstacle). Therefore, a temporal relationship between evenamide and the events can be excluded, therefore, the events are not related to evenamide 30 mg *BID*.

Subject Number: 895015 (Pneumonia)

Country of Origin	: Argentina
Type of Narrative	: Serious Adverse Event
Subject Number	: 895015
MFR Case ID	: 2024NEW000002

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term]: Pneumonia [Pneumonia]

This 76-year-old male subject with chronic schizophrenia after completing the prior study 008A and on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he received evenamide (15-30 mg *BID*). On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID*. On 30 January 2024 (Day 98) 66 days after receiving the last dose of the study medication, the subject had pneumonia.

This patient experienced other SAEs: Fall and Femur Fracture (MFR Case ID 2023NEW000006), and Acute myocardial infarction (MFR Case ID 2024NEW000003)

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 020.*

This 76-year-old male subject with chronic schizophrenia completed the prior study 008A and on 25 Oct 2023 (Day 1) entered the study 020 (open label extension of study 008A) where he started evenamide at the dose of 15 mg *BID* that was increased to 30 mg *BID* after 4-weeks.

On 26 Nov 2023 (Day 33) the subject stopped the treatment with evenamide 30 mg *BID* due to a false alert of hypokalemia. It was retested and came out within normal range, however the patients decided to stop the study medication. That was never reintroduced. The last dose was taken on 26 Nov 2023 (Day 33).

On 18 Dec 2023, 23 days after receiving the last dose of the study medication, the subject fell from his own height after tripping over a piece of furniture. Subject did not have any episode of loss of consciousness blurring of vision or dizziness before the fall. The subject did not experience any head injury or loss of consciousness after the accidental fall. On the same day, he was transferred to the hospital and was diagnosed with left femoral head fracture and on 20 Dec 2023 (Day 57) the subject underwent successful hip replacement surgery. The postoperative course was uneventful, and treatment included antibiotics and anticoagulants (name, dose, frequency, and duration not known).

On 22-Dec-2023, he was diagnosed with a non-serious AE of anemia for which he received injectable iron for the anemia, which was still ongoing. The same day, he recovered from SAE left femoral head fracture and was discharged from the hospital. On 25-Jan-2024, it was confirmed that the subject had withdrawn his informed consent form (ICF) as decided by family. On 29-Jan-2024, the subject's vitals were as follows - blood pressure (BP) was 80/50 mmHg, oxygen saturation (SaO2) was 91%, temperature (T) was 36.5 ºC and functional capacity (FC) was 97 lpm (normal range was unknown).

On 30 January 2024 (Day 98) 66 days after receiving the last dose of the study medication, the subject had pneumonia, he was treated with a broad-spectrum antibiotic. Reportedly, the subject appeared pale, had a coated tongue, refused to eat and was vomiting. His vital signs were as follows - BP was 100/70 mmHg, SaO2 was 91%, temperature was 38º C and FC was 101 lpm. No chest X-ray or CT scan was performed for the SAE. On 08 Feb 2024 he developed constipation that required treatment with a murphy enema and the event resolved the same day. On 09 Feb 2024 he recovered without sequelae and was discharged from the hospital.

Medical History and Concomitant Medication:

The subject's medical history included schizophrenia since 2003 (~20 years) and hypothyroidism since 2013. According to his family, the subject did not suffer from similar episodes of fall in the past. The subject's current antipsychotic medications included olanzapine ongoing since 2008 (the actual dose of 15 mg daily was started on March 2018). Other concomitant medication included levothyroxine 50 µg for hyperthyroidism since 2013.

Investigator Assessment:

The investigator considered the serious adverse event of "pneumonia", moderate in intensity and not related with the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

The Sponsor agrees with the investigator's assessment that the serious adverse event, that occurred 66 days after receiving the last dose of the study medication, is not related to the study medication (evenamide 30 mg *BID*). The event of "pneumonia" is assessed as serious with the seriousness criteria of hospitalization and is unexpected as per current Investigator's Brochure.

Pertinent Positives and Negatives:

This 76-year-old male subject with history of chronic schizophrenia (~20 years), treated with olanzapine, received the first dose of study medication in study 020 on 25 Oct 2023 (Day 1) and on 30 January 2024 (Day 98) had pneumonia. Evenamide has a short half-life (approximately 2-3 hour), does not lead to accumulation, and the subject had been off the study medication (evenamide 30 mg *BID*) for 66 days (since 25 Nov 2023) before the event of pneumonia. Therefore, a temporal relationship between evenamide and the events can be excluded, therefore, the events are not related to evenamide 30 mg *BID*.

Subject Number: 895021 (Intentional overdose)

Country of Origin : Argentina

Type of Narrative : Serious Adverse Event

Subject Number : 895021

MFR Case ID : 2024NEW000005

Treatment Group : Evenamide (capsule, 30 mg *BID*)

Reported Term [Preferred Term] : Possible intentional drug overdose (Intentional overdose)

This 26-year-old male subject with chronic schizophrenia, received evenamide 30 mg *BID* from 11 Oct 2023 to 07 Nov 2023 (Day 28) and from 08 Nov 2023 (Day 29) he continued to receive evenamide (15-30 mg *BID*) in the study 020 (open label extension of study 008A).

On 02 May 2024 (Day 205) the subject was found unconscious in his room, with evidence of having taken evenamide and other concomitant medications like risperidone and bromazepam (possible intentional multiple drug overdose), and for this reason he was hospitalized in intensive care unit. On 11 June 2024 the subject discontinued the study due to suicidal risk.

Clinical Summary*:

** Days in clinical summary are calculated from Day 1 on study drug in Study 008A.*

This 26-year-old male subject with chronic schizophrenia completed the prior study 008A on 07 Nov 2023 entered the study 020 (open label extension of study 008A) where he started evenamide at the dose of 15 mg *BID* that was increased to 30 mg *BID* after 4-weeks.

At baseline in study 008A (11 Oct 2023) the PANSS total score was 79 (Psychopathology 36, Positive 20, and Negative 23), a CGI-s of 4 (Moderately ill).

At baseline in study 020 the PANSS total score of 73 (Psychopathology 34, Positive 18, and Negative 21), a CGI-s of 4 (Moderately ill) and a CGI-C of 3 (Minimally improved) compared to baseline in study 008A.

At study visit for week 12 on 05 Feb 2024 (Day 118) there were no clinically significant findings in ECG, biochemistry, hematology, urinalysis, vital signs, and neurological evaluation. The subject was showing some improvement in rating scales: the PANSS total score was 64 (psychopathology 29, Positive 16, and Negative 19), the CGI-s was 3 (Mildly ill) with a CGI-C of 2 (Much improved).

An Unscheduled visit was performed on 29 Feb 2024 (Day 142) and included eye examination (unchanged from baseline), C-SSRS evaluation since last visit that did not identify any suicidal ideation or non-specific suicidal thoughts, the PANSS total score was 66 (Psychopathology 28, Positive 20, and Negative 18), the CGI-s was 3 (Mildly ill) and the CGI-C was 5 (Minimally worse).

The last patient visit was completed on 03 Apr 2024 (Day 176) for dispensing eight study medication kits (total of 128 capsules of evenamide 30 mg) to cover the following 8-week period. At this visit C-SSRS evaluation since last visit that did not identify any suicidal ideation

or non-specific suicidal thoughts, and there was no finding in vital signs. Till this study visit the subject was always compliant with study medication.

On 27-Apr-2024, the subject's mother observed his son as scattered, nervous and with an irritable behavior. He was not hallucinated but presented with strange behaviors such as urinating in the bowl and running away from the house. He also suffered from terminal insomnia and discontinuous sleep.

Since 29-Apr-2024, the subject showed episodes of unmotivated laughter.

On 01-May-2024, the subject received the most recent dose of evenamide prior to the SAE.

On 03 May 2024 at noon, subject's mother called the investigator informing that on the morning of 02 May 2024 (Day 205) the subject was found unconscious in his room with evidence of having taken evenamide and other concomitant medications like risperidone and bromazepam. An ambulance was called, and the subject was admitted to the Intensive Care Unit of the "Hospital de Dolores": the only clinical data available at the moment was the low oxygen saturation (70%). As a lifesaving procedure, he was provided with mechanical ventilatory assistance. The next day, the subject was transferred to another hospital to address the worsening respiratory function. Later, the subject regained consciousness but remained confused. Reportedly, the subject had not showed signs of suicidal ideation or schizophrenia relapse in the past that could have caught the attention of his mother, investigational site staff or physician. Further, the subject was not taking any other medications that could have led to the SAE. On 03 May 2024 the subject was transferred to "Hospital Rossi" of La Plata. However, based on the information provided by the subject's mother, no life saving, or resuscitation procedures were performed.

Subject's mother informed the investigator that from 04 May 2024 subject is being off the artificial respirator breathing on his own. Subject regained consciousness but remains confused. He is now receiving Haloperidol and Risperidone.

Subject's mother was in charge of giving medications to the subjects, however he took them while she was asleep. She was unable to establish with certainty the quantity of pills taken by the subject. She also reported that the subject experienced a worsening of symptoms in the week preceding the event.

On 08-May-2024, the subject was transferred to crisis care unit (CCU) and was administered oral lorazepam and haloperidol at a dose of 4 mg and 5 mg, respectively, at every 8 hours for possible intentional drug overdose.

On 09-May-2024, the subject showed a reticent attitude, clear consciousness, was oriented to person and partially to place and time. He was restless, responded to specific questions, had a

dysphoric mood, with bradypsychia, hypobulia and impaired judgement. No pathological, delusional or suicidal ideation was reported. Additionally, no sensory-perceptual alterations were reported or inferred, although they were not ruled out. He lacked awareness of the situation and had partial awareness of the illness. As per the investigator, involuntary hospitalization was recommended, and the presumptive diagnosis was reported to be F29 (ICD10) (International Classification of Diseases) by WHO (World Health Organization). Reportedly, the subject was treated with injectable haloperidol at a dose of 20 mg/day and lorazepam at a dose of 8 mg/day.

On 13-May-2024, the PI visited the hospital, where the subject was admitted, for a meeting with psychiatrist and head of the inter consultation area of the mental health service. The medical team recommended admission to their reference hospital with follow-up by their primary care physician. The subject was transferred to his reference hospital along with the referral reports and remains hospitalized in the mental health service. Additionally, the PI interviewed the subject, his mother and sister, and was informed that the subject ingested approximately 100 tablets including risperidone, olanzapine, evenamide, bromazepam, and sertraline with the intention of falling asleep, not to commit suicide, likely due to interpersonal conflict with his brother. At the time of the interview, he did not express suicidal ideation. Both mother and the subject expressed their intention of continuing treatment with evenamide.

Reportedly, it was confirmed that no relapse was seen due to evenamide.

On 16-May-2024 the event was considered completely resolved, the subject was in good condition and was discharged from hospital.

However, based on subject’s self-injurious behavior, on 11 June 2024 the investigator decided to discontinue the subject from study because he was considered at risk of suicide.

Medical History and Concomitant Medication:

The subject’s medical history included schizophrenia since 2020 (~3 years) and the start date of current episode is April 2023. The first diagnosis for schizophrenia was made in 2020, while in 2015 the subject received the first treatment with an antipsychotic (risperidone, dose and duration unknown), the subject has never been hospitalized for psychiatric reasons.

The subject’s current antipsychotic medications included risperidone 3 mg/day ongoing from 20 Apr 2023. Other concomitant medication included sertraline 50 mg/day for negative symptoms of schizophrenia and bromazepam 3 mg/day for anxiety from 20 Apr 2023 all these medications were ongoing at the time of event.

Patient medical history included myopia, a finding of blood glucose increased on 08 Nov 2023 (Day 29) captured as an adverse event, not related and of mild intensity, that was completely resolved by 05 Dec 2023.

Investigator Assessment:

The investigator considered the serious adverse event of intentional overdose, severe in intensity and not related to the study medication (evenamide 30 mg *BID*).

Sponsor Assessment:

The Sponsor agrees with the investigator's assessment that the serious adverse event is not related to the study medication.

The event of intentional overdose is assessed as serious with the seriousness criteria of hospitalization/ life-threatening and is unexpected as per current Investigator's Brochure.

Pertinent Positives and Negatives:

This 26-year-old male subject with a recent history of chronic schizophrenia (~3 years), treated with risperidone, received the last dose of evenamide 11 Oct 2023 (Day 1). During the course of treatment, the subject showed an improvement on 05 Feb 2024 (Day 118) with a PANSS total score of 64 (~ 20% improvement vs baseline) a CGI-s of 3 (Mildly ill) and a CGI-C of 2 (Much improved). These improvements were almost still present at the last visit (Unscheduled) assessment that was performed on 29 Feb 2024 (Day 142) with a PANSS total score of 66 (Psychopathology 28, Positive 20, and Negative 18), a CGI-s of 3 (Mildly ill), but the CGI-C was rated as 5 (Minimally worse). During the course of treatment there were no significant safety concerns and there was no report of any suicidal ideation or non-specific suicidal thoughts, as assessed by repeated C-SSRS evaluation.

On 02 May 2024 (Day 205) the subject was found unconscious in his room, with evidence of having taken evenamide and other concomitant medications like risperidone and bromazepam (possible intentional multiple drug overdose), and for this reason he was hospitalized in intensive care unit. After 2-week of hospitalization the subject was discharged with a complete resolution of the event. However, based on subject’s self-injurious behavior, on 11 June 2024 the investigator decided to discontinue the subject from study because was considered at risk of suicide.

Very minimal information is available, however a suicide attempt, by drug overdose of the prescribed drug, could not be excluded. A recent study conducted in US (Olfson et al. 2021) on a cohort of ~670000 patients with schizophrenia indicated that the risk of suicide was higher compared with the general US population and was highest among those aged 18 to 34 years.

Young age of these subjects with schizophrenia, the presence of concomitant treatment (sertraline, bromazepam) indicating possible comorbidity i.e. anxiety, depression are considered contributory factor to the onset of the event. The subjects while on treatment with evenamide for 4 months showed a significant improvement (~ 20% improvement vs baseline in PANSS). The relationship between evenamide and the events of drug overdose can be excluded, therefore, the event is not related to evenamide 30 mg *BID*.

References

Olfson, M., Stroup, T. S., Huang, C., Wall, M. M., Crystal, S., & Gerhard, T. (2021). Suicide Risk in Medicare Patients with Schizophrenia Across the Life Span. JAMA psychiatry, 78(8), 876–885.

Significant Adverse Events leading to Study Drug Discontinuation (ADOs)

Adverse events indicated as the "primary reason for discontinuation" by the investigators were reported in only 3 cases: Cellulitis (SAE) in subject 892007, Intentional overdose (SAE) in subject 895021, and Psychotic disorder (not-serious) in subject 855001. The detailed narratives of the SAEs, i.e., Cellulitis and Intentional overdose, are provided above under Section Other Serious Adverse Events, and the detailed narrative of the ADO Psychotic disorder is presented below.

Subject Number: 855001 (Psychotic Disorder)

Country of Origin	: Italy
Type of Narrative	: Adverse Drop-out
Subject Number	: 855001
Treatment Group	: Evenamide (capsule, 15 mg *BID*)
Reported Term [Preferred Term]	: Psychotic exacerbation [Psychotic disorder]

This 46-year-old White/Caucasian male subject with chronic schizophrenia, on stable dose of clozapine 300 mg/day, in Study 008A received Placebo for four weeks and completed the study on 16 Mar 2023. On 23 Mar 2023 (Day 1) he entered in the Open Label Extension Study 020 where he received evenamide at the dose 15 mg *BID* (30 mg/day). On 18 May 2023 after 57 days on evenamide, the subject experienced psychotic exacerbation. The patient was withdrawn from the study on 18 Sep 2023 (Study 020, Day 180).

The two doses of evenamide 15 mg were administered PM (taken at least 6 hours apart).

Clinical Summary:

This 46-year-old White/Caucasian male subject completed the study 008A on 16 Mar 2023, where he received placebo for 28 days. At screening visit in study 008A the PANSS total score of the subject was 79, CGI-S was severely ill (6), and C-SSRS reported that about 30 days before the screening's assessment, he describes a particular episode in which he considered jumping from a window for unclear reasons. This thought lasted a few seconds and never recurred. Physical and neurological examination were normal. At the Day 29 visit of study 008A the PANSS total score was rated as 78, CGI-S was rated as 6 (severely ill), unchanged from baseline, and the C-SSRS did not report any suicidal attempt or ideation. Physical and neurological examinations were normal.

On 23 Mar 2023 (Study 020, Day 1) he entered in the Open Label Extension Study 020 where he received evenamide at the dose of 30 mg/day (Study 020, Day 1).

On 18 May 2023 after 57 days on study medication (30 mg/day) the subject experienced psychotic exacerbation with prominent delusions featuring discrete influence on behavior and more significant affective involvement as compared with baseline. The dose of concomitant antipsychotic medication clozapine was increased at 400 mg/day.

On 15 Jun 2023 (Day 85) PANSS total score was 83, CGI-S was severely ill (6), C-SSRS was unchanged since the last visit performed, considering the lack of improvement and the concomitant worsening of symptoms, PI was in agreement with the subject not to continue the treatment. The patient took the last dose on 16 Jun 2023 (Day 85). The patient was withdrawn from the study on 18 Sep 2023 (Day 179). Psychotic exacerbation was the reason for discontinuation from the study.

Medical History and Concomitant Medication:

The patient has a history of schizophrenia since 08 Jul 1999 (~ 14 years), and the current episode started on 02 Aug 2018 (~ 5 years). Concomitant antipsychotic medication included clozapine 300 mg/day oral, once a day for schizophrenia from 02 Aug 2018 to 18 May 2023 when after the exacerbation of the existing psychotic disorder the dose was increased to 400 mg/day.

Medical history included Immune thrombocytopenia from Mar 1985 to Jul 1986, from 7 Aug 2018 to 28 Aug 2018, and from 08 Jan 2019 to 28 Mar 29; and Gastroesophageal reflux disease (GERD) since 2022.

A series of adverse events, not serious, were reported during Study 008A: cystitis, headache, abdominal pain, bloating and borderline intraocular pressure (IOP). Numerous episodes of

headache, abdominal pain, and bloating were reported before recruitment. Borderline intraocular pressure (IOP) and headache were also reported at baseline in study 020.

Concomitant medication included: Eyroobi (dorzolamide and timolol) ongoing since 21 mar 2023 for increased intraocular pressure, etizolam prn from 10 Mar 2003 for psychological anxiety, fosfomycin on 07 Mar 2023 for cystitis, nimesulide 100 mg prn for headache, and pantoprazole for GERD from 21 mar 2023.

Investigator Assessment:

The investigator rated the psychotic exacerbation as not serious, moderate in intensity, and possibly related to study medication (evenamide 30 mg/day).

Pertinent Positives and Negatives:

A 46-year-old male subject with a diagnosis of schizophrenia (approx. 14 years), receiving a stable dose of clozapine 300 mg/day, after 57 days on evenamide 30 mg/day in the open label study 020, the subject experienced psychotic exacerbation, moderate in intensity, with prominent delusions featuring discrete influence on behavior and more significant affective involvement as compared with baseline. The dose of clozapine was increased at 400 mg/day and the subject was discontinued from the study. The underlying disease, schizophrenia, not adequately controlled by the current concomitant antipsychotic, clozapine, could be considered contributory factors to the event onset. In addition, has been reported that the use of topical ocular timolol for treatment of increased IOP, could induce changes in mental status and onset of psychosis conditions (Cimolai N et al 2019). The psychotic exacerbation in this subject could be due to his psychiatric medical history and may not be related to evenamide.

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16. APPENDICES

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

16.1.2. Sample Electronic Case Report Form

16.1.3. List of Institutional Review Boards, 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

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Not applicable

16.2.13. Neurological Examination

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16.2.15. Columbia Suicide Severity Rating Scale (C-SSRS)

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Listing 16.2.17 Substance Use Assessment - 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 included and adapted in the CSR text