Statistical Analysis Plan	
Protocol Title	A Phase II, prospective, multi-center, randomized, 4-week, double-blind, placebo-controlled, multiple-dose study, designed to determine the safety, tolerability, EEG effects and preliminary efficacy of fixed oral doses of 7.5 and 15 mg bid of evenamide (NW-3509) in patients with chronic schizophrenia who are symptomatic on their current second-generation antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone) medication.
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Version 1.0	07OCT2020	Initial draft
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SIGNATURE PAGE

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2. List of Abbreviations

Abbreviation	Term
ADaM	Analysis Dataset Model
ADO	Adverse dropout (discontinuation due to adverse event)
AE	Adverse events
ALT	Alanine-aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate-aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma drug concentration vs. time curve
bid	Twice Daily
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDSS	Calgary Depression Scale for Schizophrenia
CGI-C	Clinical Global Impression - Change from baseline
CGI-S	Clinical Global Impression - Severity of illness
CI	Confidence Intervals
C_{max}	Maximum plasma concentration
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
CYP2D6	Cytochrome P450 2D6
ECG	Electrocardiogram
EEG	Electroencephalogram
EM	Extensive Metabolizers
ESRS-A	Extrapyramidal Symptom Rating Scale - Abbreviated version
HbA1c	Blood Glycosylated Hemoglobin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IM	Intermediate Metabolizers
ISMB	Independent Safety Monitoring Board
IWRS	Interactive Web Response System
KR	Kenward-Roger
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
LOF	Strauss-Carpenter Level of Functioning Scale
LLOQ	Lower limit of quantification
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat

MMRM	Mixed Model Repeated Measures analysis
MNAR	Missing not at random
MSQ	Medication Satisfaction Questionnaire
OC	Observed Cases
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetics
PM	Poor Metabolizers
PT	Preferred Term
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
$t_{1/2}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-Emergent Adverse Events
TESAE	Treatment-Emergent Serious Adverse Events
t_{max}	Time of maximum plasma concentration post-dose
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
UM	Ultra-rapid Metabolizers
UN	Unstructured
VLDL	Very low-density lipoprotein
WBC	White Blood Cells
WOCF	Worst-observation-carried forward

3. Introduction

The statistical analysis plan (SAP) describes the statistical methods to be used during the analysis and reporting of data collected under Newron Pharmaceuticals S.p.A. clinical study protocol NW-3509/008/II/2019 (Version 6, Amendment 5 dated 21 December 2020).

Clinical study NW-3509/008/II/2019 is a phase II, prospective, multi-center, randomized, 4-week, double-blind, placebo-controlled, multiple-dose study, designed to determine the safety, tolerability, EEG effects and preliminary efficacy of fixed oral doses of 7.5 and 15 mg bid of evenamide (NW-3509) in patients with chronic schizophrenia who are symptomatic on their current second-generation antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone) medication.

This SAP addresses the tolerability, safety, efficacy, and pharmacokinetic objectives of the study. The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. All analyses and data presentations will be generated using SAS® Version 9.4 (or later) Software (SAS Institute, Cary, North Carolina, USA).

Table, Figure and Listing shells will be a separate document and will be finalized with the SAP. Updated versions of mock-ups will be kept in the specific folder within the TMF. Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM) data will be used to create the subject listings, tables and figures.

The SDTM data will follow SDTM version 1.7 together with SDTM Implementation Guide version 3.3 and the SDTM Controlled Terminology version 2020-06-26. ADaM data will follow ADaM version 2.1 together with ADaM Implementation Guide version 1.2. Both SDTM and ADaM data will be validated using Pinnacle 21 version 3.0.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

This SAP will be finalized and approved before the clinical database lock. Any changes made to the SAP after the clinical database lock will be documented and discussed in the Clinical Study Report (CSR).

4. Study Objectives

4.1. Primary Objectives

- ***Safety:*** To evaluate the safety and tolerability (including EEG and ECG effects) of two fixed oral doses of evenamide (7.5 and 15 mg bid [15 and 30 mg/day]), compared to placebo, in patients with schizophrenia who are being treated with stable doses of antipsychotic medication (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone).
- ***Efficacy:*** To evaluate the efficacy of evenamide at doses of 7.5 and 15 mg *bid*, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the Positive and Negative Syndrome Scale (PANSS) total score.

4.2. Secondary Objectives

Key Secondary Efficacy:

- To evaluate the efficacy of evenamide at doses of 7.5 and 15 mg *bid*, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the Clinical Global Impression - Severity of illness (CGI-S).

Exploratory Secondary:

- To evaluate the efficacy of evenamide at doses of 7.5 to and 15 mg bid, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the rating at endpoint on the Clinical Global Impression - Change from baseline (CGI-C).
- To determine the multiple-dose pharmacokinetics (PK) of evenamide and its major metabolite, (3-butoxy-phenyl)-acetic acid, at the doses tested, and determine if the PK parameters are dose proportional.
- To determine the effect of evenamide, compared to placebo, on daily functioning, based on improvements on the Strauss-Carpenter Level of Functioning (LOF) scale.
- To determine the patient's satisfaction with treatment, compared to their previous treatment, based on improvements on the Medication Satisfaction Questionnaire (MSQ).

4.3. Tertiary Objectives

- To identify CYP2D6 "slow metabolizers" by genotyping, and to compare the PK profile for evenamide and its major metabolite, (3-butoxy-phenyl)-acetic acid, of these patients with other patients classified as having normal CYP2D6 metabolism.

5. Study Endpoints

5.1. Primary Safety Endpoints

Safety will be assessed by the following:

- Adverse events (AEs)
- Seizure Checklist
- Electroencephalogram (EEG) using 10-20 international EEG electrode application procedures

- Vital signs (systolic/diastolic blood pressure, pulse, body weight, body temperature, respiratory rate)
- Laboratory evaluations (blood chemistry, hematology, and urinalysis)
- Electrocardiogram (ECG) – 12-lead standard
- Physical examination
- Neurological examination
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Extrapyramidal Symptom Rating Scale - Abbreviated version (ESRS-A)
- 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)
- Calgary Depression Scale for Schizophrenia (CDSS).

5.2. Primary Efficacy Endpoint

- Primary efficacy will be assessed by measuring the mean change from baseline to endpoint on PANSS total score.

5.3. Key Secondary Efficacy Endpoint

- Secondary efficacy will be assessed by measuring the mean change from baseline to endpoint on CGI-S.

5.4. Exploratory Efficacy Endpoints

Exploratory efficacy will be assessed by the following measures:

- Changes from baseline to endpoint on PANSS – Positive Symptoms sub-scale
- Changes from baseline to endpoint on PANSS – Negative Symptoms sub-scale
- Changes from baseline to endpoint on PANSS – General Psychopathology sub-scale
- Responder analyses will be performed on PANSS total score and PANSS Positive Symptoms sub-scale
- Proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3) on CGI-C
- Mean change from baseline to endpoint on LOF
- Mean change from baseline to endpoint on MSQ.

5.5. Secondary Pharmacokinetic Endpoints

- To assess the multiple-dose pharmacokinetics (PK) of evenamide and its major metabolite, the following pharmacokinetic parameters of the evenamide and (3-butoxy-phenyl)-acetic acid in plasma levels will be calculated at each dose level of evenamide:
    - Maximum plasma concentration (C_{max})
    - Time to maximum plasma concentration (t_{max})
    - Terminal half-life ($t_{1/2}$)
    - Area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration (AUC_{0-t})

- Area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$).

5.6. Tertiary Endpoints

CYP2D6 metabolic phenotype will be identified based on the subject's genotype as determined from the specific alleles they are carrying.

The tertiary endpoint is to determine if genetic polymorphisms in CYP2D6 have any impact on the metabolism of NW-3509 at doses of 7.5 and 15 mg bid. On completion of the trial, a comparison of the pharmacokinetics of NW-3509 will be made between patients who are classified as "poor metabolizers" vs. those in the other categories, as determined by genotyping.

6. Study Design

6.1. Overall Design

This is a prospective, 4-week, randomized, double-blind, placebo-controlled, study designed to evaluate the safety, tolerability, including effects on EEG recordings, and efficacy of two fixed oral doses of evenamide of 7.5 mg and 15 mg, bid (15 and 30 mg/day) in patients with chronic schizophrenia receiving treatment at constant doses of one of the following antipsychotics: aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone. Approximately 120 patients will be randomized in a 1:1:1 ratio to receive either evenamide 7.5 or 15 mg, or placebo, given bid.

All patients must provide written informed consent prior to participation in the trial. For each patient, screening evaluations must be performed 3 to 21 days prior to baseline. These evaluations will consist of a review of the patient's medical and psychiatric history, their current use of medications, electroencephalogram (EEG), vital signs, 12-lead electrocardiogram (ECG), laboratory tests [hematology, blood chemistry, urinalysis, virology, HbA1c, thyroid function tests, urine drug screen, and both urine and serum pregnancy tests for all women [excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or those who have had a tubal ligation], physical and neurological examination, standard eye examination, PANSS, CGI-S, Calgary Depression Scale for Schizophrenia (CDSS) and Columbia – Suicide Severity Rating Scale (C SSRS). These evaluations will be repeated at baseline, except for the routine laboratory tests, physical and neurological examinations, and standard eye examination, which do not need to be repeated if done within 21 days of baseline. A blood test will be performed to confirm the patient's compliance with taking their background antipsychotic medication. An evaluation of adverse events, including symptoms and signs suggestive of seizures, will be performed. At the baseline visit (Day 0/1), an alcohol breath test will be done, and the urine drug screen repeated. An additional urine sample will be collected for measuring nicotine and cotinine. Urine and serum pregnancy tests will be performed for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or those who have had a tubal ligation. Baseline assessments will be performed for the PANSS, CGI S, LOF, MSQ, ESRS-A, CDSS and C-SSRS; the version of the C-SSRS to be used at baseline will be the "Since Last Visit" version. In addition, an assessment of polymorphisms in cytochrome P450 2D6 (CYP2D6) metabolic capacity, using genotyping, will be performed at the baseline visit.

Patients meeting all selection criteria at baseline will be randomized and will initiate dosing on Day 1 with a single dose of their assigned treatment being administered in the clinic. If there are no tolerability issues, the patient will be discharged and will take the evening dose at home. Beginning on Day 2, if the assigned bid dosing is not tolerated, the drug should be administered once daily for up to 7 days prior the next scheduled visit at which time bid dosing can be reinitiated if deemed clinical acceptable. Restarting bid dosing will only be allowed on a clinic visit day. If poorly tolerated after re-challenge at the planned bid dosing level, the dose will be permanently reduced to once daily for the remainder of the double-blind study. If once daily dosing is not well tolerated, the patient should be discontinued from the study.

On Day 1, a post-dose EEG and blood sampling for measuring levels of evenamide and its main metabolite will be performed, along with other safety assessments in the 4-hr post-dose period. If there are no tolerability issues, the patient will be discharged and take the evening dose at their residence, at least 6 hr after the initial dose, and continue with bid dosing. Patients will return to the clinic for scheduled visits on Days 8, 15 and 22, at which time selected safety and efficacy assessments will be performed. On Day 8 an EEG and blood sampling for measuring levels of evenamide and its main metabolite will be performed before and after the morning dose is administered in the clinic. Patients will take their last dose of study medication in the evening on Day 28 and return to the clinic for all final evaluations on Day 29.

Patients who complete 4 weeks of treatment, as well as those who discontinue prematurely, will have a follow-up safety evaluation 7 days after their last dose, with a follow-up on the occurrence of any SAEs through 30 days.

Table 1. Summary of Study Design

Period	Pre-Treatment		4-Week, Double-Blind, Treatment Period					Post-Treatment	
Visit	**Screening**	**Baseline[#]**	**Day 1[#]**	**Day 8**	**Day 15**	**Day 22**	**Final [$] (Day 29 or early d/c)**	**7-day Safety follow-up***	**30-day Safety follow-up***
Study Day(s)	-21 to -1	0/1 (pre-dose)	1 (in clinic)	1 to 7	8 to 14	15 to 22	23 to 29	7 days after last dose	30 days after last dose
Duration	3-21 days	1 day	1 day	7 days	7 days	7 days	7 days	7 days	30 days
Treatment/ Procedures	Informed consent; Screening evaluations performed (including EEG); I/E criteria assessed;	Patient checks into clinic; Baseline safety and efficacy evaluations; repeat urine drug screen; alcohol breath test; nicotine test; urine/ serum pregnancy tests in women of child-bearing potential; adverse event assessment and Seizure Checklist; confirm I/E criteria met	Randomization to evenamide (7.5 or 15 mg *bid*) or matching placebo *bid*; administer first dose in clinic on Day 1; safety assessments (including EEG) and PK sampling up to 4 hr after first dose; adverse event assessment and Seizure Checklist; discharge from clinic and continue dosing at their residence	Selected safety (including EEG) and efficacy assessments and PK sampling pre-dose and up to 4 hr post-dose; reduce dose if necessary; adverse event assessment and Seizure Checklist; discharge after 4 hr	Selected safety and efficacy assessments; adverse event assessment and Seizure Checklist	Selected safety and efficacy assessments; adverse event assessment and Seizure Checklist;	All safety (including EEG) and efficacy assessments; last dose of study medication on Day 28 (PM) at residence	Safety evaluations (vital signs and AEs) performed 7 days after last dose of study medication	Contact patient 30 days after last dose of study medication to assess occurrence of any SAEs
Telephone Contact				Day 4 (AEs, Seizure Checklist, MSQ and Conc. Medication)	Day 11 (AEs, Seizure Checklist, MSQ and Conc. Medication)	Day 18 (AEs, Seizure Checklist, MSQ and Conc. Medication)		If patient does not return for scheduled visit, contact to assess AEs	Information can be collected via telephone contact

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

[$] Final evaluation for patients who discontinue prematurely and those who complete 4 weeks of treatment.

*To be performed for patients who discontinue prematurely, and those who complete 4 weeks of treatment.

6.2. Sample Size and Power

Approximately 120 patients with schizophrenia will be included in this study. The sample size determination is not based on statistical power considerations. However, the number of patients enrolled in each treatment group should be adequate to meet the safety objectives and to provide evidence of efficacy for evenamide, compared with placebo.

6.3. Randomization

Approximately 120 patients will be randomized equally (1:1:1) to 7.5 or 15 mg evenamide, or placebo, bid. Randomization will be performed using an Interactive Web Response System (IWRS), according to a computer-generated randomization scheme. A randomization number corresponding to the blinded treatment assignment will be assigned by the IWRS to each randomized subject and must be registered in the subject's files for identification. Randomization will be done on a per site basis, and each patient randomized at the site will receive the next sequential randomization number and treatment assignment according to the randomization scheme for that site.

6.4. Replacement of Subjects

Patients who discontinue from the study after having received at least one dose of study medication will not be replaced.

6.5. Blinding

The Sponsor, the patient/caregiver, the Investigator, and all other site personnel will remain blinded.

6.6. Interim analysis

No interim analysis on efficacy data is planned. However, safety data from all patients will be examined periodically by an Independent Safety Monitoring Board (ISMB). An interim assessment of the first 60 patients who were randomized and completed 28 days of observation was performed by an independent statistician and pharmacovigilance provider, and reviewed by the CMO of Newron prior to submission to the ISMB. The ISMB review and recommendation were submitted to the FDA.

The ISMB may request modifications to the study design or request that the study be terminated, should any significant safety concerns become evident. The ISMB will be governed by a separate charter, and details will be included in the CSR.

6.7. Post-hoc Analysis

Country-wise efficacy tables may be generated, if required.

7. Analysis Populations

7.1. All Subjects Screened

This includes all subjects screened for the study.

7.2. Randomized population

The randomized population will consist of all subjects who are randomized to any treatment.

7.3. Safety Population

The safety population will consist of all subjects who took at least one dose of study medication.

7.4. Modified Intent-to-Treat Population

A modified Intent-to-Treat (mITT) population comprises all patients who have a baseline and at least one post-baseline efficacy assessment for the PANSS and receive at least one dose of the study medication.

7.5. Pharmacokinetic Concentration Population

The PK Concentration population will comprise all subjects who receive at least one dose of active treatment and who have at least one analyzable PK sample.

8. Statistical Analysis

8.1. General Considerations

All data collected in this study will be documented using summary tables, patient data listings and figures. Summary tables will present results by each dose level of evenamide and placebo.

Continuous variables (eg: Height) will be summarized using descriptive statistics, specifically the number of data points (n), mean, median, standard deviation (SD), minimum and maximum. In addition, variables describing pharmacokinetic parameters will be summarized using geometric mean, 95% confidence intervals for geometric mean, and geometric coefficient of variation (CV), calculated as $\widehat{cv}_{\ln} = \sqrt{e^{s^2_{\ln}} - 1}$, and expressed in percentages. Inferential statistics for continuous efficacy measures will include least square (LS) means and standard errors (SE), along with 95% confidence intervals (95% CI), for the change from baseline and the difference in LS means between groups.

Categorical variables (eg: Sex) will be summarized by frequencies and percentages. The percentages are derived based on the total number of subjects in each dose group within the specified population.
The mean, median, geometric mean, CI will be reported to an additional 1 decimal place, and the SD, CV, SE will be reported to an additional 2 decimal places, compared to the original result. Minimum and maximum will be reported to same decimal place as in the original result, unless otherwise specified. Percentages will be presented to 2 decimal points; except percentage will not be presented when the count is zero and 100% will be presented as an

integer. The values will be rounded to the specified decimal places as above. P-values will be rounded to 3 decimal places; *P*-values smaller than 0.001 will be presented as '<0.001' and greater than 0.999 will be presented as '>0.999'.

Baseline is defined as the last non-missing (including unscheduled visits) measurement prior to the administration of the first dose of study drug. For the PANSS endpoints, the baseline value will be defined as follows:

1. If the Baseline (Day 0) value is a greater than 10% improvement from the Screening value, the baseline will be set to missing. These values will be excluded as this change in the PANSS, and variability, does not provide an unbiased assessment of the subject's baseline measure for the study.
2. If the Baseline (Day 0) value is missing, then baseline will be the last non-missing value prior to administration of the first dose of study drug unless the screening assessment was performed more than 21 days before baseline.
3. The Baseline (Day 0) value, if the assessment is done prior to one hour* after first dose of study drug.

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

Unscheduled Visits: Unscheduled assessments will be listed.

Missing Date: If an AE has a completely missing onset date then the AE will be considered a treatment emergent adverse event (TEAE).

A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial missing start or stop date, and to calculate the duration of current episode/ duration of illness the following rules will be used to impute the date. For the medication imputed date will be used to determine whether it is a prior or concomitant medication.

Commented [RH1]: New section?

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

	same as the year of first dose date	

Missing data: For the measurement of endpoints there will be no imputation of missing data, except for the analysis of efficacy endpoints. The following imputation approaches will be used to impute missing data:

a) The LOCF approach will impute the missing data for the scheduled visits by the latest completed observation from the previous scheduled visits. Only post-baseline value will be carried forward. Baseline data will not be carried forward to post baseline visit.
b) The OC approach will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

Other missing data imputation techniques used for the analyses will be explained at corresponding analysis sections.

8.1.1. Rescue Medication and Censoring

Dose adjustments for atypical antipsychotics of 25% or more, upwards, or downwards or any new antipsychotic administered in the treatment period due to significant worsening and use of the medication is not temporary (5 days or less) is considered as rescue medication.

At screening and during the treatment period, a patient will only be on one antipsychotic medication, which can be recognized from its start date (preceding the screening date).

A dose reduction due to an AE, or an increase in dose because of worsening symptoms for this antipsychotic medication, can be identified by the stop date for the original dose and entry for the new dose.

If a new antipsychotic is added on, with a start date after baseline, this would be considered "rescue medication" and will have an indication of "worsening psychosis" or "worsening of schizophrenia symptoms".

In efficacy outputs the following rules will be applied to subjects who received rescue medication:

- Data post rescue medication will be flagged in the listings and a footnote added to explain.
- In summary tables and summary figures datapoints after rescue medication will be censored and a footnote added to explain.

8.1.2. Site Effects

Site effects are not accounted for the analysis due to large number of sites.

8.1.3. Adjustments for Multiplicity

The study level error rate will be controlled by following a hierarchical fixed sequence testing procedure for the primary and key secondary efficacy endpoints. The effects of the 15mg bid dose group versus placebo will be analyzed first for the primary and key secondary efficacy endpoints followed by the comparison of the 7.5mg bid dose group versus placebo in a pre-specified order. The order of testing will be:

- Mean change from baseline to endpoint (Day 29 or early discontinuation) on the PANSS total score for the 15 mg bid dose group versus placebo.
- Change from baseline to endpoint on the CGI-S for the 15 mg bid dose group versus placebo.
- Mean change from baseline to endpoint (Day 29 or early discontinuation) on the PANSS total score for the 7.5 mg bid dose group versus placebo.
- Change from baseline to endpoint on the CGI-S for the 7.5mg bid dose group versus placebo.

All tests will be performed at the two-sided 0.05 level following the pre-specified order. All other efficacy endpoints will be exploratory and statistical tests will be performed to investigate statistical significance between each evenamide dose group and placebo.

8.1.4. Analysis Visits

The value identified as baseline will be assigned with analysis visit "Baseline". The table below defines the 'analysis visits' for the efficacy analysis. If 2 or more visits occur within a window, the closest visit to the target day will be used as that analysis visit; if 2 visits are equidistant from the scheduled analysis visit day, the later analysis visit will be used. The nominal visits are to be considered in the case of telephone contacts regardless of the analysis window for MSQ.

Planned Analysis Visit	**Target Study Day**	**Analysis Window**
Screening	NA	NA
Baseline	NA	NA
Day 1	1	NA
Day 8	8	2 to 11
Day 15	15	12 to 18
Day 22	22	19 to 25
Day 29 (Endpoint)	29	26 to 35/ the endpoint assessment for the discontinued subject also will be accounted

8.2. Background Characteristics

8.2.1. Subject Disposition

Screen failures will be summarized with primary reason for screen failure. A subject enrollment listing with enrollment details and screen failure reasons, if applicable, will be provided.

The number and percentage of subjects in each analysis population (Randomized Population, Safety Population, Modified Intent-to-Treat Population**,** PK Concentration Population), disposition category (completed study, discontinued or early withdraw with a breakdown of the reasons for early discontinuation) of randomized subjects will be summarized by each evenamide dose group, placebo and total.

Subject listings will be presented for disposition, including details of randomization and reason for discontinuation for all randomized subjects.

8.2.2. Protocol Deviations

Protocol deviations will be collected by the clinical team and provided to biostatistics prior to database lock. Protocol deviations will be 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, and covid-19 related deviations will be summarized, and all protocol deviations will be listed.

8.2.3. Demographics and Baseline Characteristics

The demographic characteristics and baseline characteristics (age, gender, ethnicity, race, weight, height, BMI, waist circumference, education, marital status, employment, housing status, childbearing potential, CYP2D6 polymorphism) will be summarized by each evenamide dose group, placebo and total for mITT and safety population.

Demographics and baseline characteristics will be presented in individual subject data listings for screened subjects.

8.2.4. Disease Characteristics

The disease characteristics including, duration of illness, duration of current episode, number of hospitalizations, family history of schizophrenia, baseline depressive symptoms assessed by CDSS of the safety population will be summarized. Family history of schizophrenia will also be summarized as first-degree and second-degree relatives, by considering subject's parent, sibling, or child as first-degree relatives and others as second-degree relatives.

The duration of current episode will be calculated as:

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

The duration of illness will be calculated as:

Duration of Illness schizophrenia (months) = (Date of randomization - Date of First diagnosis + 1)/30.4167

8.2.5. Inclusion/Exclusion Criteria

A listing of all inclusion/exclusion criteria deviations will also be provided for all subjects screened. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

8.2.6. Medical History

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available. Summaries will be presented for the safety population by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages for each evenamide dose group, placebo, and total. Each subject will be counted only once in each SOC or SOC/PT summary.

Individual subject listing will be provided with all levels of MedDRA hierarchy for screened subjects.

8.2.7. Psychiatric History

The count and percentage of subjects in each of the reported psychiatric history will be provided by each evenamide dose group, placebo, and total for the safety population.

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

8.2.8. Prior and Concomitant Medication

Concomitant medications are defined as medications taken from the time of the first dose of the study medication through completion of the final (Day 29) evaluations. Also, the medication with start date and end date missing and with the ongoing status considered as concomitant medication. Prior medications are defined as all medications taken within 1 year of the first dose of study medication. Those medications taken with a start date prior to the initial dose of study drug and a stop date on or after the initial dose of study drug will be considered as prior and concomitant medications.

Prior and concomitant medications will be coded using the latest WHO Drug Dictionary version available. Medication will be presented for the safety population by Anatomical Therapeutic Chemical (ATC) level 4 and Preferred Term (PT) with counts and percentages for each dose group, placebo, and total. A subject who took more than one medication will be counted only once if these medications belong to the same extended ATC classification.

Prior and concomitant medications will be provided on the subject listings. Concomitant procedures will be presented in a separate subject listing.

8.2.9. Prior and Current Antipsychotic Medication

The prior and current antipsychotic medication will be summarized by each evenamide dose group, placebo, and total for the safety population. A listing of prior and current antipsychotic medication will be provided.

A table will be provided to summarize the dose of rescue medication taken during the study. A subject data listing of the rescue medication details will also be presented for safety population. Listings will be provided for baseline plasma levels of atypical antipsychotic medications. ANC levels measured during routine clozapine blood monitoring will be listed.

8.2.10. Study Drug Accountability

Study drug accountability data will be presented as individual data listing.

8.3. Efficacy Analysis

8.3.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS 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). 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 will be conducted at Screening, Baseline (Day 0), and at Days 8, 15, 22 and 29 (or at early discontinuation), and will be used as the primary efficacy measure in the trial.

Mean change from baseline to endpoint (Day 29 or early discontinuation) on the PANSS total score will be compared between the evenamide dose groups and placebo using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline PANSS total score obtained at the scheduled visits at Days 8, 15, 22 and 29, respectively. An unstructured covariance (UN) matrix will be used to model the within-subject errors. The Kenward-Roger (KR) approximation will be used to estimate denominator degrees of freedom. If the model for unstructured covariance matrix fails to converge, the heterogeneous Toeplitz covariance structure, followed by heterogeneous auto regressive covariance structure, will be used. The assumptions of the model, including normality, will be evaluated using residual and other diagnostic plots of model fit. The null hypothesis is that the mean difference between the dose groups and placebo is zero, versus the alternative hypothesis that this difference is not zero. The order of testing will be as described in Section 8.1.3. Inferential statistics to be presented based on this model are least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals will be estimated for each time point.

The primary sensitivity analysis using Multiple Imputation (MI) methods, assuming non-monotone missing data patterns, and assuming the data are missing not at random (MNAR), will be performed to assess the effects of missing data in the analysis of the primary efficacy endpoint. Under an assumption of MNAR, a pattern-mixture model (PMM) with control-based pattern imputation will be used as the primary sensitivity analysis for the primary efficacy endpoint. SAS/STAT procedures using multiple imputation methodology will be implemented

for applying the PMM. Control-based imputation will be applied so that there is no direct use of observed data from the evenamide treatment groups in estimating the imputation model. The method is derived such that it builds its imputation only on the placebo group data. Using the available non-missing placebo data in scheduled visits, a total of 15 complete data sets are imputed using SAS MI procedure. The imputed datasets will be analysed with an analysis of covariance (ANCOVA) model fitted for the fixed, categorical effects of treatment, and the continuous, fixed covariate of Baseline PANSS Total Score. The LS mean difference estimates will be averaged and the associated SEs will be summarized based on within-imputation and between-imputation variance using the SAS MIANALYZE procedure to yield a final estimate with associated 95% CI and p-value.

The second sensitivity analysis will use the worst post-baseline score to impute the missing endpoint data. Within a given patient, the worst (largest) observed total score will be used for the imputation of the value for their missing endpoint visit. An ANCOVA analysis will be performed at the endpoint visit to compare treatment groups. The ANCOVA-WOCF model is fitted for the fixed, categorical effects of treatment, and the continuous, fixed covariate of Baseline PANSS Total Score.

The treatment difference in least square means, 95% CI and p-value from both sensitivity analyses (ANCOVA) will be compared to the corresponding inferential statistics at Day 29 from the MMRM model for PANNS Total score.

Change from baseline to endpoint on the total scores on the PANSS – Positive Symptoms sub-scale, PANSS – General Psychopathology sub-scale, and PANSS – Negative Symptoms sub-scale will be compared between the evenamide and placebo groups using ANCOVA (LOCF and OC) fitted for the fixed, categorical effects of treatment, and the continuous, fixed covariate of baseline PANSS score.

For PANSS – Positive Symptoms sub-scale, PANSS – General Psychopathology sub-scale, and PANSS – Negative Symptoms sub-scale, different imputation techniques (LOCF and OC) for the ANCOVA model will be compared with inferential statistics (treatment difference in least square means, 95% CI and p-value) at Day 29 from each analysis.

'Responder' analyses will be performed using a logistic regression model (chi-square test) to compare the proportion of patients in the evenamide and placebo groups with different categories of improvement (PANSS score change <=30% and PANSS score change >30%) from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale. Logistic regression model (chi-square test) will be performed by considering different categories of improvement (PANSS score change <=30% and PANSS score change >30%) as dependent variable and dose groups and placebo as independent variable. For the responder analysis a forest plot will be presented.

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

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

8.3.2. Clinical Global Impression (CGI)

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

The CGI rating scale permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S is performed, in which the investigator rates the severity of a subject's condition on a 7-point scale ranging from 1 (Normal, not at all ill) to 7 (Among the most extremely ill subjects). At subsequent visits, the investigator assesses the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at baseline using the CGI-C, a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating "no change". The CGI-S assessment will be conducted at Screening, Baseline (Day 0), and Days 8, 15, 22 and 29 (or at early discontinuation), while the CGI-C will be assessed on Days 8, 15, 22 and 29 (or at early discontinuation). The CGI-S will be used as the key secondary efficacy measure in the trial.

Mean change from baseline to endpoint (Day 29 or early discontinuation) on CGI-S score will be compared between the evenamide dose groups and placebo using a mixed-effects repeated measures model approach (MMRM) with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value as covariate. The repeated measures are the change from baseline on CGI-S obtained at the scheduled visits at Days 8, 15, 22 and 29, respectively. An unstructured covariance (UN) matrix will be used to model the within-subject errors. The Kenward-Roger (KR) approximation will be used to estimate denominator degrees of freedom. If the model for unstructured covariance matrix fails to converge, the heterogeneous Toeplitz covariance structure, followed by heterogeneous auto regressive covariance structure, will be used. The assumptions of the model, including normality, will be evaluated using residual and other diagnostic plots of model fit. The null hypothesis is that the mean difference between the dose groups and placebo is zero, versus the alternative hypothesis that this difference is not zero. The order of testing will be as described in Section 8.1.3. Inferential statistics to be presented based on this model are least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals will be estimated for each time point.

The primary sensitivity analysis using Multiple Imputation (MI) methods, assuming non-monotone missing data patterns, and assuming the data are missing not at random (MNAR), will be performed to assess the effects of missing data in the analysis of the secondary efficacy endpoint. Under an assumption of MNAR, a pattern-mixture model (PMM) with control-based pattern imputation will be used as the primary sensitivity analysis for the secondary efficacy endpoint. SAS/STAT procedures using multiple imputation methodology will be implemented for applying the PMM. Control-based imputation will be applied so that there is no direct use of observed data from the evenamide treatment groups in estimating the imputation model. The method is derived such that it builds its imputation only on the placebo group data. Using the available non-missing placebo data in scheduled visits, a total of 15 complete data sets are imputed using SAS MI procedure. The imputed datasets will be analysed with an analysis of covariance (ANCOVA) model fitted for the fixed, categorical effects of treatment, and the continuous, fixed covariate of Baseline CGI-S score. The LS mean difference estimates will be averaged and the associated SEs will be summarized based on within-imputation and between-imputation variance using the SAS MIANALYZE procedure to yield a final estimate with associated 95% CI and p-value.

The second sensitivity analysis will use the worst post-baseline score to impute the missing endpoint data. Within a given patient, the worst (largest) observed total score will be used for the imputation of the value for their missing endpoint visit. An ANCOVA analysis will be performed at the endpoint visit to compare treatment groups. The ANCOVA-WOCF model is fitted for the fixed, categorical effects of treatment, and the continuous, fixed covariate of Baseline CGI-S score.

The treatment difference in least square means, 95% CI and p-value from both sensitivity analyses (ANCOVA) will be compared to the corresponding inferential statistics at Day 29 from the MMRM model for CGI-S score.
The proportion of patients rated improved on the CGI-C at endpoint (Day 29 or early discontinuation), will be compared between evenamide and placebo groups using a logistic regression model (chi-square test). The model will be performed by considering different categories of improvement (CGI-C score change <=3 and CGI-C score change >3) as dependent variable and dose groups and placebo as independent variable. For the responder analysis a forest plot will be presented. In addition, the mean score at endpoint for the CGI-C will be compared using ANOVA.

A line graph, including standard deviation bars, of mean change from baseline of CGI-S of the treatment groups will be presented by visit.

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

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

The LOF has been widely used as an instrument to evaluate clinical outcome in patients with schizophrenia. The LOF is a semi-structured, clinician-administered scale containing nine items. The individual items fall into four domains, with higher scores on a 5-point scale (0 - 4) reflecting better functioning. The subscales are Social Contacts (frequency and quality of social contacts), Work (quantity and quality of useful work), Symptomatology (absence of symptoms and recent hospitalization), and Function (ability to meet basic needs, fullness of life, and overall level of function). Subscale scores 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. The LOF will be conducted at Baseline (Day 0) and on Day 29 (or at early discontinuation).

Change from baseline to endpoint of the modified Intent-to-Treat (mITT) population on LOF will be compared between the dose groups and placebo using ANCOVA with fixed, categorical effects of treatment, and the continuous, fixed covariate of baseline LOF total score. The treatment difference in least square means, 95% CI and p-value at Day 29 from ANCOVA models will be compared for mITT population.

8.3.4. Patient's Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item, 7-point Likert-type scale for patients with schizophrenia to rate their satisfaction with their antipsychotic medication. The patient's response to the question "Overall, how satisfied are you with your current antipsychotic medication(s)?" is rated by the clinician as follows: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = somewhat dissatisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat satisfied, 6 = very satisfied, and 7 = extremely satisfied. The MSQ will be assessed at Baseline, during telephone contacts on Days

4, 11 and 18, and in the clinic at scheduled visits on Days 8, 15, 22, and 29 (or at early discontinuation).

Change from baseline to endpoint of the modified Intent-to-Treat (mITT) population on MSQ will be compared between the dose groups and placebo using ANCOVA (LOCF and OC) with fixed, categorical effects of treatment, and the continuous, fixed covariate of baseline MSQ value. All these models will be compared using treatment difference in least square means, 95% CI and p-value for Day 29. A line graph of mean change from baseline to endpoint of MSQ of the treatment groups will be presented by visit for mITT population.

8.4. Safety and Tolerability Analyses

8.4.1. Exposure and Treatment Compliance

Drug exposure table will summarize the duration of exposure and treatment compliance, by evenamide dose group and placebo for the safety population.

Duration of exposure will be the days from Treatment start date to Treatment end date.
Dosing compliance (% compliance) will be 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.

Compliance will be summarized overall.

Study exposure data will be 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, will be provided. Note that more than one reason per subject may be provided for dose adjustment due to multiple modifications.

Reasons for unscheduled dose adjustment are listed below:

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

A subject listing of dose adjustments over the course of the study will be provided for the safety population.

8.4.2. Adverse Events

Adverse events (AEs) will be coded according to MedDRA version 23.0.

Treatment-emergent AEs (TEAEs) are adverse events that are newly occurring or worsened in severity after the first administration of the study medication. The following criteria will be used to define treatment emergence for AEs with missing start or stop dates:

- If both the start and stop dates for a particular event are missing, then that event is considered treatment-emergent;

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

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

The frequency and percentage of subjects experiencing a TEAE for the safety population will be summarized using the MedDRA system organ class (SOC) and preferred term (PT), by evenamide dose group, placebo, and total.

AE summary tables will include the following:

- Overall incidence of SAEs, AEs leading to withdrawal, AEs leading to study drug discontinuation (ADOs), AEs leading to deaths for all TEAEs.
- Summary of TEAEs by SOC by PT
- Summary of TESAEs 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 are the TEAEs which are possibly or probably related to study drug, or the relationship is unknown (not reported).

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

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

Any information collected during the 30-day safety telephone follow up will be merged in the pharmacovigilance database.

8.4.3. Seizure Checklist

The counts and percentages of occurrence of subjects for each seizure-associated symptom will be tabulated by visit, time point (pre-dose and 4 hours post dose), dose group and placebo for the safety population. A subject level data listing will be provided.

8.4.4. Electroencephalogram (EEG)

All Electroencephalograms will be performed for at least 45 min, using 10-20 international EEG electrode application procedures. At Screening, the EEG will be performed two times, with an interval of approximately 1 hour between the recordings (if acceptable to the patient). These screening EEGs should include both hyperventilation and photic stimulation. Hyperventilation and photic stimulation will be performed only at Screening but will not be included in any of the post-baseline EEGs. The EEG will be repeated, with a duration of at least 45 min, between 1 and 3 hr post-dose on Day 1, pre-dose and 1-3 hr post-dose on Day 8, and at the final visit on Day 29.

For those patients who have their dose reduced to once daily dosing during the first week and have an increase back to twice daily dosing at Day 8, an additional EEG should be conducted at the next weekly visit (i.e., Day 15) after the dose increase.

Changes from baseline at each visit and at endpoint (Day 29 or early discontinuation) in overall EEG findings will be summarized by dose group and placebo. EEG findings of the safety population will be listed along with the clinically significant abnormalities observed.

8.4.5. Vital Signs

Vital signs assessments will be performed at all scheduled evaluations. Vital signs will include height (screening only; used to calculate BMI), body weight, temperature, respiratory rate, pulse, and systolic and diastolic blood pressure. For all vital sign assessments, pulse and blood pressure will be measured after the subject has been in the supine position for at least 5 minutes, and 1 minute and 3 minutes after standing. At the baseline visit, prior to the first dose of study medication, measurements of temperature, respiratory rate, and blood pressure and pulse (supine, standing 1 minute, standing 3 minutes), will be repeated 3 times, at least 10 minutes apart, and the values will be averaged to obtain the baseline values (body weight needs to be measured only once). The mean values should be used in determining eligibility for the study and assessing changes from baseline. On Day 1 and Day 8, vital signs will be repeated at 1 and 4 hr after the first dose of study medication.

Tables presenting descriptive statistics for all the observed vital signs will be provided. Changes from baseline at each visit and at endpoint (Day 29 or early discontinuation) will be presented by evenamide dose group and placebo for temperature, respiratory rate, pulse, weight, BMI, waist circumference, systolic blood pressure and diastolic blood pressure at each time point.

At all-time points where weight is collected BMI will be calculated using the formula.

$$\text{BMI } (kg/m^2) = \text{Weight } (kg)/(\text{Height}(m))^2$$

Based on the Appendix 2, counts and percentage of number of subjects in each visit meeting the clinically notable abnormalities criteria will be provided for each evenamide dose group and placebo.

A listing of data containing individual subject vital signs values will be provided.

The analysis of vital signs data will be done on the safety population.

8.4.6. Laboratory Evaluations

The counts and percentage of number of subjects at each visit meeting the clinically notable abnormalities criteria (Appendix 2) will be presented for each evenamide dose group and placebo in safety population.

The summary of change from baseline to each visit will be provided for hematology and chemistry parameters mentioned in Appendix 3 by evenamide dose groups and placebo.

The individual values collected at local laboratories will be standardized and then normalized using either of the following normalization formulas for each of the parameters mentioned in Appendix 4. Metropolis Healthcare Ltd will be considered as the standard laboratory for normalization.

1) Location-scale normalization formula

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

Here we assume that the distribution of standard values and the original values belong to the same location-scale family of distributions.

2) Scale normalization formula

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

Lower limits can be used instead of upper limits in the formula based on the clinical relevance range for each parameter.

Here we assume that the distribution of standard values and the original values belong to the same scale family of distributions.

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 limits 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

Whenever both the lower and upper limits are available for a parameter use the location-scale formula. For all other cases use scale formula.

For High Density Lipoprotein, Low Density Lipoprotein, and Cholesterol normalization will not be performed, since the units and normal reference ranges are identical.

The following laboratory parameters will be listed only:

- Thyroid function: TSH, free triiodothyronine (T3), and free thyroxine (T4)
- Virology: Hepatitis B and C; HIV
- HbA1c
- Urine drug screen
- Alcohol breath test
- Serum/urine pregnancy tests
- Serum prolactin
- Nicotine and cotinine in urine

A listing of any laboratory measurements recorded throughout the treatment period will be presented along with reference range.

8.4.7. Electrocardiogram (ECG)

All subjects will have a standard 12-lead ECG performed as specified in the schedule of evaluations. At the baseline visit, at least 1 hour prior to the first dose, the 12-lead ECG will be repeated 3 times, at least 10 minutes apart, and the values for the different parameters will be averaged to obtain the baseline values. The mean value for each of the parameters should be used in determining eligibility for the study and assessing changes from baseline. On Day 1, the ECG will be repeated at 1 and 4 hr after the first dose of study medication. Additional ECGs will be performed on Day 8 (pre-dose and 1 hr and 4 hr post-dose) and Day 29.

The summary will be provided for the following by evenamide dose group and placebo at each scheduled time point in the safety population:

1) Change from baseline at each visit and at endpoint (Day 29 or early discontinuation) for ECG parameters (Mean Heart Rate, RR Interval, PR Interval, QRS Duration, QT Interval, QTcB Interval, and QTcF Interval).
2) Abnormalities in ECG findings.
3) The number (%) of patients meeting the following categorical criteria will be summarized by treatment group:
    a. Change from baseline in QTc interval: > 60 msec, > 30 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.

Individual subject listing will be presented with findings from Principal Investigator and central reader.

8.4.8. Physical Examinations

A physical examination will be performed at Screening, Baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline) and at the final visit (Day 29 or at early discontinuation).

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

8.4.9. Neurological Examinations

A neurological examination will be performed at Screening, Baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline) and at the final visit (Day 29 or at early discontinuation).

Treatment-emergent post-baseline abnormal findings on any body system in neurological examination (Mental status, Cranial nerves, Muscle strength and tone, Reflexes, Sensory

System, Coordination, and Gait) will be summarized and listed by evenamide dose group and placebo for the safety population.

8.4.10. Standard Eye Examination

A standard eye examination will be performed at Screening, Baseline (optional; to be repeated only if screening examination was done more than 21 days prior to baseline) and Day 29 (or at early discontinuation).

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

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

The C-SSRS is a standardized suicidal rating system. All questions in the 'suicidal ideation' category will be summarized using counts and percentages of subjects who answered "Yes" to those questions, for each visit by dose group and placebo for the safety population using the C-SSRS "Since Last Visit" version. In addition, summaries will also be presented for Intensity of suicidal ideation and suicidal behavior since last visit. Changes in C-SSRS suicidal ideation scores from baseline will also be presented for the safety population.

Individual subject listing for the safety population will be provided separately for the "Screening" and "Since Last Visit" versions of the C-SSRS.

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

The ESRS-A is a 33-item scale designed to examine changes in motor function associated with pharmacologic treatment. It has a 'subjective' part (12 items, 0 - 4 rating) and a part scored 'objectively' on the basis of observation and examination (parkinsonism: eight items, dystonia: two items, dyskinesia: seven items; all scored on a 0 - 6 scale described for each item separately in terms of frequency and severity, some subdivided for body-parts). Each movement sub-domain (Parkinsonism, dystonia, dyskinesia, akathisia) includes a total subdomain score and a global subdomain score. The ESRS-A will be performed at Baseline (Day 0), Day 1 (2-4 hr post-dose) and on Day 29 (or at early discontinuation).

Ratings of ESRS-A will be summarized for the safety population by total and global subdomain scores by visit and presented by dose group and placebo. The mean change from baseline score and observed score in the total score and sub-scale scores on the ESRS-A for the safety population will be presented by evenamide dose group and placebo. All the findings will also be listed.

8.4.13. Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a nine-item, observer-rated, semi-structured, goal-directed interview, validated for diagnosing depression in patients with schizophrenia. Each item is scored between 0 and 3 based on operational criteria. A total score of 6 or above is considered predictive of a major

depressive episode. In the current study, the CDSS will be performed at screening and baseline to assess depressive symptoms. A score of **7** or more at baseline will exclude the patient from participating in the study. In addition to its use as a screening tool, the CDSS assessment will also be performed at the final visit (Day 29 or at early discontinuation) to assess changes from baseline in depressive symptoms.

The change from baseline to the final assessment in the CDSS total score for the safety population will be presented by evenamide dose group and placebo.

CDSS scores at baseline and final assessment in the safety population will be listed.

8.5. Pharmacokinetic Analysis

The concentrations of evenamide and its main human plasma metabolite, (3-butoxy-phenyl)-acetic acid, in plasma samples taken on Days 1, 8 and 29 will be determined. Blood samples will be taken on Baseline Day 0 / Day 1 prior to the first dose (blank), and at 30, 60, 120 and 240 minutes after the first dose of study drug on Day 1. Similar post-dose sampling will be performed on Day 8. In addition, a sample for measuring steady state trough plasma levels of evenamide and its major metabolite will be taken before dosing on Day 8. A sample will also be taken in the morning on Day 29 to measure trough plasma levels of evenamide and its major metabolite following the last dose of study medication given in the evening on Day 28. Pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$) for each dose level of evenamide will be calculated corresponding to each dose consumption event.

The plasma PK concentrations and derived PK parameters will be listed and plotted by subject/analyte and summarized by dose groups. Mean concentration versus time curves will be provided for each dose group by visit. The PK concentration and PK parameters will also be summarized by CYP2D6 genotype.

The PK concentration population will be used for the analysis of the PK concentrations and the PK parameter population will be used for the descriptive statistics of the PK parameters.

The concentration values below the lower limit of quantification will be labelled as "< X" where X is the numerical value of the LLOQ established by the laboratory. These values are ignored prior to computing standard statistical summaries of PK concentrations.

All PK analyses will be performed at the end of the study subsequent to the completion of the analyses of the clinical data. This action is being undertaken as the shipment of samples from the sites in batches, and the subsequent time spent in bioanalysis, QC, QA would require a significant amount of time.

A separate PK SAP and PK study report will be issued.

8.6. Exploratory Analysis

8.6.1. Polymorphism in CYP2D6 Metabolism

Using genotyping, patients can be classified as "ultra-rapid metabolizers", "extensive metabolizers", "intermediate metabolizers" or "poor metabolizers", based on the specific alleles they are carrying.

To investigate the potential effects of polymorphisms in CYP2D6 on metabolism of evenamide, PK parameters $AUC_{(0-t)}$ and C_{max} of evenamide and its major metabolite will be compared for ultra-rapid metabolizers (UM), extensive metabolizers (EM) and intermediate metabolizers (IM) against poor metabolizers (PM) for each dose group on Day 1.

The differences between the groups UM, EM and IM, and the PM group will be evaluated by calculating the geometric mean ratio (GMR, UM/PM, EM/PM, IM/PM) and 90% CI. When the 90% CI is included in the equivalence range (80%–125%), no difference between the UM, EM and IM groups and the PM group will be assessed.

A figure of the PK profiles of evenamide and its metabolites according to CYP2D6 genotypic groups will be presented. Analysis will be done on the PK parameter population with valid genotyping result.

9. Changes from Planned Analysis

- PANSS considered as the primary efficacy endpoint.
- CGI-S considered as the key secondary efficacy endpoint.
- The study level error rate will be controlled by following a hierarchical fixed sequence testing procedure for the primary and key secondary efficacy endpoints as described in Section 8.1.3.

10. References

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Appendix 1: Schedule of Evaluations

Table 1. Schedule of Evaluations:

Period	Pre-Treatment		Treatment Phase								Post-Treatment	
Visit / Assessment	Screening Days -21 to -3	Baseline[A] Day 0[T]	Day 1[T]	Day 4	Day 8[U]	Day 11	Day 15[V]	Day 18	Day 22[W]	Day 29 (Final) [E]	7-day Safety follow-up[I]	30-day Safety follow-up[K]
Informed consent (before any study procedure is completed)	X											
Inclusion/Exclusion Criteria	X	X										
Demography/Background Information	X											
Psychiatric History	X											
Medical History and Current Medical Conditions	X											
Physical Examination	X	X[B]								X		
Neurological Examination	X	X[B]								X		
ESRS-A		X	X							X		
Standard Eye Examination	X	X[B]								X		
Seizure Checklist	X	X[Q,R]	X[Q,S]	X	X[Q,R,S]	X	X[Q,R,S]	X	X[Q,R,S]	X[R]		
C-SSRS evaluation	X	X			X		X		X	X		
Electroencephalogram (EEG)	X[G]		X[G]		X[G]		(X)[G]			X[G]		
Electrocardiogram (12-lead ECG)	X[D]	X[D]	X[D]		X[D]					X[D]		
Vital Signs	X [O]	X[C]	X[C]		X[C]		X[C]		X[C]	X[C,O]	X[C]	
Laboratory (Hematology, Biochemistry, Urinalysis)	X	X[B]			X		X			X		
Virology (Hepatitis B/C, HIV)	X											
HbA1c	X									X		
Thyroid Function Tests (TSH, free T3 and T4)	X											
Serum prolactin		X								X		
Alcohol Breath Test		X										
Urine Drug Screen	X	X								X		
Urine/Serum Pregnancy Test [M]	X	X								X		
Nicotine and cotinine in urine		X										
CYP2D6 Polymorphism assessment		X										
Blood sample for atypical antipsychotic plasma levels		X[P]										

Period	Pre-Treatment		Treatment Phase								Post-Treatment	
Visit Assessment	Screening Days -21 to -3	Baseline[A] Day 0[T]	Day 1[T]	Day 4	Day 8[U]	Day 11	Day 15[V]	Day 18	Day 22[W]	Day 29 (Final) [E]	7-day Safety follow-up[I]	30-day Safety follow-up[K]
Pharmacokinetic blood samples for evenamide and (3-butoxy-phenyl)-acetic acid plasma levels		X[F]	X[F]		X[F]					X[N]		
Dosage administration and drug label record			X[A]		X[L]		X[L]		X[L]	X[X]		
Prior and Concomitant Medications and Significant Non-Drug Therapies	X	X		X	X	X	X	X	X	X		
Adverse Events	X	X[R]	X[S]	X[R]	X[R,S]	X[R]	X[R,S]	X[R]	X[R,S]	X[R]	X[R]	X[K]
PANSS	X	X			X		X		X	X		
CGI-S	X	X			X		X		X	X		
CGI-C					X		X		X	X		
CDSS	X	X								X		
LOF		X								X		
MSQ		X		X	X	X	X	X	X	X		
Clozapine blood monitoring (venipuncture for measuring ANC)	X[Y]	X[Y]			X[Y]		X[Y]		X[Y]	X[Y]		
Telephone contact				X[H]		X[H]		X[H]			(X)[I]	(X)[K]
Study Completion											X	

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

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

[C] Vital signs are to be performed at baseline in triplicate, with measurements at least 10 min apart, and then on Day 1 at 1 hr and 4 hr post-dose, just prior to taking blood samples for PK measurements. On Day 8, vital signs will be performed prior to dosing, and then at 1- and 4-hours post-dose. On Days 15 and 22 vital signs will be performed prior to the morning dose of study medication and at 1 hr post-dose. On Day 29 and at the Safety Follow-up visit, vital signs can be performed at any time during the visit. At each assessment, blood pressure and pulse will be repeated in 3 positions (supine for 5 minutes, within 1 minute of standing and after 3 minutes of standing). Baseline (Day 0) vital signs do not need to be repeated if dosing is postponed until the following day (Day 1).

[D] On Day 1 a single 12-lead ECG will be obtained 1 hr and 4 hr post-dose, just prior to the collection of the PK blood samples. On Day 8 ECGs will be obtained prior to the morning dose of study medication and again 1 hr and 4 hr post-dose. A single reading is acceptable for all planned ECG evaluations, except for Baseline, where a triplicate ECG will be collected with an interval of at least 10 min between readings.

[E] All Day 29 evaluations should be performed when a subject discontinues from the study prematurely before completing the 4-week treatment period. See Table 11 for more details.

[F] On Baseline/Day 0 a pre-dose (blank) PK blood sample will be collected, and on Day 8 a pre-dose PK blood sample will be taken to measure steady state trough levels of evenamide and (3-butoxy-phenyl)-acetic acid. Additional PK blood samples will be collected on Day 1 and Day 8 at 30 min, 60 min, 120 min and 240 min post-dose. The

timing windows for blood sampling should be ± 5 min for the early post-dose PK samples (30 and 60 minutes), and ± 15 min for the later sample (120 and 240 minutes post dose).

[G] Electroencephalograms should use 10-20 international EEG electrode application procedures. Recordings will be made two times at Screening (approximately one hour apart, if feasible for the patient), and on Day 1 (post-dose), Day 8 (pre- and post-dose) and Day 29, and should be at least 45 minutes long. On Days 1 and 8, post-dose EEGs should be completed 60 to 180 min after dosing. An additional EEG should be performed at Day 15 prior to the morning dose for patients who received once daily dosing during the first week and have an increase back to twice daily dosing at Day 8.

[H] Patients being treated as outpatients will be contacted by telephone on Days 4, 11 and 18; medication satisfaction, adverse events (including Seizure Checklist) and concomitant medication use will be assessed. If the patient reports significant intolerance, a dose reduction can be performed, and he/she may be asked to return to the hospital for an unscheduled visit.

[I] To be performed 7 days after the last dose of study medication for patients who discontinue prematurely, and those who complete 4 weeks of treatment. If the patient does not attend the in-clinic visit, a phone call will be made to the patient (or caregiver) to encourage attendance; or if unavailable, to collect adverse event information via the telephone.

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

[L] On Days 8, 15 and 22, the morning dose of study medication will be administered in the clinic. Prior to the visit, patients should be reminded not to take their morning dose of study medication at home.

[M] Urine and serum pregnancy tests will be performed for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), or who are surgically sterilized. A serum pregnancy test will be performed at Screening, Baseline and Day 29. In addition, at Screening and Baseline, a urine pregnancy test will be performed for an immediate result, with the serum test providing confirmation. If the local laboratory is unable to perform the serum pregnancy test, it can be sent out to another laboratory for analysis. Results of the serum test must be available before the Baseline visit.

[N] On Day 29, a blood sample for measurement of trough plasma levels of evenamide and (3-butoxy-phenyl)-acetic acid will be taken in at the clinic.

[O] Weight and height will be measured at screening and used for calculating BMI, and waist circumference will be measured at screening and Day 29, in addition to routine vital signs.

[P] A blood sample for measuring levels of the concomitant atypical antipsychotic will be taken prior to the dose of study medication at baseline.

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

[R] Assess since prior visit.

[S] Assess since prior observed dosing.

[T] See Table 7 for more details.

[U] See Table 8 for more details.

[V] See Table 9 for more details.

[W] See Table 10 for more details.

[X] The last dose of study medication will be taken in the evening on Day 28 at home.

[Y] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

Table 2. Detailed Schedule of Evaluations: Days 0 (Baseline) and 1

Assessment	DAY 0 Baseline [A] Pre-dose	DAY 1 Post-First Dose
Inclusion/Exclusion Criteria	X	
Physical Examination	X[B]	
Neurological Examination	X[B]	
ESRS-A	X	X[N]
Standard Eye Examination	X[B]	
Seizure Checklist	X[I]	X[I]
C-SSRS	X	
Electroencephalogram (EEG)		X[F]
Electrocardiogram (12-lead ECG)	X[D]	X[D]
Vital Signs	X[C]	X[C]
Laboratory (Hematology, Biochemistry, Urinalysis)	X[B]	
Serum prolactin	X	
Alcohol Breath Test	X	
Urine Drug Screen	X	
Urine/Serum Pregnancy Test	X[H]	
Nicotine and cotinine in urine	X	
CYP2D6 Polymorphism assessment	X	
Blood sample for atypical antipsychotic plasma levels	X[O]	
Pharmacokinetic blood samples for evenamide and (3-butoxy-phenyl)-acetic acid plasma levels	X[E]	X[E]
Dosage administration and drug label record		X[G]
Concomitant Medications and Significant Non-Drug Therapies	X	
Adverse Events	X[K]	X[L]
PANSS	X	
CGI-S	X	
CDSS	X	
LOF	X	
MSQ	X	
Clozapine blood monitoring (venipuncture for measuring ANC)	X[J]	

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

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

[C] Vital signs are to be performed at baseline in triplicate, with measurements at least 10 min apart, and then on Day 1 at 1 hr and 4 hr post-dose, just prior to taking blood samples for PK measurements. At each assessment blood pressure and pulse will be repeated in 3 positions (supine for 5 minutes, within 1 minute of standing and after 3 minutes of standing). Baseline vital signs do not need to be repeated if dosing is postponed until Day 1.

[D] A 12-lead ECGs will be obtained at baseline in triplicate with an interval of at least 10 min between readings. On Day 1 a single ECG reading will be obtained 1 hr and 4 hr post-dose, just prior to the collection of the PK blood samples.

[E] On Day 0 a pre-dose PK blood sample (blank) will be collected, and additional PK blood samples will be collected on Day 1 at 30 min, 60 min, 120 min and 240 min post-dose to measure levels of evenamide and its major metabolite [(3-butoxy-phenyl)-acetic acid]. The timing windows for blood sampling should be $\pm$ 5 min for the early post-dose PK samples (30 and 60 minutes), and $\pm$ 15 min for the later samples (120 and 240 minutes post dose).

[F] Electroencephalograms should use 10-20 international EEG electrode application procedures. The recording will be made on Day 1 from 60 to 180 min after the initial dose of study medication and should be at least 45 minutes long.

[G] On Day 1, patients will be randomized to treatment and the first dose of study medication will be administered in the clinic. Patient will be instructed not to take the evening dose on Day 1 (*od*).

[H] A serum and urine pregnancy test will be performed at baseline for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or who are surgically sterilized. In

addition, a urine pregnancy test will be performed for an immediate result, with the serum test providing confirmation. If the local laboratory is unable to perform the serum pregnancy test, it can be sent out to another laboratory for analysis.

[I] The Seizure Checklist will be completed before administration of study drug on Day 0, assessing the period since the prior visit (screening), and 4 hours after dosing on Day 1, assessing the entire 4-hour post-dose period.

[J] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

[K] Assess since prior visit (Screening).

[L] Assess since prior observed dosing.

[N] To be performed between 2 and 4 hr post-dose.

[O] A blood sample for measuring levels of the concomitant atypical antipsychotic will be taken prior to the dose of study medication at baseline.

Table 3. Detailed Schedule of Evaluations: Day 8

Assessment	DAY 8 Pre-dose	DAY 8 Post Dose
Vital signs	X[A]	X[A]
Electroencephalogram (EEG)	X[D]	X[D]
Seizure Checklist	X[F]	X[F]
Electrocardiogram (12-lead ECG)	X[B]	X[B]
Laboratory (Hematology, Biochemistry, Urinalysis)	X	
C-SSRS	X	
Pharmacokinetic blood samples for evenamide and metabolite plasma levels	X[C]	X[C]
Dosage administration and drug label record	X[E]	
Concomitant Medications and Significant Non-Drug Therapies	X	
Adverse Events	X[G]	X[H]
PANSS		X
CGI-S		X
CGI-C		X
MSQ	X	
Clozapine blood monitoring (venipuncture for measuring ANC)	X[I]	

[A] Vital signs are to be performed on Day 8, with pulse and blood pressure measured in each of the 3 positions, prior to dosing, and then at 1- and 4-hours post-dose, just prior to the collection of the PK blood samples.

[B] On Day 8 a single 12-lead ECG will be obtained prior to the morning dose of study medication and at 1 hr and 4 hr post-dose, just prior to the collection of the PK blood samples.

[C] On Day 8 a pre-dose PK blood sample will be taken to measure steady state trough levels of evenamide and (3-butoxy-phenyl)-acetic acid. Additional PK blood samples will be collected at 30 min, 60 min, 120 min and 240 min post-dose. The timing windows for blood sampling should be $\pm$ 5 min for the early post-dose PK samples (30 and 60 minutes), and $\pm$ 15 min for the later samples (120 and 240 minutes post dose).

[D] Electroencephalograms should use 10-20 international EEG electrode application procedures and should be at least 45 minutes long. The recordings will be made on Day 8 prior to the morning dose of study medication in the clinic, and at 60 to 180 min after dosing.

[E] Prior to the visit, patients should be reminded not to take their morning dose of study medication at home.

[F] The Seizure Checklist will be completed before administration of study drug on Day 8, assessing the period since the prior visit (Day 1), and again 4 hours after dosing, assessing the entire 4-hour post-dose period.

[G] Assess since prior visit (Day 1)

[H] Assess since prior observed dosing.

[I] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

Table 4. Detailed Schedule of Evaluations: Day 15

Assessment	DAY 15 AM Pre-dose	DAY 15 Post-Dose
Vital signs	X[A]	X[A]
Electroencephalogram (EEG)	(X)[G]	
Seizure Checklist	X[C]	X[C]
Laboratory (Hematology, Biochemistry, Urinalysis)	X	
C-SSRS	X	
Dosage administration and drug label record	X[B]	
Concomitant Medications and Significant Non-Drug Therapies	X	
Adverse Events	X[D]	X[E]
PANSS		X
CGI-S		X
CGI-C		X
MSQ	X	
Clozapine blood monitoring (venipuncture for measuring ANC)	X[F]	

[A] Vital signs are to be performed on Day 15, with pulse and blood pressure measured in each of the 3 positions, prior to dosing, and then at 1 hour-post-dose.

[B] The morning dose of study medication will be administered in the clinic. Prior to the visit, patients should be reminded not to take their morning dose of study medication at home.

[C] The Seizure Checklist will be completed before administration of study drug on Day 15, assessing the period since the prior visit (Day 8), and 4 hours after dosing, assessing the entire 4-hour post-dose period.

[D] Assess since prior visit (Day 8).

[E] Assess since prior observed dosing.

[F] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

[G] An additional EEG should be performed at Day 15 prior to the morning dose, using 10-20 international EEG electrode application procedures, for patients who receive once daily dosing during the first week and have an increase back to twice daily dosing at Day 8.

Table 5. Detailed Schedule of Evaluations: Day 22

Assessment	DAY 22 AM Pre-dose	DAY 22 Post-Dose
Vital signs	X[A]	X[A]
Seizure Checklist	X[C]	X[C]
C-SSRS	X	
Dosage administration and drug label record	X[B]	
Concomitant Medications and Significant Non-Drug Therapies	X	
Adverse Events	X[D]	X[E]
PANSS		X
CGI-S		X
CGI-C		X
MSQ	X	
Clozapine blood monitoring (venipuncture for measuring ANC)	X[F]	

[A] Vital signs are to be performed on Day 22, with pulse and blood pressure measured in each of the 3 positions, prior to the morning dose of study medication and at 1 hr post-dose.

[B] The morning dose of study medication will be administered in the clinic. Prior to the visit, patients should be reminded not to take their morning dose of study medication at home.

[C] The Seizure Checklist will be completed before administration of study drug on Day 22, assessing the period since the prior visit (Day 15), and 4 hours after dosing, assessing the entire 4-hour post-dose period.

[D] Assess since prior visit (Day 15).

[E] Assess since prior observed dosing.

[F] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

Table 6. Detailed Schedule of Evaluations: Day 29 (End of Double-Blind Study)

Assessment	DAY 29 [C]
Vital Signs	X[A,I]
Physical Examination	X
Neurological Examination	X
Seizure Checklist	X[J]
Standard Eye Examination	X
Electroencephalogram (EEG)	X[D]
C-SSRS	X
Laboratory (Hematology, Biochemistry, Urinalysis)	X
HbA1c	X
Serum prolactin	X
Urine Drug Screen	X
Urine/Serum Pregnancy Test	X[G]
Pharmacokinetic blood sample for trough evenamide plasma levels	X[H]
Electrocardiogram (12-lead ECG)	X[B]
ESRS-A	X
Dosage administration and drug label record	X[F]
Concomitant Medications and Significant Non-Drug Therapies	X
Adverse Events	X[K]
PANSS	X[E]
CGI-S	X[E]
CGI-C	X[E]
CDSS	X
MSQ	X
LOF	X
Clozapine blood monitoring (venipuncture for measuring ANC)	X[L]

[A] Vital signs, including weight, will be completed once, with blood pressure and pulse performed in the 3 positions.

[B] A single 12-lead ECG will be performed.

[C] All Day 29 evaluations should be performed when a subject discontinues from the study prematurely, before completing the 4-week treatment period.

[D] Electroencephalograms should use 10-20 international EEG electrode application procedures. The recordings should be at least 45 minutes long.

[E] Key efficacy assessments (PANSS, CGI-S and CGI-C) to be performed shortly after the patient arrives for the clinic visit.

[F] The last dose of study medication will be taken in the evening on Day 28 at home.

[G] A serum pregnancy test will be performed for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or who are surgically sterilized. If the local laboratory is unable to perform the serum pregnancy test, it can be sent out to another laboratory for analysis.

[H] On Day 29, a blood sample for measuring trough levels of evenamide and its major metabolite [(3-butoxy-phenyl)-acetic acid] will be taken.

[I] Height will be measured at screening and used for calculating BMI, and waist circumference will be measured at screening and Day 29, in addition to routine vital signs.

[J] The Seizure Checklist can be completed at any time during the visit, assessing the period since the prior visit (Day 22).

[K] Assess since prior visit (Day 22)

[L] Routine clozapine blood monitoring (absolute neutrophil count) to be done weekly if clozapine was started < 6 months ago, bi-weekly if clozapine was started 6 - 12 months ago, or every 4 weeks if clozapine was started more than 12 months ago.

Appendix 2: Clinically Notable Values

The following guidelines, established by the Division of Neurology Products of the FDA, will be used for determining clinically notable values for laboratory and vital signs parameters.

Notable Values for Laboratory Parameters and Vital Signs

CLINICALLY NOTABLE BLOOD CHEMISTRY VALUES

Parameter	Synonym	S.I. units			Other units		
		Unit	Lower Limit	Upper Limit	Unit	Lower Limit	Upper Limit
Albumin		g/L	≤ 14	≥ 62	g/dL	≤ 1.4	≥ 6.2
Alkaline Phosphatase	ALP	IU/L	NA	≥ 250			
Alanine Aminotransferase	ALT (SGPT)	IU/L	NA	≥ 3.0 x ULN			
Aspartate Aminotransferase	AST (SGOT)	IU/L	NA	≥ 3.0 x ULN			
Bicarbonate		mmol/L	≤ 18	≥ 33			
Bilirubin total		µmol/L	NA	≥ 34	mg/dL		≥ 2.0
Calcium total		mmol/L	≤ 1.9	≥ 2.7	mg/dL	≤ 7.5	≥ 11
Chloride		mmol/L	≤ 90	≥ 113			
Cholesterol		mmol/L	NA	≥ 7.25	mg/dL		≥ 280
Creatinine kinase	CPK	IU/L	NA	≥ 400			
Creatinine		µmol/L	NA	≥ 177	mg/dL		≥ 2.0
Gamma-GT	GGT	IU/L	NA	≥ 3.0 x ULN			
Glucose		mmol/L	≤ 2.8	≥ 11.1	mg/dL	≤ 50	≥ 200
High Density Lipoprotein	HDL	mmol/L	≤ 0.8	≥ 2.3	mg/dL	≤ 30	≥ 90
Lactate Dehydrogenase	LDH	IU/L	NA	≥ 500			
Low Density Lipoprotein Cholesterol	LDL	mmol/L		≥ 4.1	mg/dL		≥ 160
Phosphate		mmol/l	NA	≥ 2			
Potassium		mmol/L	≤ 3.0	≥ 6.0			
Protein total		g/L	≤ 45	NA			
Sodium		mmol/L	≤ 127	≥ 152			
Triglycerides		mmol/L	NA	≥ 4.5	mg/dL		≥ 400
Urea nitrogen	BUN	mmol/L	NA	≥ 84.0	mg/dL		≥ 30
Uric acid Male		µmol/L	NA	≥ 624	mg/dL		≥ 10.5
Uric acid Female		µmol/L	NA	≥ 505	mg/dL		≥ 8.5
Very Low-Density Lipoprotein Cholesterol (a)	VLDL	mmol/L		≥ 2.1	mg/dL		≥ 80

ULN: upper limit of normal; (a) Calculated

CLINICALLY NOTABLE HEMATOLOGY VALUES

Parameter		Synonym	S.I. units			Other units		
			Unit	Lower Limit	Upper Limit	Unit	Lower Limit	Upper Limit
Basophils			10^9/L	NA	≥ 0.20	%	NA	≥ 15
Eosinophils			10^9/L	NA	≥ 1.5			
Erythocytes	Male	RBC	10^{12}/L	≤ 2.5	NA			
	Female		10^{12}/L	≤ 2.0	NA			
ESR	Male		mm/hr	NA	≥ 25			
	Female		mm/hr	NA	≥ 35			
Hematocrit		EVF	L/L	≤ 0.85 x LLN	≥ 1.15 x ULN	%	≤ 0.85 x LLN	≥ 1.15 x ULN
Hemoglobin			mmol/L	≤ 0.85 x LLN	≥ 1.15 x ULN	g/L	≤ 0.85 x LLN	≥ 1.15 x ULN
Leukocytes		WBC	10^9/L	≤ 3.0	≥ 15.0			
Lymphocytes			10^9/L	NA	≥ 8	%	NA	≥ 80
MCHC			g/L	≤ 200	≥ 450	g/dL	≤ 20	≥ 45
MCV			10^{-15}L	≤ 60	≥ 120			
Monocytes			10^9/L	NA	≥ 1.5	%	NA	≥ 40
Neutrophils			10^9/L	≤ 1.0	NA			
Thrombocytes		Platelets	10^9/L	≤ 100	≥ 600			

CLINICALLY NOTABLE URINALYSIS VALUES

Variable	Clinically Notable Values
Protein	>2+
Glucose	>2+
Specific Gravity	> 1.035
Ketones	>1+
Leukocytes (WBC) casts	>2+
Erythrocyte (RBC) casts	>2+
Casts	>2+

CLINICALLY NOTABLE VITAL SIGNS VALUES

Parameter	Unit	Decrease	Increase
Sitting/Supine SBP	mmHg	Value ≤ 90 and ≥ 20 decrease from Baseline	Value ≥ 180 and ≥ 20 increase from Baseline
Sitting/Supine DBP	mmHg	Value ≤ 50 and ≥ 15 decrease from Baseline	Value ≥ 105 and ≥ 15 increase from Baseline
Orthostatic Hypotension (based on standing SBP/DBP)	mmHg	Decrease in SBP/DBP from Supine to Standing position > 30 mmHg	NA
Sitting pulse rate	bpm	Value ≤ 50 and ≥ 15 decrease from Baseline	Value ≥ 120 and ≥ 15 increase from Baseline
Weight	kg	≥ 7% decrease from Baseline	≥ 7% increase from Baseline
Respiration rates*	Breaths/ minute	< 12	> 25
Temperature	ºC	NA	Value ≥ 38.3 and ≥ 1.1 increase from Baseline
Temperature	˚F	NA	Value ≥ 101.0 and ≥ 2.0 increase from baseline

* For respiration rate, values are relevant, not decrease/increase.

Appendix 3: Summary of Laboratory Analytes

LABORATORY ANALYTES			
Hematology	**Blood Chemistry**		**Urinalysis**
hematocrit	sodium	triglycerides	pH
hemoglobin	potassium	AST	specific gravity
RBC count	chloride	ALT	Protein
WBC count	bicarbonate	alkaline phosphatase	glucose
differential WBC count	calcium	GGT	ketones
platelets	glucose	LDH	RBC, WBC, casts
	BUN	total cholesterol	Nitrites
	creatinine	HDL, LDL, VLDL	bilirubin
	total bilirubin	CPK	hemoglobin
	albumin	total protein	

Special Diagnostic Tests (evaluated at screening and/or baseline)

- Thyroid function: TSH, free triiodothyronine (T_3), and free thyroxine (T_4) (screening)
- Virology: Hepatitis B and C; HIV (screening)
- HbA1c (screening and final visit)
- Urine drug screen (screening, baseline and final visit)
- Alcohol breath test (baseline)
- Nicotine and cotinine in urine (baseline) - Serum prolactin (baseline and final visit)
- Serum/urine pregnancy tests (Screening, Baseline and final visit) – for all women, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months)) or have had a tubal ligation.

Appendix 4: Standard Laboratory Reference Ranges – Metropolis Healthcare Ltd

CHEMISTRY

Parameter		S.I. Unit	Male	Female
Albumin	14 <= age <= 19	g/L	34 - 49	34 - 49
	19 < age <= 60	g/L	35 - 52	35 - 52
	60 < age <= 90	g/L	32 - 46	32 - 46
Alkaline Phosphatase		IU/L	40 - 150	40 - 150
Alanine Aminotransferase		IU/L	0 - 45	0 - 34
Aspartate Aminotransferase		IU/L	0 - 35	0 - 31
Bicarbonate		mmol/L	21 - 32	21 - 32
Bilirubin total		umol/L	3.42 - 20.52	3.42 - 20.52
Calcium total	14 <= age <= 60	mmol/L	2.1 - 2.55	2.1 - 2.55
	age > 60	mmol/L	2.2 - 2.5	2.1 - 2.55
Chloride		mmol/L	98 - 107	98 - 107
Creatinine kinase		IU/L	30 - 200	29 - 168
Creatinine		umol/L	54.9072 - 95.325	43.4682 - 84.6486
Gamma-GT		IU/L	12 - 64	9 - 36
Glucose		mmol/L	3.885 - 5.55	3.885 - 5.55
Lactate Dehydrogenase		IU/L	125 - 220	125 - 220
Potassium		mmol/L	3.5 – 5.1	3.5 – 5.1
Protein total	14 <= age <= 60	g/L	64 - 83	64 - 83
	age > 60	g/L	62 - 81	62 - 81
Sodium		mmol/L	136 - 145	136 - 145
Triglycerides		mmol/L	< 1.695	< 1.695
Urea nitrogen	14 <= age <= 60	mmol/L	3.1773 - 7.3542	2.499 - 6.6759
	age > 60	mmol/L	2.9988 - 9.1749	3.4986 - 7.1757
Very Low-Density Lipoprotein Cholesterol		mmol/L	0.1554 - 0.9842	0.1554 - 0.9842

HEMATOLOGY

Parameter	S.I. Unit	Male	Female
Basophils	10^9/L	0.02 – 0.1	0.02 – 0.1
Eosinophils	10^9/L	0.02 – 0.5	0.02 – 0.5
Erythrocytes	10^12/L	4.4 - 6	4.2 – 5.4
Hematocrit	fraction of 1	0.42 – 0.52	0.37 – 0.47
Hemoglobin	g/L	140 - 180	120 - 160
Leukocytes	10^9/L	4.3 – 10.3	4.3 – 10.3
Lymphocytes	10^9/L	1 - 3	1 - 3
MCHC	g/L	315 - 360	315 - 360
MCV	fL	82-101	82-101
Monocytes	10^9/L	0.2 - 1	0.2 - 1
Neutrophils	10^9/L	2 - 7	2 - 7
Thrombocytes	10^9/L	140 - 440	140 - 440

Appendix 5: Sample SAS Code

A sample of the SAS code for MMRM analysis is provided as below:

```
proc mixed data = data;
  class usubjid trta avisit ;
  model chg = base trta avisit trta*avisit/ddfm=KR;
  repeated avisit / subject = usubjid  type=UN;
  lsmeans trta*avisit / cl alpha = 0.05 diff e ;
  ods output lsmeans=lsmeans diffs=diffs;
run ;
quit;
```

A sample of the SAS code for MI is provided as below:

```
proc mi data = <dataset name> out =  out1 nimpute = 15 seed = <seed number> minimum =
<lowest value> maximum = <Highest value> minmaxiter=75000 noprint;
   class treatment;
   fcs reg(/details);
   mnar model(panss_day8 panss_day15 panss_day22 panss_day29/ modelobs=(Trt='0'));
   var panss_baseline panss_day8 panss_day15 panss_day22 panss_day29;
run;

*Before analyzing using PROC MIXED, the data sets need to be transposed in which one
variable represents all outcome with different values of visit and finding the change from
baseline (chg).;

proc mixed data = ancova ;
    class trta;
    model chg = trta base;
    by dtype;
    lsmeans trta / cl alpha=0.05 diff e ;
    ods output lsmeans=lsmeans diffs=diffs;
run;

proc mianalyze data =  lsmeans  ;
  by trta ;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=lsm;
run;

proc mianalyze data =  diffs  ;
  by trta ;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=diff;
run;
```

A sample of the SAS code for ANCOVA is provided as below:

```
proc mixed data = <dataset name>;
  class treatment;
  model change = treatment baseline;
  estimate treatment /cl;
  lsmeans treatment /cl;
  ods output Estimates = e_ancova;
  where visit = "Day 29";
run;
```

A sample of the SAS code for Logistic regression is provided as below:

```
proc logistic data = <dataset name> order=data;
  class treatment;
  model resp(event ='1') = treatment /alpha=0.05;
  oddsratio treatment / cl=wald;
run;
```

A sample of the SAS code for ANOVA is provided as below:

```
proc sort data = <dataset name>; by treatment; run;
proc glm data = <dataset name>;
 class treatment;
 model aval = treatment;
 means treatment;
 lsmeans treatment /pdiff cl stderr;
 ods output Means = Means OverallANOVA = OverallANOVA LSMeans = LSMeans
 LSMeanDiffCL = LSMeanDiffCL LSMeanCL = LSMeanCL;
run;
```