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

Evenamide (NW-3509)

Protocol No: NW-3509/008/II/2019

IND No: 104,708

Final

19 September 2019

Protocol Incorporates:
Amendment 1, 05 December 2019
Amendment 2, 23 December 2019
Amendment 3, 03 March 2020
Amendment 5, 21 December 2020

Protocol Version: 6.0, 21 December 2020

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1 SYNOPSIS

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.

Protocol No.: NW-3509/008/II/2019

Phase of Development: II

Centers/Countries: 15-18 centers in India and the US

Planned Trial Period (first subject enrolled - last subject out)	First Subject In (FSI): 2nd Quarter 2020 Last Subject In (LSI): 4th Quarter 2020 Last Subject Last Visit (LSLV): 1st Quarter 2021

Rationale:
Evenamide is intended to be administered as an adjunct to atypical antipsychotics in patients with schizophrenia who are not responding adequately to their current treatment. As it will be added to other antipsychotics that may be associated with seizures and QTc prolongation, this four-week study will be performed to determine if evenamide may accentuate these risks.

This study will evaluate the safety, tolerability and efficacy of evenamide (7.5 and 15 mg, *bid*) treatment in patients with schizophrenia. This study will include evaluation of vital signs, ECGs, a Seizure Checklist (see Appendix 4), and EEGs, in addition to other standard safety and efficacy parameters, and will explore the pharmacokinetics (PK) of evenamide and its major metabolite (3-butoxy-phenyl)-acetic acid. Doses of evenamide to be evaluated in this study, compared to placebo, will be 7.5 mg *bid*, and 15 mg *bid*, with key information being collected at or near the time of the predicted maximal plasma concentration (T_{max}) for evenamide. The doses selected are based on preliminary evidence of safety and efficacy derived from animal models, a safety study in healthy volunteers (NW-3509A/001/I/2011 [Study 001]) which evaluated single doses of evenamide from 1 to 30 mg, and an early safety and efficacy study (NW-3509A/002/II/2015 [Study 002]) in which patients with schizophrenia were treated with multiple ascending doses of 15, 20 and 25 mg *bid*.

Both the 30 mg single and the 25 mg *bid* doses of evenamide were well tolerated and not associated with any dose-related CNS events. This study will evaluate the tolerability and safety of a maximum dose of 15 mg *bid*, with extensive precautions to ensure the safety of patients enrolled in the trial. The extensive safety precautions will include initiation of dosing in a hospital setting, evaluation of pre- and post-dosing vital signs and ECGs, exhaustive evaluation of symptoms and signs suggestive of seizure-like activity through the completion of a Seizure Checklist by a physician, and the performance of pre-dosing and post-dosing EEGs to detect any evidence of seizure-like activities after administration of evenamide. EEGs will be performed at the end of study (Day 29) to detect any changes in the EEGs from baseline. If well tolerated, the 15 mg *bid* dose will be used as the maximum dose in future efficacy studies in patients with schizophrenia.

Objectives:
The objectives of the study are as follows:

Primary:

- 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.

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 and 15 mg *bid*, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the rating at endpoint on the CGI - 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).

Tertiary:

- 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.

Study Design and Methods:
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 who are receiving treatment at constant doses of one of the following atypical 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*.

Study Drug Dosing

Randomized patients will initiate dosing on Day 1. Initial treatment will begin at the randomly assigned dose of 7.5 or 15 mg evenamide, or placebo, given *bid*. If the assigned *bid* dosing is not tolerated, the drug should be administered once daily (*od*) 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. In addition, prior to each dose, the patient will be evaluated through careful open-ended questioning for possible CNS signs or symptoms suggestive of seizures, including EEG spike and wave activity, or any of the

following symptoms suggestive of seizures: seizures, fits, jerks, jerky movements, easy startle, convulsions, absence seizures, gazing, staring, falls, fainting, syncope, auditory/visual auras, myoclonus, automatism, unconsciousness, biting of tongue. If any of these signs or symptoms are identified, dosing will be withheld until the symptoms abate. Once abated, depending on sign or symptom severity, the clinician may decide to discontinue the patient or resume treatment with *od* dosing.

Screening Visit

All patients must provide written informed consent prior to participation in the trial. For each patient, screening evaluations (Table 6) must be performed from 3 to 21 days prior to baseline. Screening evaluations will consist of confirmation of the patient's psychiatric diagnosis, collection of information on the patient's medical and psychiatric history, and past and current medications, and review of selection criteria. Screening safety evaluations will include physical and neurological examinations, a standard eye examination, completion of a Seizure Checklist evaluating symptoms and signs suggestive of seizures (e.g., seizures or fits, convulsions, absence seizures, unconsciousness, biting of tongue), vital signs, an electroencephalogram (EEG) using the international 10-20 system (performed two times with approximately one hour in between, if feasible for the patient), a 12-lead electrocardiogram (ECG), laboratory tests (hematology, blood chemistry, urinalysis, virology, thyroid function tests, HbA1c, urine drug screen, serum and urine pregnancy tests in women [excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or surgically sterilized] and the Columbia – Suicide Severity Rating Scale (C-SSRS) ("Baseline/Screening" version). Efficacy evaluations to be performed at screening are the PANSS and CGI-S. The Calgary Depression Scale for Schizophrenia (CDSS) will be used to screen out patients with significant depressive symptoms. All patients who are taking clozapine must agree to routine blood monitoring (venipuncture for measuring absolute neutrophil count [ANC] – see Appendix 5), with weekly testing (if within 6 months of starting clozapine), bi-weekly testing (if clozapine was started from 6 to 12 months ago), or testing every 4 weeks (if clozapine has been taken for more than 12 months).

Baseline (Day 0)

At the baseline visit (Day 0), the detailed baseline schedule of evaluations outlined in Table 7 will be completed. This will include review of adverse events, updating any change in current medications, assessment of vital signs, completion of the Seizure Checklist, assessment of abnormal movements using the ESRS-A, ECG, the C-SSRS ("Baseline/Screening" version), an alcohol breath test, a urine drug screen, and review of the selection criteria. An additional urine sample will be collected for measuring nicotine and cotinine. Serum and urine 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 surgically sterilized, with the results of the urine testing being used for determining eligibility, and the serum test being used for subsequent confirmation. A serum prolactin level will also be obtained, and a blood sample collected to confirm the patient's compliance with taking their background antipsychotic medication. In addition, an assessment of polymorphisms in cytochrome P450 2D6 (CYP2D6) metabolic capacity, using genotyping, will be done. Hematology, blood chemistry and urinalysis laboratory tests, physical and neurological examinations, and the eye examination do not need to be repeated if previously done within 21 days of baseline. The CDSS will be repeated to assess depressive symptoms. Baseline efficacy evaluations that will be completed include the PANSS, CGI-S, MSQ, and LOF.

Day 1

Upon completion of the baseline pre-dosing safety and efficacy evaluations, patients meeting entry criteria will be randomized and begin Day 1 dosing. In this study, all Day 0 (pre-dose) and Day 1 (post-dose) procedures are expected to be completed on the same day, if possible. After the initial dose of study medication, the post-dose battery of safety evaluations outlined in Table 7 will be completed. These will include an ECG, vital signs, ESRS-A and EEG recording to be conducted near the predicted T_{max} of evenamide, 1-3 hours (60 to 180 min) after dosing with the study drug, and a Seizure Checklist of terms suggestive of potential seizure activity to be performed 4 hours after dosing and assessing the entire 4-hour post-dose period.

Blood samples will be collected to measure plasma levels of evenamide and its major metabolite, (3-butoxy-phenyl)-acetic acid, before dosing (as a blank sample) and 30 min, 60 min, 120 min and 240 min after the initial dose.

If no significant side effects are noted during the 4-hr period of post-first dose safety evaluations, the patient will be discharged and given a supply of study medication for the remainder of the first week's treatment; the patient will be instructed to take the next dose of study drug at his/her residence in the evening of the first day at least 6 hours after the initial dose. Treatment should continue as prescribed until the next scheduled study visit, unless significant tolerability issues arise during the week. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance.

Patients will be proactively contacted by telephone on Day 4 to assess the tolerability of their current dose, and to review the Seizure Checklist and AEs. If any tolerability issue does arise, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work-up.

Day 8

Patients will be asked not to take their study medication before coming to the clinic on Day 8 and will receive their dose in the clinic. The detailed assessment schedule outlined in Table 8 will be followed. If significant safety or tolerability issues are detected during the pre-dose assessments on Day 8, further dosing will be reduced to *od* and the patient will remain on *od* dosing for the duration of the study. If the safety or tolerability issues are severe, the study drug should be discontinued.

On Day 8 a pre-dose EEG will be performed and a PK blood sample will be collected to measure steady state trough plasma 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. Post-dose safety assessments will include, an EEG recording to be conducted near the predicted T_{max} of evenamide, 1-3 hours (60 to 180 min) after dosing with the study drug, and a Seizure Checklist of terms suggestive of potential seizure activity to be performed 4 hours after dosing and assessing the entire 4-hour post-dose period.

If no significant safety or tolerability issues are identified in the 4-hour post-dose period during completion of the safety assessments, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on Day 8 in the evening at their residence at least 6 hr after the morning dose.

Patients will be proactively contacted by telephone on Day 11 to assess the tolerability of their current dose, and to review the Seizure Checklist and AEs. If significant tolerability issues arise during the week, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 15

Patients will be asked not to take their study medication before coming to the clinic on Day 15, as the dose will be administered in the clinic. The detailed assessment schedule outlined in Table 9 will be followed at this visit. If significant safety or tolerability issues are detected during the pre-dose assessments, further dosing may be reduced to *od,* and the patient will remain on *od* dosing for the duration of the study. If the safety or tolerability issues are severe the study drug should be discontinued.

Post-dose safety assessments will be performed as outlined in Table 9. Among these, the Seizure Checklist and assessment of adverse events will be performed. If no significant safety or tolerability issues are identified after the 4 hours of post-treatment observation, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on the evening of Day 15 at their residence and continue treatment as prescribed until their next study visit. If significant tolerability issues arise during the week, patients should be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Patients will be proactively contacted by telephone on Day 18 to assess the tolerability of their current dose, and to review the Seizure Checklist and AEs. If significant tolerability issues arise during the week, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 22

Patients will be asked not to take their study medication before coming to the clinic on Day 22, as the dose will be administered in the clinic. The detailed assessment schedule outlined in Table 10 should be followed. If significant safety or tolerability issues are detected during the pre-dose assessments, further dosing will be reduced to *od*. If the safety or tolerability issues are severe the study drug should be discontinued.

Post-dose safety assessments will also be performed as outlined in Table 10. If no significant safety or tolerability issues are identified after 4 hours of post treatment observation, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on the evening of Day 22 at their residence and continue treatment as prescribed until their next study visit. If significant tolerability issues arise during the week, patients should be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 29 or Final Visit

The patient will be instructed to take a final dose of study medication in the evening on Day 28, and on Day 29 (or at early discontinuation) the patient will return to the clinic for all final safety and efficacy evaluations. The detailed schedule of evaluations outlined in Table 11 should be followed. In addition, a PK blood sample will be collected to measure trough plasma levels of evenamide and its major metabolite (3-butoxy-phenyl)-acetic acid during this final day of assessment.

Safety Follow-up Visit

For all patients who complete 4 weeks of treatment, as well as those who discontinue prematurely, a safety follow-up visit will be performed one week after the final double-blind dose (Day 35 or after early discontinuation), during which vital signs and an assessment of adverse events will be performed. The patient will be contacted by phone 30 days after the last dose of study medication to assess the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose of study medication.

Telephone Contacts

Patients will receive a telephone contact from the Investigator/site staff on Days 4, 11 and 18 to inquire about their medication satisfaction, any safety or tolerability issues, and use of concomitant medication. The investigator will evaluate if the patient is experiencing any of the following symptoms and signs suggestive of seizures: seizures, fits, jerks, jerky movements, easy startle, convulsions, absence seizures, gazing, staring, falls, fainting, syncope, auditory/visual auras, myoclonus, automatism, unconsciousness, biting of tongue, through careful open-ended questioning. If the patient reports any of these symptoms the patient will be asked to return to the hospital immediately for an unscheduled visit, an examination of the patient will be performed to determine the presence of symptoms or signs suggestive of seizures, including an EEG. If the EEG shows spike and wave activity suggestive of seizures, dosing will be interrupted, and the patient kept in the hospital pending a full evaluation. A decision on the patient's continued participation in the trial will be made by the Investigator based on a full review of the patient's history and other safety data collected during the study.

Throughout the study, if the examination of the patient confirms symptoms or signs suggestive of seizures or significant cardiac events, if the EEG detects activity suggestive of seizures, or the ECG shows significant changes, dosing should be interrupted, and the patient kept in the hospital pending a full evaluation. A decision on the patient's further participation in the trial will be made by the Investigator based on a full review of the patient's history and data collected in the study.

Planned Study Duration:
The study will last up to 51 days, including a 3- to 21-day screening period, a one-day baseline evaluation, a 28-day randomized treatment period, and a one-day final evaluation. In addition, patients will have a safety follow-up visit 7 days after the patient's last dose and a SAE follow-up assessment after 30 days.

Study Population:
Approximately 120 patients with chronic schizophrenia will be randomized (1:1:1) to one of the two doses of evenamide or placebo.

Inclusion Criteria:
The patient must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Demographics

1. Age - 18 years, or older.
2. Sex - male, or female. *For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with adequate contraception (barrier method and/or hormonal contraceptive).*
3. Body mass index (BMI) of at least 17.5 and less than 35. *Patients with a BMI of 35 or higher may be considered for enrollment on a case-by-case basis if, in the Investigator's opinion, this does not put the patient at any additional risk for participating in the trial. These cases should be discussed with the Medical Monitor and documented in the source records.*

Psychiatric

4. Has a current diagnosis of schizophrenia in accordance with DSM-5. *Other Axis-I disorders may be present only as lifetime diagnoses if they are not relevant to the current episode of schizophrenia. [see Exclusion criteria below]*
5. Has been treated with antipsychotics for at least 2 years.
6. Has a total score on the PANSS < 80.
7. Has a Clinical Global Impression – Severity of disease (CGI-S) rating of mildly, moderately or moderately severely ill (score of 3, 4 or 5).
8. Needs antipsychotic treatment and is currently receiving a stable dose (minimally for 4 weeks prior to screening) of aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone (at least 2 mg risperidone dose-equivalent).
9. Current symptoms have been stably present for at least one month.

Procedural

10. Patient has provided written informed consent prior to participating in the study.
11. Patient is able to take oral medication and is willing to complete all protocol-defined aspects of the study.
12. Patient resides at home or in a residential care facility with a caregiver who is available to ensure compliance with dosing and scheduled office visits. *For US only: "Caregiver" is defined as someone who has at least 5 contacts with the patient each week, of which at least 2 are face-to-face.*
13. Patient agrees to be hospitalized overnight if required for trial purposes or if the investigator deems it necessary to ensure the safety of the patient.
14. If taking clozapine, patient agrees to blood monitoring (venipuncture for measuring ANC) weekly during their first 6 months of clozapine treatment, every 2 weeks from 6 to 12 months, and every 4 weeks after 12 months of treatment.

Exclusion Criteria:
The presence of any of the following will exclude a patient from study enrollment:

Psychiatric

1. DSM-5 diagnosis of schizophreniform disorder (295.40), schizoaffective disorder (295.70), or other primary psychiatric diagnosis, such as bipolar disorder or major depressive disorder. (Comorbid

depression will be assessed at screening and baseline using the Calgary Depression Scale for Schizophrenia [CDSS]. A score of 7 or higher will be exclusionary.)

2. History (within three months of study entry) or current diagnosis of Substance Use Disorder as defined by the DSM-5 criteria, with a severity of 'moderate' or 'severe', or patient is currently abusing drugs or alcohol or has done so in the past year. *A history of nicotine or caffeine dependence is acceptable*
3. Severity of current episode of psychosis requires that the patient be hospitalized. *Patients who are chronically hospitalized or in psychiatric day-care, whose hospitalization is for logistic reasons and not due to the severity of their illness, will be eligible for the study*.
4. Severity of psychosis is rated severe or higher (CGI-S of 6 or greater).
5. History or current diagnosis of other psychiatric (Axis I diagnosis) or behavioral disorders that may interfere with the conduct or interpretation of the study.
6. Known suicidal risk. *A "yes" response on the C-SSRS Suicidal Ideation Item 4 or Item 5,* ***or*** *a "yes" response on any of the five C-SSRS Suicidal Behavior items, at screening,* ***or*** *a suicide attempt within the past 6 months, excludes the patient from the study.*
7. "Treatment resistant" defined significant persistent symptoms of schizophrenia after adequate doses of two standard antipsychotic medications (from two different chemical classes, including at least one atypical antipsychotic) following 6 weeks of treatment with each at adequate doses. Treatment resistant patients on clozapine for at least 6 months will be permitted if they have shown minimal improvement in the Investigator's judgement.
8. History of neuroleptic malignant syndrome, priapism.
9. History of severe tardive dyskinesia; or current moderate or severe tardive dyskinesia.

Medical Status

10. Abnormal epileptiform phenomena (3 per second spike and slow wave discharges) observed on screening EEG.
11. An advanced, severe, or unstable disease of any type that may interfere with any of the study evaluations, including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical or mental status of the patient to a significant degree or put the patient at special risk (e.g., respiratory, liver or kidney disease; malignancy);
12. A disability that may prevent the subject from completing all study requirements (e.g., blindness, deafness, severe language difficulty);
13. Insulin-dependent diabetes mellitus. Patients with non-insulin-dependent diabetes will be eligible if the following criteria are satisfied:
    a. HbA1c < 7.0% at screening,
    b. Diabetes is considered well controlled, with no changes in treatment regimen for at least 4 weeks prior to screening,
    c. Diabetes is not newly diagnosed at screening;
14. History or current diagnosis of any neurodegenerative illness, dementia or significant concomitant neurological disease; organic cerebral disease, cerebrovascular disease, focal neurological lesions or history of any trauma resulting in loss of consciousness (during the past 2 years).
15. History or current diagnosis of epilepsy or seizure disorder (other than febrile seizures in childhood).
16. Loss of 500 ml or more of blood during the 3-month period before study enrollment, e.g. as a donor.
17. Prior surgery or current medical condition which might interfere with the absorption, distribution, metabolism or excretion of the study drug, e.g. gastric or intestinal surgery, impaired renal or hepatic function, cardiovascular abnormalities, inflammatory bowel disease, chronic symptoms of pronounced constipation or diarrhea, or conditions associated with total or partial obstruction of the urinary tract.

Cardiovascular

18. A current diagnosis of severe or unstable cardiovascular disease, including ischemic heart disease; vasovagal syncope, sick-sinus syndrome, arrhythmia, conduction deficits [e.g., sino-atrial block, second or third degree atrio-ventricular block (PR >0.20)], congestive heart failure, myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.
19. Any clinically significant ECG abnormality, including a disorder of rate, rhythm, or conduction, or other morphological changes, or a QTcF interval prolongation (Fridericia's correction formula) on the ECG (>450 msec for males; >470 msec for females).

A 12-lead ECG will be used for determining the suitability of the patient for inclusion in the study (determined by the investigator); the values averaged from the 3 ECG measurements at baseline should be used in determining eligibility.

20. Vital signs (supine) outside the following ranges (measured after 5 minutes supine):
    a. Systolic blood pressure below 100 or above 150 mmHg;
    b. Diastolic blood pressure below 50 or above 95 mmHg;
    c. Radial pulse (from vital signs) below 50 or above 100 bpm;
    d. Orthostatic hypotension (decrease in SBP/DBP from supine to standing position exceeding 30 mmHg);
21. History of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

Laboratory abnormalities

22. Clinically significant abnormalities in routine laboratory examinations (hematology; blood chemistry, including electrolytes and liver and kidney function tests; urinalysis), as determined by the Principal Investigator in consultation with the Medical Monitor, at the screening evaluation. *Tables of clinically notable values for laboratory parameters in Appendix 2 should be used as a guide in making this determination*;
23. History of hepatitis B and/or C, and/or positive serology results, which indicate the presence of hepatitis B and/or C (Hepatitis B surface antigen and/or antibody to Hepatitis C); as identified by any of the following:
    a. Hepatitis B: hepatitis B surface antigen (HBsAg) or with isolated anti-HBc (HBsAg negative, anti-HBc positive, and anti-HBs negative);
    b. Hepatitis C: antibody to hepatitis C positive and HCV RNA positive.
    Patients with positive hepatitis B surface antibody (anti-HBs), but with negative HBsAg and negative hepatitis B core antibody (anti-HBc), who have documented evidence of hepatitis B vaccination, will be eligible for this study. If a documented record of vaccination cannot be obtained, the Investigator will discuss the case with the Medical Monitor and will provide information of the patient's hepatic function tests (including bilirubin, reports of jaundice, etc.). In the absence of abnormal findings, the patient may be considered eligible.
    Patients with a history of documented successful treatment for Hepatitis C, i.e. HCV antibody positive, and HCV RNA negative patients showing this sustained viral response (SVR) for at least 24 weeks after the end of treatment, will be considered eligible for inclusion.
24. Positive results from the HIV serology.
25. Positive results of the drug and alcohol tests at screening and/or baseline. Patients who test positive for drugs of abuse at screening, but have negative test results at baseline, may be eligible, depending on the type of drug and the likelihood of continued abuse during the study.
    Possible inclusion of these patients in the study should be discussed with the Medical Monitor.
26. Clinically significant hypothyroidism or hyperthyroidism, unless stabilized by medication for at least 3 months before screening.

Concomitant therapy

27. Patients treated with anticholinergic drugs whose dose is not stable at baseline.
28. If receiving benzodiazepine therapy, this treatment has not been stabilized for at least 2 months. *The lowest dose possible should be used. Occasional prn use is permitted.*
29. Treatment with tri- and tetra-cyclic antidepressants, MAO inhibitors, and metoclopramide.
30. Treatment with SSRIs that are moderate/potent inhibitors of CYP2D6 (e.g. fluoxetine). *Patients on a stable dose of an SSRI that is a weak inhibitor of CYP2D6 (e.g. escitalopram), for at least 4 weeks before screening, will be eligible.*
31. Treatment with drugs capable of inducing/inhibiting hepatic enzyme metabolism (e.g. barbiturates, carbamazepine, phenylbutazone, phenytoin, primidone, rifampicin) four weeks prior to baseline or during the study.
32. Current treatment with sodium channel blockers (e.g. Class I antiarrhythmic agents, anticonvulsants, local anesthetics) or mood stabilizers (e.g. lithium, carbamazepine, oxcarbazepine, lamotrigine). *Valproic acid will be permitted, if used as maintenance treatment*.
33. Exposure to any investigational drug within 5 weeks or 5 half-lives (whichever is longer) prior to screening.

34. A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to evenamide (e.g. lamotrigine, carbamazepine, oxcarbazepine, topiramate, etc.), or any components of the evenamide or matching placebo capsules.
35. Treatment with a drug or treatment known to cause major organ system toxicity, e.g. tamoxifen, within 4 weeks, or received radiation therapy or a drug with cytotoxic potential, e.g. chemotherapy, during the past year.
36. Electroconvulsive therapy (ECT) or treatment with a transcranial magnetic stimulation (TMS) device within 6 months prior to screening.

General

37. If female, patient is of childbearing potential, pregnant or breastfeeding. *For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with a barrier method and hormonal contraceptive*
38. Patients with a reasonable likelihood of non-compliance with the protocol, or any other reason that, in the Investigator's opinion, would prohibit the inclusion of the patient in the study.

Study Medication Description:
Evenamide is formulated as hard gelatin capsules of 7.5- and 15-mg dosage strengths.

Study Medication – Dose and Mode of Administration:
The study medication will be administered as capsules of 7.5 and15 mg dosage strength of evenamide or an equal number of matching placebo capsules. Study medication with each different dosage (7.5 and 15 mg evenamide or placebo) will be provided in blinded 30 ml HDPE bottles. The study medication (evenamide or placebo) for each patient will be allocated using an Interactive Web Response System (IWRS). Treatment assignments will be determined according to a computer-generated randomization scheme. The Sponsor, the patient/caregiver, the Investigator and all other site personnel will remain blinded. A 1-week supply of study medication will be dispensed at the appropriate dose level for the patient at each scheduled visit.

Comparator – Dose and Mode of Administration:
Patients randomized to the placebo group will be administered an equal number of matching placebo capsules (1 capsule *bid*).

Methodology:

Safety Evaluations – Primary Objective
Safety will be assessed by the following:

- Adverse events (AEs)
- Seizure Checklist (see Appendix 4)
- 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).

Efficacy Evaluations – Secondary Objective
Efficacy will be assessed by the following measures:

- PANSS total score – mean change from baseline to endpoint
- CGI-S – mean change from baseline to endpoint
- CGI-C – proportion of patients with improvement from baseline to endpoint (score of 1, 2 or 3)
- LOF – mean change from baseline to endpoint
- MSQ – mean change from baseline to endpoint

Pharmacokinetics – Secondary Objective
In addition to the blood samples taken for laboratory tests, 5-ml blood samples will be collected in Li-heparinized test tubes for measurement of plasma concentrations of evenamide and its main human plasma metabolite (3-butoxy-phenyl) acetic acid. 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.

Appropriate pharmacokinetic parameters for each dose level of evenamide will be calculated using non-compartmental methods, e.g. $C_{max,}$ t_{max}, $t_{1/2}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The derived pharmacokinetic parameters will be listed and plotted by subject/analyte and summarized by treatment.

The concentration of evenamide and (3-butoxy-phenyl)-acetic acid in plasma samples will be determined using a validated LC-MS/MS method.

CYP2D6 Polymorphism
The potential effects of polymorphisms in CYP2D6 on metabolism of evenamide will also be investigated. At baseline (Day 0), a blood sample will be collected for performance of CYP2D6 genotyping. Each patient's phenotype for CYP2D6 metabolism will be identified as "ultra-rapid metabolizer", "extensive metabolizer", "intermediate metabolizer" or "poor metabolizer," based on their genotype as determined from the specific alleles they are carrying.

Safety Monitoring Board
Safety data from all patients will be examined periodically by an Independent Safety Monitoring Board (ISMB). The ISMB may request modifications to the study design or request that the study be terminated, should any significant safety concerns become evident.

Statistical Methods:
Sample Size:
Approximately 120 patients with schizophrenia will be included in this study, with approximately 40 patients randomly assigned (1:1:1) to receive evenamide doses of 7.5 or 15 mg *bid,* or matching placebo *bid*. 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.

Patient Characteristics:
The background and demographic characteristics (age, race, ethnicity, weight, height, smoking history, education, marital status, employment, housing status, past and current medical conditions, etc.) and disease characteristics (severity of illness, duration of illness, concomitant psychotropic medication, etc.) of enrolled patients will be summarized by treatment group. Continuous variables will be summarized by minimum, maximum, mean, median, and standard deviation, and discrete variables will be summarized using frequencies and percentages.

Analysis Populations
The safety population will consist of all subjects who took at least one dose of study medication. The efficacy analyses will be performed on a modified Intent-to-Treat (mITT) population comprising all patients who have a baseline efficacy assessment, receive at least one dose of the study medication, and have at least one post-baseline efficacy assessment.

Safety Analysis:
All AEs will be summarized by body system and preferred term. The incidence (%) of SAEs, treatment-emergent AEs (TEAEs) that are newly occurring or worsened after administration of study medication, and AEs leading to discontinuation (ADOs) will also be summarized; severity of each AE and relatedness to study medication will be assessed and presented. Changes from baseline in 3 per second EEG spike and slow wave activity (as provided by a trained clinician reviewer), vital signs, ECG and laboratory values, and physical/neurological examination and eye examination findings will be summarized, with abnormal and clinically notable values/findings being identified. A comparison will be made between the evenamide and placebo groups in the proportion of patients experiencing SAEs, ADOs, TEAEs and any clinically significant abnormalities in other safety parameters. Mean changes from baseline in the total score and sub-scale scores on the ESRS-A, and total score on the CDSS will be presented.

Efficacy Analysis:
Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be provided for the PANSS, CGI-C, CGI-S, MSQ and LOF for actual values and changes from baseline at each time-point.

The primary efficacy endpoint and key secondary efficacy endpoint are the mean changes from baseline to endpoint on the PANSS and CGI-S, respectively. These endpoints will be compared between treatment groups (placebo vs all doses of evenamide) using a Mixed Model Repeated Measures (MMRM) analysis, with treatment, visit and treatment-by-visit interaction as fixed effects, and baseline value as covariate.

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 15-mg *bid* dose group versus placebo will be analyzed first for the primary and key secondary efficacy endpoints, followed by the comparison of the 7.5-mg *bid* dose group versus placebo, in a pre-specified order.

All other efficacy endpoints will be exploratory. The proportion of patients rated improved on the CGI-C at endpoint will be compared between groups using a logistic regression model (chi-square test). Mean changes from baseline to endpoint on the PANSS – Positive Symptoms sub-scale, PANSS – General Psychopathology sub-scale, PANSS – Negative Symptoms sub-scale, MSQ and LOF will be compared between the evenamide and placebo groups using ANCOVA.

2 SIGNATURE PAGE

Study 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.

Study Code:
NW-3509/008/II/2019

Center No. _____

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The Sponsor has transferred all responsibilities for the conduct of the trial to the CRO.

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4 ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	=	Absorption, distribution, metabolism and excretion
ADO	=	Adverse dropout (discontinuation due to adverse event)
ADR	=	adverse drug reaction
AE	=	adverse event
ALT	=	alanine-aminotransferase
ANC	=	absolute neutrophil count
ANCOVA	=	analysis of covariance
ANOVA	=	analysis of variance
AP	=	action potential
AST	=	aspartate-aminotransferase
AUC	=	area under the plasma drug concentration vs. time curve
bid	=	twice daily
BMI	=	body mass index
BUN	=	blood urea nitrogen
CDSS	=	Calgary Depression Scale for Schizophrenia
CGI-C	=	Clinical Global Impression – Change from baseline
CGI-S	=	Clinical Global Impression – Severity of illness
CI	=	confidence intervals
C_{max}	=	maximum post-dose plasma drug concentration
CNS	=	Central Nervous System
C-SSRS	=	Columbia Suicide Severity Rating Scale
CRF	=	Case Report Form
CYP2D6	=	Cytochrome P450 2D6
CPK	=	Creatine phosphokinase
DBP	=	diastolic blood pressure
DSM-5	=	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
ECG	=	Electrocardiogram
ECT	=	Electroconvulsive therapy
EEG	=	Electroencephalogram
EPS	=	Extrapyramidal symptoms
ESR	=	Erythrocyte sedimentation rate
ESRS-A	=	Extrapyramidal Symptom Rating Scale – Abbreviated version
GCP	=	Good Clinical Practice
GGT	=	gamma-glutamyl transpeptidase
HbA1c	=	blood glycosylated hemoglobin
HCV	=	Hepatitis-C Virus
HDL	=	high density lipoprotein
hERG	=	human *Ether-a-go-go* Related Gene
HIV	=	human immunodeficiency virus
hr	=	hour(s)
hs	=	*hora somni* (at bedtime)
ICH	=	International Council for Harmonisation

IEC	=	Independent Ethics Committee
i.p.	=	Intraperitoneal
IRB	=	Institutional Review Board
ISMB	=	Independent Safety Monitoring Board
IWRS	=	Interactive Web Response System
LDH	=	lactate dehydrogenase
LC-MS/MS	=	Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
LDL	=	low density lipoprotein
LOCF	=	Last Observation Carried Forward
LOF	=	Strauss-Carpenter Level of Functioning scale
LS	=	least square
MAO	=	monoamine oxidase
MBq	=	Megabecquerel (1 MBq = 27 microcuries)
MI	=	Multiple Imputation method
MED	=	minimal effective dose
min	=	minute(s)
mITT	=	modified Intent to Treat
MNAR	=	Missing not at random
MMRM	=	Mixed Model Repeated Measures analysis
MSQ	=	Medication Satisfaction Questionnaire
NMDA	=	N-methyl-D-aspartate
NOAEL	=	No observed adverse effect level
NOEL	=	No observable effect level
OC	=	Observed Cases
od	=	once daily
OTC	=	Over-The-Counter
PANSS	=	Positive and Negative Syndrome Scale
PK	=	Pharmacokinetics
PMM	=	Pattern-mixture model
PNS	=	peripheral nervous system
PPI	=	Pre-pulse inhibition
prn	=	as needed
q.s.	=	*quantum satis* (amount that is sufficient)
RBC	=	red blood cells
SAE	=	Serious Adverse Event
SBP	=	systolic blood pressure
SD	=	standard deviation
SE	=	standard error
SSRI	=	Selective serotonin reuptake inhibitor
$t_{1/2}$	=	half-life
T_3	=	triiodothyronine
T_4	=	thyroxine
TEAE	=	treatment-emergent adverse event
THC	=	tetrahydrocannabinol

t_{max}	=	time of maximum plasma concentration post-dose
TMS	=	Transcranial magnetic stimulation
TRS	=	treatment-resistant schizophrenia
TSH	=	Thyroid Stimulating Hormone
TST	=	Tail suspension test
VGSC	=	Voltage-gated sodium channels
VLDL	=	very low density lipoprotein
WBC	=	white blood cells

5 TITLE OF STUDY

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.

6 PROTOCOL NUMBER

This study is being conducted under protocol no.: NW-3509/008/II/2019.

7 INTRODUCTION

7.1 Background Information

Overview

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

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

Pharmacology

It is hypothesized that there is a dysfunction of the glutamatergic and dopaminergic systems in schizophrenia and bipolar disorders. Current antipsychotic drugs target the dysregulation of mesolimbic and mesocortical dopaminergic / serotoninergic systems. However, this approach to treating the symptoms of schizophrenia still appears to be inadequate, with a very high proportion (74%) of patients discontinuing their antipsychotic (first or second generation) due to intolerance, inadequate benefit or both within 18 months of starting treatment (Lieberman et al, 2005). This suggests a failure to modulate other important mechanisms that are critical for anti-psychotic benefit. Aberrant electrical connectivity in schizophrenia that leads to abnormal cortical activity and glutamate transmission largely contributes to the pathophysiology of this psychiatric disorder; however, it is not targeted by existing therapies.

Evenamide (NW-3509) is an orally available new chemical entity that specifically targets voltage-gated sodium channels (VGSCs) in a state-dependent manner, with a higher affinity for the inactivated state of the channel, and modulates sustained repetitive firing, without inducing impairment of the normal

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

NW-3509 appears to be highly selective in its effects on VGSCs. Radio-ligand binding assays demonstrated that NW-3509 showed less than 20% inhibition against a panel of > 130 receptors, ion channels, transporters and kinases when tested at 10 μM, i.e. at concentrations many fold higher than likely to be achieved in humans. Acute treatment with doses of NW-3509 (2.5 mg/kg po) active in preclinical models, did not alter monoamines (dopamine, serotonin, norepinephrine) or their metabolite levels in the brain, while functional electrophysiology studies did not detect any significant activity of NW-3509 on other ion channels, such as voltage-gated Ca^{2+} channels and NMDA receptor channels, up to extremely high concentrations (IC_{50} >>100μM). Evenamide showed an affinity for the human sigma-1 receptor (Sig-1R) in a radioligand binding assay in the range of 0.49-1.11 μM. However, evenamide showed antagonist activity at the Sig-1R only at concentrations 140 times the anticipated maximum therapeutic exposure of 0.02 μM.

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

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

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

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

In the rat model of PPI deficit induced by amphetamine (2.5 mg/kg, s.c.), ineffective doses of NW-3509 (0.625 mg/kg and 1.25 mg/kg p.o.) in combination with sub-threshold doses of haloperidol (0.05 mg/kg i.p.) or risperidone (0.05 mg/kg i.p.) produced a reversal of the PPI deficit. The combination of haloperidol (0.3 mg/kg i.p.) and inactive doses of NW-3509 (10 and 20 mg/kg p.o.) also significantly increased PPI compared to haloperidol alone in a model of spontaneous PPI deficit in C57BL/6J mice.

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

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

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

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

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

Safety pharmacology

Evenamide (NW-3509) was evaluated for its potential to induce exaggerated pharmacology, i.e. CNS side effects in a range of *in vitro* and *in vivo* safety pharmacology and respiratory studies [modified Irwin study in rats, rotarod test, spontaneous locomotor activity, rat whole body plethysmography]; effects on the cardiovascular system [cardiac channels Na^+ 1.5, Ca^{2+} 1.2 and hERG, canine purkinje fibers and telemetry in the conscious dog], as well its potential to induce phospholipidosis *in vitro*. The safety pharmacology studies did not reveal any findings that pose a risk for humans; the most conservative safety margin is greater than x20; this is based on the lowest efficacious concentration in any of the add-on experimental paradigms (i.e. 20 ng*h/ml in the rat and risperidone PPI model), and the most conservative NOAEL dose in any of the species tested (i.e. 5.0 mg/kg/bid in the 4 week dog study C_{max} = 414 ng/ml). A single-dose study in healthy male volunteers did not detect any pattern of treatment–related adverse changes at doses up to and including 30 mg (mean C_{max} = 93 ng/mL; range 65.3-113 ng/mL). Similarly, multiple doses of 15, 20 and 25 mg *bid* were well tolerated in patients with schizophrenia (Study 002 – see details below under Clinical Studies).

Pharmacokinetics and metabolism

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

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

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

In the first Phase I study, single oral doses of 1, 2, 5, 10, 20 and 30 mg of NW-3509 were administered to 6 healthy subjects per dose level. Absorption was rapid, and t_{max} was reached between 0.75 and 2.0 hours.

C_{max}- and AUC-values increased with increasing doses. The mean terminal elimination half-life observed in the six cohorts ranged between 1.6 and 4.0 hours.

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

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

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

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

Clinical Pharmacology Study NW3509-007

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

An average of 113% of the radioactivity administered was recovered in excreta over a 144-hour sampling period, with the majority of radioactivity (approximately 111% of the dose) recovered in the urine. Exposure to NW-3509 accounted for approximately 5% of circulating plasma total radioactivity based on AUC(0-inf), indicating extensive biotransformation of NW-3509 following oral administration; this proportion was not notably different in the two CYP2D6 poor metabolizers. There was limited distribution of radioactivity into blood cells.

This study detected a major metabolite of NW-3509, (3-butoxy-phenyl)-acetic acid, representing approximately 68% of circulating radioactive material, and a glucuronide of hydroxyl NW-3509, representing 10% of circulating drug-related material. The (3-butoxy-phenyl)-acetic acid was not a major urinary metabolite, has been detected in both rat and dog chronic studies, and has been shown to be devoid

of any activity at 89 CNS targets in in-vivo studies. Individual subject pools of urine and plasma have been generated, and metabolite profiling by radio-HPLC, and structural characterization are in progress.

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

Toxicology studies

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

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

The doses in the 26-week toxicity study (CG15GG) were the same as those in the 13-week study. There were 13 decedent animals, most of which were attributable to gavage errors. However, there were unexplained deaths in the low-dose (one) and high-dose (four) male groups. In females, there was one unexplained death at the low dose. In the absence of unexplained deaths in the mid- and high-dose groups of females, this single death was regarded as a chance event. In males, the lack of a mid-dose unexplained death suggests that the low-dose unexplained death may also be a chance event. A few animals sporadically exhibited CNS clinical signs. There was no effect of treatment on body weight gain, food consumption or in the ophthalmic examinations. There were minor changes in various hematology and clinical pathology parameters, but in the absence of corroborative pathology; and as there was evidence of recovery following 4 weeks off-dose, these alterations were considered not to be adverse. The pathology examinations revealed no test item-related lesions (main study and recovery period). In view of the unexplained deaths, a NOEL for rat deaths could not be established.

In **dog toxicity studies**, CNS symptoms again predominated (underactivity, uncoordinated movement and unsteadiness). Dogs were treated twice daily 8 hours apart. In the 4-week toxicity study (ONP0081), one female at 10 mg/kg/bid was sacrificed moribund on Day 18 due to severe CNS signs. There were no treatment-related histopathological changes. In the 13-week toxicity study (ONP0104), the doses were: 0, 2.5, 5, 7.5, mg/kg/bid. There were no deaths and no treatment-related histopathological findings. Clinical signs (tremor, activity) were recorded at ≥2.5 mg/kg/bid. The 39-week toxicity study (1017-5022) was performed with the same doses as in the 13-week study. The analysis of this study indicates that 7.5 mg/kg *bid* was associated with adverse CNS effects including convulsions in three females. CNS signs and gastro-intestinal toxicity declined in frequency and severity after the first three weeks of dosing. At 2.5 and 5 mg/kg *bid*, evenamide was well tolerated although there were minor clinical signs. There were no effects on body weights, body weight gains, food consumption, clinical pathology parameters, ophthalmology, electrocardiography, organ weights, macroscopic or microscopic evaluations at any dose level. Based upon the relatively low incidence and minimal to mild severity of CNS clinical findings at 5 mg/kg *bid*, the NOAEL is considered to be 2.5 mg/kg *bid*.

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

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

Clinical studies

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

Study 001 was a single dose, randomized, placebo-controlled, independent, sequential cohort (9 subjects in each cohort) study performed to determine the safety, tolerability and the maximum tolerated dose (MTD) of escalating single oral doses of evenamide (1, 2, 5, 10, 20 and 30 mg; n=6 at each dose) or placebo (n=3 in each cohort) in healthy male volunteers. The safety, tolerability and plasma level data at each dose were evaluated by a Safety Monitoring Board before proceeding to the next higher dose.

Results of standard safety assessments did not indicate any adverse effects of evenamide at any dose on laboratory tests, vital signs, ECG parameters or physical and neurological examinations. No SAEs were reported. A total of 33 non-serious AEs were reported in 21 subjects; however, most were of mild intensity, except for two rated moderate (headache and somnolence at 30 mg evenamide; both resolved). Mild postural orthostatic tachycardia was reported in two subjects at 30 mg, one of which had a C_{max} of 113 ng/mL. A second subject had a C_{max} of 110 ng/mL; however, this subject did not experience any AEs. Holter recordings in healthy subjects did not detect any adverse effects of evenamide on the morphology of the ECGs or QTc measurements at doses of 1-30 mg. No effect of evenamide was detected on PR or QTc interval or QRS duration. Analyses of the correlation between log plasma concentrations of NW-3509 and placebo-subtracted changes from baseline in values for QTcF and QRS did not detect any relationship between plasma exposure and change from baseline. Mean heart rate was decreased slightly at all doses, but did not show a relationship with plasma concentrations.

A decision was made to terminate dose escalation at 30 mg, based on limitations of the available dosage strengths (1, 2.5 and 5-mg capsules). The plasma levels (C_{max}) in healthy volunteers at the 20 and 30 mg doses exceeded levels that were efficacious (i.e., 20-40 ng/mL) in preclinical pharmacology experiments.

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

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

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

Patient Population. Patients included in the study were primarily male (86%) and 19 to 60 years of age. The study enrolled 61 patients in the US and 28 in India. This study was designed primarily to evaluate safety and tolerability; therefore, it was essential to limit enrollment to patients who would be capable of providing accurate feedback on any adverse experience in the trial. For the overall patient population, the mean (SD) duration of schizophrenia was 217.6 (131.3) months. The mean duration of schizophrenia was much shorter in India (127.1 months) compared to the US (259.1 months). The mean (SD) number of prior hospitalizations for schizophrenia was 2.9 (5.48) with a range of 0 to 30. The number of prior hospitalizations was greater in the US compared to India [4.2 (6.24) vs. 0.3 (0.59)]. The severity of illness of the populations was similar in the US and India, based on mean (SD) baseline scores on the PANSS [61.4 (7.03) vs. 66.1 (7.30)] and CGI-S [3.3 (0.47) vs. 3.7 (0.48)].

Disposition. Overall, 9 of 89 subjects (10.1%) discontinued prematurely: 8 subjects (16.0%) in the evenamide treatment group and 1 subject (2.6%) in the placebo treatment group. The most common reason for premature discontinuation was withdrawal by subject (5 subjects; 5.6%). Only 2 (2.2%) subjects, both in the evenamide group, discontinued due to adverse events.

Pharmacokinetics. Pharmacokinetic profiles were defined in each patient on Day 1 (15 mg) up to 12 hours post-dose and on Day 8 (20 mg *bid*) and Day 15 (25 mg *bid*) up to 8 hours post-dose. The systemic exposure of evenamide increased with increasing dose over the dose range 15 to 25 mg *bid*. Comparing C_{max} values at the different dose levels between subjects who were CYP2D6 extensive metabolizers (EM) and those who were intermediate or poor metabolizers (IM/PM) indicated that there was no clear impact of CYP2D6 genotype. Less than 1% of the dose was recovered as evenamide in urine.

Safety Results. Evenamide in the range of 15-25 mg *bid* (30-50 mg/day) was well tolerated. The most frequent treatment-emergent adverse events (TEAEs) (evenamide vs. placebo) were somnolence [8 (16.0%) vs. 5 (12.8%)], insomnia [5 (10.0% vs. 1 (2.6%)], overdose [3 (6.0%) vs. 1 (2.6%)], dry mouth [3 (6.0%) vs. 2 (5.1%)], headache [3 (6.0%) vs 0], and cold sweat/hyperhidrosis [2 (4.0%) vs. 0]. Most TEAEs were of mild severity [evenamide, 58 of 69 (84%); placebo, 30 of 34 (88%)]; 9 of 69 (13%) AEs for evenamide and 4 of 34 (12%) for placebo were assessed as moderate.

Two patients in the evenamide group discontinued treatment due to AEs: seizure (n=1), which occurred at a dose of 20 mg *bid* on Day 14, and atrial fibrillation (n=1), which occurred at a dose of 25 mg *bid* on Day 23. Both of these events were reported as serious AEs. The highest plasma concentration of NW-3509 measured in the patient with atrial fibrillation (91.3 ng/mL) was ~11-18 fold less than the concentration producing cardiac effects in animals. The highest plasma concentration in the patient with the seizure (74.8 ng/mL) was ~16-40 fold less than that associated with seizures in animals.

The proportions of patients with clinically notable abnormalities in vital signs or laboratory values were very low and were similar in the evenamide and placebo groups. The proportion of patients with clinically significant ECG abnormalities was low and similar between groups, and there was no evidence of effects on QTc. Assessment of extrapyramidal symptoms (EPS) using the Extrapyramidal Symptoms Rating Scale did not reveal any treatment-emergent EPS with evenamide treatment.

Efficacy results. Patients had a mean baseline PANSS total score of 62.9 ± 7.4, and were experiencing break-through psychotic symptoms while on stable and adequate doses of risperidone (mean dose: 4.2 ± 2.0 mg/day; n=70) or aripiprazole (mean dose: 19.7 ± 7.0 mg/day; n=19), the atypical antipsychotics to which they had responded previously.

The results of the study indicate that patients treated with evenamide showed improvement on the symptoms of schizophrenia assessed by the Positive and Negative Syndrome Scale (PANSS). For the PANSS Positive Symptoms sub-scale, a statistically significant/near significant improvement from baseline (mean baseline score: 14.8 ± 2.8) to Day 28 for evenamide, compared to placebo [LS mean difference (SE)], was noted in the ANCOVA-LOCF [-1.28 (0.632), p=0.046)], ANCOVA-OC [-1.48 (0.641), p=0.024], and MMRM [-1.19 (0.643), p=0.068] analyses.

The mean (SD) change from baseline at Day 28 for the PANSS Total score was greater for evenamide [-5.1 (9.67)] than for placebo [-3.7 (9.65)]. Numerically greater improvement with evenamide vs. placebo was also observed for patients' functioning, assessed by the Strauss-Carpenter Level of Functioning (LOF) scale [0.72 (3.321) vs. 0.31 (3.130)], and CGI - Severity of illness (CGI-S) [-0.3 (0.60) vs. -0.2 (0.74)], compared to their standard antipsychotic alone.

An analysis of the data by country showed a greater benefit for patients in India, compared to the US, for PANSS total score. A post-hoc analysis revealed that 3 patients (2 in the placebo group; 1 in the evenamide group) in 1 center in the US were extreme outliers, i.e. they had an improvement in PANSS total score of >27 points (more than 3 SD above the mean change). An exploratory analysis performed for the PANSS total score excluding data from these 3 patients showed a mean (SD) improvement in the PANSS Total score at Day 28 in the evenamide group [-4.5 (9.0)] that was more than 2 points greater than in the placebo group [-2.3 (7.4)]. In a similar analysis conducted for the patients from US centers, a level of benefit paralleling that seen in non-US centers was noted.

A global assessment of change from baseline in the patient's overall condition (CGI-C), performed by a clinician, showed a greater proportion (p=0.0855; Fisher's exact chi-square test) of evenamide-treated patients rated as improved (55.3%), compared to placebo (35.9%) at Day 28/endpoint. An additional 'responder' analysis demonstrated that the proportion of patients who showed improvement on the PANSS Positive sub-scale at Day 28/endpoint was significantly greater (p=0.0043; Fisher's exact chi-square test) for the evenamide group (74.5%) compared to the placebo group (43.6%).

Conclusions. Evenamide was generally safe and well tolerated in Study 002 at doses of 15, 20 and 25 mg *bid*. Despite the limitations of the study design (i.e., small sample size, unequal randomization, short duration [4 weeks], limited to milder patients to enable them to provide meaningful feedback on side-effects, outpatient treatment), there was a strong signal for efficacy for evenamide, based on results for the PANSS Total and Positive Symptoms sub-scale, as well as global assessments of disease severity and change from baseline (CGI-S and CGI-C), and an assessment of daily function (LOF).

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

7.2 Chemistry and Pharmacy of NW-3509

The structure and chemical properties of NW-3509 and the composition of the available dosage forms (7.5 and 15.0-mg capsules) are provided in Table 1 and Table 2 below.

Table 1. Description of NW-3509

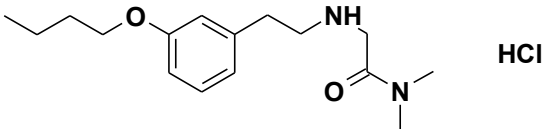
Structure	
Chemical Name	2-[2-(3-Butoxy-phenyl)-ethylamino]-N,N-dimethyl-acetamide hydrochloride
Molecular Formula	$C_{16}H_{26}N_2O_2$.HCl
Molecular Weight	Free base: 278.40 g/mol Hydrochloride salt: 314.85 g/mol
Physical Form	White to off white powder
Polymorphism	Preliminary screening finished. Most stable polymorphic form identified

Table 2. Proposed Composition of Dosage Forms for NW-3509		
	Theoretical Quantity	
Dose	**7.5 mg**	**15 mg**
Material	**[mg/capsule]**	**[mg/capsule]**
Intra-granular		
NW-3509	8.54*	17.09*
Microcrystalline Cellulose	91.46	82.91
Granulation Fluid		
Purified Water	q.s.	q.s.
Total	100	100

*equivalent to 7.5 mg and 15 mg free base; values adjusted for the fact that the API assay (anhydrous) is 99.5%, and it contains 0.1% residual water and 0.1% residual solvent

7.3 Study Rationale

Rationale for design

The primary objectives of this study are to evaluate the safety, tolerability and EEG effects of two fixed doses of evenamide (7.5 and 15 mg, *bid*), compared to placebo, in patients with schizophrenia who are being treated with stable doses of one of the following antipsychotic medication: aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone. Administration of evenamide has shown efficacy in animal models predictive of antipsychotic activity. In addition, preliminary evidence of efficacy in treating the symptoms of schizophrenia was obtained in Study 002, a 4-week, randomized, double-blind, placebo-controlled, multiple ascending dose study evaluating the safety, tolerability and preliminary efficacy of evenamide in patients with chronic schizophrenia not responding adequately to their current antipsychotic (risperidone or aripiprazole). In this study, doses of evenamide in the range of 15-25 mg *bid* (30-50 mg/day) were well tolerated. The results of Study 002 are described in detail in Section 7.1.

A double-blind, placebo-controlled study design is being used for the current study so that a background rate of spontaneous occurrence of adverse events, as well as changes in other safety parameters and efficacy measures, can be established in placebo-treated patients, against which the active treatment will be compared, without introducing a bias from knowledge of the treatment by the investigators. The treatment period of the study will be 4 weeks (28 days). The endpoint for assessment of efficacy will be at the final Day 29 or at early discontinuation) time-point.

The study incorporates a fixed dose design in which patients will receive target doses of 7.5 or 15 mg of evenamide, or placebo, twice daily. Patients assigned to the evenamide low dose and higher dose groups will start on their target dose (7.5 or 15 mg, respectively, *bid*). The dose may be reduced to once daily dosing (Drop-back Dose) if intolerance develops. If the reduced dose is well tolerated, investigators will be encouraged to reattempt *bid* dosing (target dose) at the next scheduled visit so that as many patients as possible receive the target dose in each group. Restarting *bid* dosing will only be allowed on a clinic visit day. If intolerance again develops, the patient may continue on once daily dosing for the remainder of the study. The first dose (Starting/Target Dose) will be administered in a hospital setting, and patients will be closely monitored for at least 4 hours after their initial dose. If there are no safety issues, patients will be discharged, and will be instructed not to take their evening dose on the first day at their residence at least 6 hours after the initial dose. Approximately 120 patients will be randomly assigned (1:1:1) to treatment with evenamide 7.5 or 15 mg, or placebo, given twice daily. The number of patients to be included was not based on statistical power considerations.

Patients will receive their first dose of study medication on Day 1 and will return for scheduled visits on Days 8, 15 and 22 for safety and efficacy assessments, blood sampling for measuring plasma evenamide levels, and dispensing of medication for the next dosing period. Final evaluations for the 4-week double-blind treatment period will be performed on Day 29 (or at early discontinuation). EEG evaluations will be performed in the clinic at Screening, 1-3 hr post-dose on Day 1, pre and post-dose on Day 8, and at the final visit. All patients who complete 4 weeks of treatment, as well as those who discontinue prematurely, will be required to return for a safety follow-up visit 7 days after the last dose of study medication to assess vital signs and any adverse events occurring following treatment discontinuation. If the patient does not attend his/her follow-up visit after 7 days, attempts will be made to contact the patient to assess his/her condition. If the patient cannot be reached, the caregiver will be contacted. In addition, the patient will be contacted 30 days after the last dose of study medication to determine if any Serious Adverse Events (SAEs) have occurred within 30 days after the final dose.

Safety data from all patients will be evaluated periodically by an Independent Safety Monitoring Board (ISMB) throughout the study, to help ensure patient safety. The ISMB will have the power to request modification of the study protocol or termination of the study if significant safety issues are observed.

Rationale for pharmacokinetic (PK) sampling times

Additional information on the pharmacokinetic profile of evenamide and its main human plasma metabolite, (3-butoxy-phenyl)-acetic acid, in patients with schizophrenia will be obtained in the current study. Based on the results from Studies 001 and 002, as well as the need to minimize the amount of time patients spend in the clinic during scheduled visits, limited PK sampling will be performed in Study 0008. Blood samples will be collected for measurement of plasma concentrations of NW-3509 at its metabolite at 30, 60, 120 and 240 min after the first dose of study drug on Day 1 (starting/target dose). A blood sample for PK analysis will also be collected just prior to dosing (steady state trough plasma level of previous dose) on Day 8 and additional samples will be taken at 30, 60, 120 and 240 min after dosing, as on Day 1. A trough level sample will be collected in the morning on Day 29, following administration of the final dose of study medication in the evening on Day 28. The concentrations measured in these samples will be used for determining PK parameters for individual patients, as well in Population PK analyses.

In addition to the PK sampling for evenamide, an additional sample will be collected at Baseline for measurement of plasma levels of the concomitant atypical antipsychotics. This will be done to assess whether patients were being compliant with dosing of their current antipsychotic medication prior to entering the double-blind treatment period.

Rationale for choice of patient population

The proposed indication for evenamide is add-on therapy in patients with schizophrenia not responding adequately to their current atypical antipsychotic. The rationale for using evenamide in this population, based on its pharmacology, is presented in Section 7.1. Both male and female (not of childbearing potential, unless using adequate contraception) patients, ages 18 years and older, with a DSM-5 diagnosis of schizophrenia, who are on a stable dose of an atypical antipsychotic (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone), are mildly to moderately severely ill (CGI-S of 3 to 5), have a PANSS total score <80, and do not have any significant medical conditions that would put them at risk, will be eligible.

This population has been chosen, as they are still symptomatic on their current antipsychotic or are experiencing return of their symptoms of psychosis, and therefore, may benefit from and adjunctive treatment that might improve efficacy. However, the population is not too severe such that they can provide feedback on potential side effects and be treated as outpatients, if appropriate.

The absence of significant or severe concomitant medical illnesses and limiting the use of concomitant medications will prevent bias in determining the tolerability and safety of evenamide. Female patients of childbearing potential, who are not using adequate contraception, will be excluded, as reproductive and

embryo-fetal toxicity studies have not yet been performed with evenamide. Results from the ongoing reproductive toxicology studies will be submitted to Regulatory Authorities once they are completed, and restrictions on enrollment of women of childbearing potential may be lifted/relaxed, based on these results. Other selection criteria are designed to maximize the safety of patients and to minimize current medical conditions or concomitant treatments that may confound the assessment of safety parameters or alter the pharmacokinetics of evenamide in this study.

Rationale for doses

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

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

The doses to be tested in the current study will be 7.5 mg and 15 mg *bid*. These doses are expected to be well tolerated and within the efficacious dose range, as single doses of 30 mg (Study 001), as well as multiple doses of 25 mg *bid* (Study 002), are well-tolerated. Having two parallel dose groups will allow assessment of dose dependency for efficacy and adverse effects.

Safety Ratios (SRs) using patient exposure data at 15 mg *bid* (C_{max} = 40.4 ng/mL, total AUC = 336 ng.h/mL, Study NW-3509A/002/II/2015) are presented below.

Dog

SR calculations based on C_{max} and AUC exposures at 39 weeks in the dog report (1017-5022), at the NOAEL for CNS-related clinical signs (2.5 mg/kg *bid*, mean both sexes):

SR (C_{max}) = 249 ng/mL (NOAEL)/40 ng/mL (mean subject) = x 6.2.

SR (AUC) = 1210 ng.hr/mL (NOAEL)/336 ng.hr/mL (mean subject) = x 3.6.

Rat

In view of the undetermined causes of the single deaths at the low dose of 10 mg/kg/*bid*, in males and females in the 26-week rat study (CG15GG), there is no NOEL for death, and therefore, no SR. The exposures at 10 mg/kg/*bid* in rats (mean both sexes) are compared below, to patient exposure at 15 mg *bid*.

The margin at 10 mg/kg/*bid* (C_{max}) = 352 ng/mL/40 ng/mL (mean subject) = x 8.8.

The margin at 10 mg/kg/bid (AUC) = 1325 ng.hr/mL /336 ng.hr/mL (mean subject) = x 3.9.

Rationale for selection of concomitant atypical antipsychotics

Aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, and risperidone will be the allowed concomitant antipsychotic medications to which evenamide will be added in the current study. All patients enrolled in the study will be required to be on a stable dose of one of these drugs, at a minimally effective or higher dose (e.g. equivalent to 2 mg/day risperidone, or maximum tolerated dose), according to local practice, for at least 4 weeks prior to screening. These 6 atypical (second generation) antipsychotics have been selected based on their use in treating patients with schizophrenia, and their improved tolerability or efficacy profile, compared to first generation antipsychotics, with regard to the development of EPS.

Evenamide is extensively metabolized, with demethylation and hydroxylation as the major metabolic routes *in vitro*. CYP450 2D6 was the main metabolizing enzyme *in vitro*, however a comparison of values in clinical study NW-3509A/002/II/2015 indicated no clinically important impact of CYP2D6 genotype on C_{max}. In this study, the mean (SD) C_{max} at doses of evenamide of 15, 20 and 25 mg *bid*, was somewhat higher in patients who were poor metabolizers [57.0 (18.6), 78.4 (23.4) and 121.0 (77.1), respectively] compared to patients categorized as extensive metabolizers [35.6 (20.8), 67.4 (31.2) and 89.0 (48.8), respectively]. However, the number of patients who were poor metabolizers was very small (n=3-4 per dose); therefore, no firm conclusions could be drawn from these data. Exposure to evenamide in the CYP2D6 poor metabolizer population was a maximum of 1.78-fold (Cmax) and 2.28-fold (AUC) higher when compared to the extensive metabolizer population. In summary, while CYP2D6 poor metabolizers appear to demonstrate a higher plasma exposure to evenamide and the metabolite 3-BPAA, the metabolic pathways are considered similar, and remain capable of removal of almost the entire dose of evenamide drug-related material into the urine for excretion in both populations.

Evenamide has low potential to inhibit the activity of CYP1A2, 2D6 and 3A4 (IC_{50} >100µM). Also, the induction potential for CYP1A2 and 3A4 is low (EC_{50} >50µM). As the C_{max} at doses investigated in Study 002, and planned for the current study, are substantially lower than the lowest IC_{50}, a drug interaction caused by enzyme induction or inhibition is unlikely. Given this, and the lack of evident impact of CYP2D6 genotype on evenamide C_{max}, a clinically relevant interaction of evenamide on the pharmacokinetics of the permitted concomitant atypical antipsychotics, i.e. risperidone and aripiprazole (both mainly metabolized by CYP2D6 and CYP3A4), clozapine (metabolized primarily by CYP1A2 and 3A4), olanzapine (mainly metabolized by CYP1A2 and CYP2D6), quetiapine (mainly metabolized by CYP3A4), and paliperidone (no single CYP450 isoform has significant role in its metabolism), or vice versa, is considered unlikely.

In summary, given the lack of *in vitro* inhibition/induction caused by evenamide, the assessment of low potential for interactions with drug transporters, the lack of clinically important impact of CYP2D6 genotype on evenamide C_{max}, and the drug interaction profiles of the permitted antipsychotic drugs (aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, and risperidone), it has been concluded that evenamide is unlikely to be associated with a drug interaction with any of these compounds. The role of CYP2D6 in the metabolism of evenamide will be investigated further by performing CYP2D6 genotyping on all patients enrolled in the study, and evaluating the impact on their PK profile.

Safety measures and safety follow-up period

Adverse events (AEs) will be assessed throughout the study and will include an assessment of CNS symptoms and signs, with a particular focus on identifying any seizure-like events (see Appendix 4). In addition, EEGs will be performed for at least 45 min, using 10-20 international EEG electrode application procedures, at Screening (performed two times with approximately one hour in between, if feasible for the patient), between 1 and 3 hr post-dose (corresponding to expected Tmax for evenamide) on Day 1, prior to dosing and 1-3 hr post-dose on Day 8, and at the final visit on Day 29. If there is evidence of seizure-like activity, e.g. spike and wave, the patient's study medication will be withheld, and appropriate follow-up assessments will be performed. Other standard safety assessments will be performed at baseline, following the first dose, and periodically throughout the study, including vital signs, laboratory tests (hematology, blood chemistry, urinalysis, serum prolactin, HbA1c), ECGs (12-lead standard), and physical and neurological examinations. In addition, the Extrapyramidal System Rating Scale - Abbreviated version (ESRS-A) will be used to evaluate potential treatment-related movement disorders. The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to assess suicidality throughout the trial, so that appropriate measures can be taken if a patient is exhibiting suicidal ideation or behavior. Depressive symptoms will be assessed using the Calgary Depression Scale for Schizophrenia (CDSS). A standard eye examination has been included to assess any potential ocular effects of evenamide.

Patients will be proactively contacted by telephone on Days 4, 11 and 18 to assess the tolerability of their dose of study medication, and to review the Seizure Checklist and AEs. If any tolerability issue does arise,

patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work-up.

A follow-up safety assessment (vital signs and AEs) will be performed 7 days after the last dose of study medication, to look for any delayed effects of withdrawing patients from evenamide treatment. In addition, the occurrence of any Serious AEs will be followed for 30 days after the final dose of study medication.

Treatment with clozapine has been associated with blood dyscrasias, e.g. neutropenia and agranulocytosis, which can be fatal; therefore, in the US, it is a requirement that patients taking clozapine have venous blood samples taken at regular intervals (weekly during the first 6 months of treatment, every 2 weeks from 6 to 12 months, and every 4 weeks after 12 months of treatment) for measuring absolute neutrophil count (ANC) [Clozaril® (clozapine) Prescribing Information (US)]. This procedure will be employed in the current study, and to be eligible, all patients who are currently being treated with clozapine must agree to have this routine blood monitoring performed throughout their participation in the trial. In addition, as a precaution, patients will be excluded if they have a WBC count of <3500 cells/µL and/or an ANC of <2000 cells/µL at screening. The guidelines for routine ANC monitoring during clozapine treatment, and additional measures to be undertaken if neutropenia is observed, are provided in Appendix 5.

Rationale for efficacy measures

Assessment of efficacy is a secondary objective of this study. The efficacy of evenamide in treating the symptoms of schizophrenia will be assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinician's Global Impression - Change from baseline (CGI-C) and Severity of illness (CGI-S). The PANSS is a standard scale for assessing the individual symptoms of schizophrenia, and has been widely used as the primary efficacy measure in many antipsychotic trials. Additionally, the PANSS Positive Symptoms sub-scale will be used as a secondary efficacy measure, as the effect of evenamide is expected to be primarily on the positive symptoms of schizophrenia, based on the findings in the previous study (Study 002). The Negative Symptoms and General Psychopathology sub-scales will also be analyzed separately as secondary measures. To ensure consistency in the ratings of the PANSS, CGI-C and CGI-S, all assessments will be done approximately 2 hours after the morning dose of study medication during the scheduled visits on Days 8, 15, 22 and 29.

The effect of evenamide on patients' daily functioning will be evaluated using the LOF. The MSQ will be completed by the patient and used to evaluate the patients' satisfaction with the study medication, compared to their previous treatment.

8 STUDY OBJECTIVES

The objectives of the study are as follows:

Primary:

- ***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 their current 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.

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 and 15 mg *bid*, compared to placebo, based on improvements in symptoms of schizophrenia, as assessed by the rating at endpoint on the CGI - 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 to 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 the study medication, compared to their previous treatment, based on improvements on the Medication Satisfaction Questionnaire (MSQ).

Tertiary:

- 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.

9 INVESTIGATIONAL PLAN

9.1 Study 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.

An overview of the study design is provided in Table 3.

Table 3. 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.

9.2 Study Population

9.2.1 Inclusion Criteria

The patient must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Demographics

1. Age - 18 years, or older.
2. Sex - male, or female. *For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with adequate contraception (barrier method and/or hormonal contraceptive).*
3. Body mass index (BMI) of at least 17.5 and less than 35. *Patients with a BMI of 35 or higher may be considered for enrollment on a case-by-case basis if, in the Investigator's opinion, this does not put the patient at any additional risk for participating in the trial. These cases should be discussed with the Medical Monitor and documented in the source records.*

Psychiatric

4. Has a current diagnosis of schizophrenia in accordance with DSM-5. *Other Axis-I disorders may be present only as lifetime diagnoses if they are not relevant to the current episode of schizophrenia. [see Exclusion criteria below]*
5. Has been treated with antipsychotics for at least 2 years.
6. Has a total score on the PANSS < 80.
7. Has a Clinical Global Impression – Severity of disease (CGI-S) rating of mildly, moderately or moderately severely ill (score of 3, 4 or 5).
8. Needs antipsychotic treatment and is currently receiving a stable dose (minimally for 4 weeks prior to screening) of aripiprazole, clozapine, quetiapine, olanzapine, paliperidone, or risperidone (at least 2 mg risperidone dose-equivalent).
9. Current symptoms have been stably present for at least one month.

Procedural

10. Patient has provided written informed consent prior to participating in the study.
11. Patient is able to take oral medication and is willing to complete all protocol-defined aspects of the study.
12. Patient resides at home or in a residential care facility with a caregiver who is available to ensure compliance with dosing and scheduled office visits. *For US only: "Caregiver" is defined as someone who has at least 5 contacts with the patient each week, of which at least 2 are face-to-face.*
13. Patient agrees to be hospitalized overnight if required for trial purposes or if the investigator deems it necessary to ensure the safety of the patient.
14. If taking clozapine, patient agrees to blood monitoring (venipuncture for measuring ANC) weekly during their first 6 months of clozapine treatment, every 2 weeks from 6 to 12 months, and every 4 weeks after 12 months of treatment.

9.2.2 Exclusion Criteria

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

Psychiatric

1. DSM-5 diagnosis of schizophreniform disorder (295.40), schizoaffective disorder (295.70), or other primary psychiatric diagnosis, such as bipolar disorder or major depressive disorder. (Comorbid depression will be assessed at screening and baseline using the Calgary Depression Scale for Schizophrenia [CDSS]. A score of 7 or higher will be exclusionary.)
2. History (within three months of study entry) or current diagnosis of Substance Use Disorder as defined by the DSM-5 criteria, with a severity of 'moderate' or 'severe', or patient is currently abusing drugs or alcohol or has done so in the past year. *A history of nicotine or caffeine dependence is acceptable*
3. Severity of current episode of psychosis requires that the patient be hospitalized. *Patients who are chronically hospitalized or in psychiatric day-care, whose hospitalization is for logistic reasons and not due to the severity of their illness, will be eligible for the study*.
4. Severity of psychosis is rated severe or higher (CGI-S of 6 or greater).
5. History or current diagnosis of other psychiatric (Axis I diagnosis) or behavioral disorders that may interfere with the conduct or interpretation of the study.
6. Known suicidal risk. *A "yes" response on the C-SSRS Suicidal Ideation Item 4 or Item 5,* ***or*** *a "yes" response on any of the five C-SSRS Suicidal Behavior items, at screening,* ***or*** *a suicide attempt within the past 6 months, excludes the patient from the study.*
7. "Treatment resistant" defined significant persistent symptoms of schizophrenia after adequate doses of two standard antipsychotic medications (from two different chemical classes, including at least one atypical antipsychotic) following 6 weeks of treatment with each at adequate doses. Treatment resistant patients on clozapine for at least 6 months will be permitted if they have shown minimal improvement in the Investigator's judgement.
8. History of neuroleptic malignant syndrome, priapism.
9. History of severe tardive dyskinesia; or current moderate or severe tardive dyskinesia.

Medical Status

10. Abnormal epileptiform phenomena (3 per second spike and slow wave discharges) observed on screening EEG.
11. An advanced, severe, or unstable disease of any type that may interfere with any of the study evaluations, including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical or mental status of the patient to a significant degree or put the patient at special risk (e.g., respiratory, liver or kidney disease; malignancy);
12. A disability that may prevent the subject from completing all study requirements (e.g., blindness, deafness, severe language difficulty);
13. Insulin-dependent diabetes mellitus. Patients with non-insulin-dependent diabetes will be eligible if the following criteria are satisfied:
    a. HbA1c < 7.0% at screening,
    b. Diabetes is considered well controlled, with no changes in treatment regimen for at least 4 weeks prior to screening,

c. Diabetes is not newly diagnosed at screening;

14. History or current diagnosis of any neurodegenerative illness, dementia or significant concomitant neurological disease; organic cerebral disease, cerebrovascular disease, focal neurological lesions or history of any trauma resulting in loss of consciousness (during the past 2 years).
15. History or current diagnosis of epilepsy or seizure disorder (other than febrile seizures in childhood).
16. Loss of 500 ml or more of blood during the 3-month period before study enrollment, e.g. as a donor.
17. Prior surgery or current medical condition which might interfere with the absorption, distribution, metabolism or excretion of the study drug, e.g. gastric or intestinal surgery, impaired renal or hepatic function, cardiovascular abnormalities, inflammatory bowel disease, chronic symptoms of pronounced constipation or diarrhea, or conditions associated with total or partial obstruction of the urinary tract.

Cardiovascular

18. A current diagnosis of severe or unstable cardiovascular disease, including ischemic heart disease; vasovagal syncope, sick-sinus syndrome, arrhythmia, conduction deficits [e.g., sino-atrial block, second or third degree atrio-ventricular block (PR >0.20)], congestive heart failure, myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.
19. Any clinically significant ECG abnormality, including a disorder of rate, rhythm, or conduction, or other morphological changes, or a QTcF interval prolongation (Fridericia's correction formula) on the ECG (>450 msec for males; >470 msec for females).

    A 12-lead ECG will be used for determining the suitability of the patient for inclusion in the study (determined by the investigator); the values averaged from the 3 ECG measurements at baseline should be used in determining eligibility.
20. Vital signs (supine) outside the following ranges (measured after 5 minutes supine):
    a. Systolic blood pressure below 100 or above 150 mmHg;
    b. Diastolic blood pressure below 50 or above 95 mmHg;
    c. Radial pulse (from vital signs) below 50 or above 100 bpm;
    d. Orthostatic hypotension (decrease in SBP/DBP from supine to standing position exceeding 30 mmHg);
21. History of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal coronary angioplasty.

Laboratory abnormalities

22. Clinically significant abnormalities in routine laboratory examinations (hematology; blood chemistry, including electrolytes and liver and kidney function tests; urinalysis), as determined by the Principal Investigator in consultation with the Medical Monitor, at the screening evaluation. *Tables of clinically notable values for laboratory parameters in Appendix 2 should be used as a guide in making this determination*;
23. History of hepatitis B and/or C, and/or positive serology results, which indicate the presence of hepatitis B and/or C (Hepatitis B surface antigen and/or antibody to Hepatitis C); as identified by any of the following:

a. Hepatitis B: hepatitis B surface antigen (HBsAg) or with isolated anti-HBc (HBsAg negative, anti-HBc positive, and anti-HBs negative);

b. Hepatitis C: antibody to hepatitis C positive and HCV RNA positive.

Patients with positive hepatitis B surface antibody (anti-HBs), but with negative HBsAg and negative hepatitis B core antibody (anti-HBc), who have documented evidence of hepatitis B vaccination, will be eligible for this study. If a documented record of vaccination cannot be obtained, the Investigator will discuss the case with the Medical Monitor and will provide information of the patient's hepatic function tests (including bilirubin, reports of jaundice, etc.). In the absence of abnormal findings, the patient may be considered eligible.

Patients with a history of documented successful treatment for Hepatitis C, i.e. HCV antibody positive, and HCV RNA negative patients showing this sustained viral response (SVR) for at least 24 weeks after the end of treatment, will be considered eligible for inclusion.

24. Positive results from the HIV serology.
25. Positive results of the drug and alcohol tests at screening and/or baseline. Patients who test positive for drugs of abuse at screening, but have negative test results at baseline, may be eligible, depending on the type of drug and the likelihood of continued abuse during the study. *Possible inclusion of these patients in the study should be discussed with the Medical Monitor*.
26. Clinically significant hypothyroidism or hyperthyroidism, unless stabilized by medication for at least 3 months before screening.

Concomitant therapy

27. Patients treated with anticholinergic drugs whose dose is not stable at baseline.
28. If receiving benzodiazepine therapy, this treatment has not been stabilized for at least 2 months. *The lowest dose possible should be used. Occasional prn use is permitted.*
29. Treatment with tri- and tetra-cyclic antidepressants, MAO inhibitors, and metoclopramide.
30. Treatment with SSRIs that are moderate/potent inhibitors of CYP2D6 (e.g. fluoxetine). *Patients on a stable dose of an SSRI that is a weak inhibitor of CYP2D6 (e.g. escitalopram), for at least 4 weeks before screening, will be eligible.*
31. Treatment with drugs capable of inducing/inhibiting hepatic enzyme metabolism (e.g. barbiturates, carbamazepine, phenylbutazone, phenytoin, primidone, rifampicin) four weeks prior to baseline or during the study.
32. Current treatment with sodium channel blockers (e.g. Class I antiarrhythmic agents, anticonvulsants, local anesthetics) or mood stabilizers (e.g. lithium, carbamazepine, oxcarbazepine, lamotrigine). *Valproic acid will be permitted, if used as maintenance treatment*.
33. Exposure to any investigational drug within 5 weeks or 5 half-lives (whichever is longer) prior to screening.
34. A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to evenamide (e.g. lamotrigine, carbamazepine, oxcarbazepine, topiramate, etc.), or any components of the evenamide or matching placebo capsules.
35. Treatment with a drug or treatment known to cause major organ system toxicity, e.g. tamoxifen, within 4 weeks, or received radiation therapy or a drug with cytotoxic potential, e.g. chemotherapy, during the past year.
36. Electroconvulsive therapy (ECT) or treatment with a transcranial magnetic stimulation (TMS) device within 6 months prior to screening.

General

37. If female, patient is of childbearing potential, pregnant or breastfeeding. *For inclusion, female patients must be post-menopausal (age 50 or older with confirmed amenorrhea for >12 months), surgically sterilized, or protected with a barrier method and hormonal contraceptive*

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

9.2.3 Documentation of Randomization

Only patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase. In addition to violations of inclusion and exclusion criteria, reasons for randomization failure include a major protocol deviation, lost to follow-up, voluntary withdrawal, and study termination; the primary reason must be noted on the applicable Case Report Form (CRF). Randomization will be on Day 1 at the start of dosing, after all baseline evaluations have been completed.

9.2.4 Premature Discontinuation

Patients who discontinue from the study prematurely (i.e. before completing the 28-day randomized treatment period) must have their reason for discontinuation entered in the CRF. Patients who discontinue from the study after having received at least one dose of study medication will not be replaced. All patients who discontinue prematurely will be asked to return for a final assessment at which time all Day 29 assessments are to be performed. Patients will also be requested to return for the safety follow-up assessment 7 days after their last dose of study medication.

9.2.5 Record of Screening Failures

Investigators must account for all patients who failed screening and have signed informed consent forms on the screen failure CRF.

The primary reason for screen failure will be recorded using the following categories:

- Did not meet entry criteria
- Pretreatment Event/Adverse Event
- Lost to follow-up
- Withdrawal of consent (specify reason)
- Other (specify reason).

Subject numbers assigned to patients who fail screening will not be reused.

9.2.6 Record of Study Participants

The investigator will be required to maintain a confidential record of all study participants, including all patients who were screened for the study, but were not actually randomized to treatment. The confidential record must include sufficient information so that it would be possible to contact the study patient.

10 STUDY MEDICATION

10.1 Description, Labeling and Packaging

10.1.1 Description of the Supplies

The supplies for the study will consist of evenamide capsules with each different dosage (7.5 and 15 mg) provided to each site in blinded 30 ml HDPE bottles with a child-proof screw cap. Blinded bottles with matching placebo will also be provided. Each bottle will contain a 1-week supply of study medication for twice daily *(bid)* dosing, plus additional medication in case of loss/damage (e.g. 1-week supply: 14 capsules + 2 extra capsules for 1 extra day of dosing = 16 capsules). One bottle will be dispensed for each week of dosing prior to the next scheduled visit.

10.1.2 Labelling

The following information will appear on the medication bottles provided to the patient:

- Protocol No. NW-3509/008/II/2019
- Investigator's name and contact information (to be provided on separate label based on country-specific requirements)
- Quantity of capsules
- Lot number
- Expiry date
- Dose: blinded
- Storage conditions (typically room temperature, which is between 15°C and 25°C).
- Cautions required by regulatory authorities [such as "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only" and "Keep out of Reach of Children"]
- Name of study sponsor
- Randomized inventory management number (Kit number)
- Patient's subject number (entered by site)
- Date of dispensing (entered by site).

10.1.3 Packaging

Study medication will be packaged in 30 mL HDPE bottles with child-proof screw caps by the drug product manufacturer and dispensed at each site according to the Interactive Web Response System (IWRS). For each patient, the study medication bottles should be labeled with the patient's number and date of dispensing, along with the appropriate labelling information as described in Section 10.1.2 above. Capsules containing the active drug (7.5 or 15 mg evenamide) or matching placebo capsules will be used to achieve the planned doses of 7.5 and 15 mg, or placebo, which will be given twice daily. The packaging of the medication for each dose level is presented in Table 4 below. Each patient will receive the appropriate number of bottles, each containing 16 capsules (designated for one week of dosing) for each dosing period, i.e. one bottle on Days 1, 8, 15 and 22. Two extra capsules will be provided in each bottle for each week of *bid* dosing in case of lost or damaged medication, or a delay in the patient returning for a scheduled visit.

Patients who have had their dose reduced to once daily dosing will still receive the same number of bottles of study medication that would be used for twice daily dosing at the target dose but will be instructed to take only one capsule per day in the morning.

Table 4. Drug Packaging According to the Planned Dosing Schedule by Treatment Group

Study Days	No. of Bottles*	Evenamide		
		7.5 mg *bid*	**15 mg *bid***	**Placebo**
1-7	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x Placebo
8-14	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x Placebo
15-21	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x Placebo
22-28	1	16 caps x 7.5 mg	16 caps x 15 mg	16 caps x Placebo

*16 capsules/bottle

10.2 Administration

The test drug (evenamide) will be provided by the Sponsor in the form of capsules at dosage strengths of 7.5 and 15 mg for oral administration. The placebo will be provided in matching capsules. All study medication, together with relevant documentation, will be supplied to the Pharmacy at the investigational site.

In order to preserve the double-blind design of the study, all study medication will be blinded, and the appropriate dose and treatment will be dispensed according to a computer-generated randomization scheme using an IWRS. In this way, neither the Principal Investigator, study coordinator, nurses or other site staff, nor the patients, will be informed about what is being administered. The first dose of study medication (Starting Dose) will be administered to the patient in the clinic in the presence of a licensed physician. Following administration of the study drug, appropriate hand and/or mouth checks will be performed to ensure that the dose was swallowed. The date, time, and number of capsules taken during the in-patient period will be recorded on the CRFs. The oral doses of evenamide or matching placebo to be taken by the patient for each randomized dose level are summarized in Table 5.

Table 5. Capsules to Be Administered for Planned Doses of Study Medication

Dose Type	**Evenamide 7.5 mg *bid***	**Evenamide 15 mg *bid***	**Placebo**
Starting Dose	7.5 mg *bid*	15 mg *bid*	Placebo *bid*
Target Dose	7.5 mg *bid*	15 mg *bid*	Placebo *bid*
Drop-back Dose *	7.5 mg *od*	15 mg *od*	Placebo *od*

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

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

Assessment of Antipsychotic Medication Adherence

Blood samples will be collected at baseline to measure plasma levels of the concomitant antipsychotics to aid in determining if patients have been taking their medication, as prescribed, prior to entering the treatment period of the study. The concentrations of the concomitant antipsychotics in plasma samples will be determined using a validated LC-MS/MS method

Dosing during the Randomized Treatment Period

All randomized patients will receive their initial dose (7.5 or 15 mg evenamide, or placebo) on Day 1 in the clinic and will take their evening dose of 7.5 or 15 mg at home. Patients in the low dose group will start at a dose of 7.5 mg *bid*, while patients in the higher dose group will start at a dose of 15 mg *bid*. After one week, patients in the evenamide dose groups will continue to receive their target doses of 7.5 or 15 mg *bid*, if well tolerated. The planned dose levels to be used in the study are shown in Table 5 above. If significant intolerance develops, the patient may drop back to once daily (*od*) dosing. If the reduced dose is well tolerated, an increase to the starting/target dose should be attempted at the next scheduled visit. Patients who receive once daily dosing during the first week and have an increase back to twice daily dosing at Day 8 should have an additional EEG performed prior to the morning dose in the clinic at the next scheduled visit (i.e. Day 15). If intolerance again develops, the patient may have a reduction to *od* dosing, and may continue for the remainder of the study at this reduced dose. Dose reductions due to intolerance can be performed at any time, whereas dose increases can only be done at scheduled visits.

When patients are taking their medication at their residence, they should be instructed to take their morning dose of study medication at least 10 minutes after the time of dosing for their concomitant antipsychotic. If possible, the study medication should be taken with food or after a meal. The evening dose should be taken at least 6 hours after the morning dose. Any other medications should be taken according to their usual schedule. However, on the day of a scheduled office visit (Days 8, 15 and 22), the patient should be reminded to withhold their morning dose of study medication, as it will be administered in the clinic. The last dose of study medication in the double-blind period will be taken by the patients at the residence in the evening on Day 28. The doses of their concomitant antipsychotic and any other medications should be taken at their residence according to their usual schedule.

10.3 Storage

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

10.4 Blinding and Randomization

Subject Number

Each screened patient will receive a six-digit **subject number**, with the first three digits specifying the center number and the last three digits the subject at the center. The subject number will be entered in the CRF and will appear in the header of each CRF page

The Investigator will contact the IWRS to assign the six-digit subject number to each patient at the Screening visit. The subject number should be assigned sequentially, beginning with ###-001, in the order of the patient's signing of the informed consent form at the center. This six-digit number should be entered in the CRF for a given patient.

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

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

Patient Randomization

Approximately 120 patients will be randomized in this study. Patients will be randomized equally (1:1:1) to 7.5 or 15 mg evenamide, or placebo, *bid*. Randomization will be performed using an 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.

Breaking the Blind

Should it be necessary to break the blind for reasons of safety, the Investigator can break the blind through the IWRS. If the blind is broken for a patient, the Investigator will be asked to inform the Sponsor and/or their representative (CRO) of this as soon as possible, and to also provide a reason for the unblinding.

10.5 Accountability

In accordance with ICH and FDA requirements, the Investigator or Drug Dispensing Person (e.g., pharmacist) must always be able to account for all study drugs furnished to the institution. The pharmacist or the Investigator must sign the Drug Receipt Form, confirming that he/she has received the clinical supplies for the study and provide assurance that the investigational products will be handled and stored properly.

The investigational treatments must only be dispensed to subjects in accordance with the protocol. At the end of the study, it must be possible to reconcile delivery records with those of usage and returned stocks. Account must be given of any discrepancy. Any unused products must be returned to the Drug Broker. Certificates of returns must be signed with assurance from the pharmacist/Investigator that all unused investigational drugs and all medication containers provided for the stated study have been returned.

Under no circumstances is the Investigator allowed to use the study medication other than as directed by the protocol.

To maintain the blind, the Investigator and other staff involved with the study must not have access to any unblinded information related to the treatment assignment for an individual patient. Monitoring of drug accountability records and information on medication dispensed to patients in the study will be done periodically by a monitor from the CRO.

All patients will be required to return all used and unused study medication bottles to the site at each scheduled visit, in order to receive their new supply of study medication for the next dosing period. Any study medication that is lost, damaged or discarded by the patient must be fully documented.

10.6 Overdosage

To date, the maximum single dose of evenamide given to a subject was 30 mg. This dose was administered to 6 healthy volunteers in Study NW-3509A/001/I/2011 and was well tolerated. No information is available on single doses greater than 30 mg. In Study NW-3509A/002/II/2015, in which multiple doses of

evenamide up to 25 mg *bid* were administered to patients with schizophrenia for up to 27 days, there were 3 reports of overdose for patients on evenamide, based on capsule counts of returned medication. None of these overdoses were associated with adverse events. Therefore, in case of an accidental overdosage, conservative management of symptoms and signs is advised. The procedure for reporting an overdose is described in Section 13.1.6.

10.7 Occupational safety

Evenamide (NW-3509) is not expected to pose any significant occupational safety risks to investigational staff under normal conditions of use and administration.

11 EVALUATIONS AND PROCEDURES

11.1 Written Informed Consent

Written Informed Consent must be obtained from the subject at Screening. The details of the study should be discussed with the subject prior to obtaining informed consent and initiating any study procedures required by the protocol. The Informed Consent Form must be signed and dated by the subject and by the Investigator or his/her designee.

11.2 Study Conduct

11.2.1 Overview of Study Procedures

Screening Visit

All patients must provide written informed consent prior to participation in the trial. For each patient, screening evaluations (Table 6) must be performed from 3 to 21 days prior to baseline. Screening evaluations will consist of confirmation of the patient's psychiatric diagnosis, collection of information on the patient's medical and psychiatric history, and past and current medications, and review of selection criteria. Screening safety evaluations will include physical and neurological examinations, a standard eye examination, completion of a Seizure Checklist evaluating symptoms and signs suggestive of seizures (e.g., seizures or fits, convulsions, absence seizures, unconsciousness, biting of tongue), vital signs, an electroencephalogram (EEG) using the international 10-20 system (performed two times with approximately one hour in between, if feasible for the patient), a 12-lead electrocardiogram (ECG), laboratory tests (hematology, blood chemistry, urinalysis, virology, thyroid function tests, HbA1c, urine drug screen, urine and serum pregnancy tests in women [excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or surgically sterilized] and the Columbia – Suicide Severity Rating Scale (C-SSRS) ("Baseline/Screening" version). Efficacy evaluations to be performed at screening are the PANSS and CGI-S. The Calgary Depression Scale for Schizophrenia (CDSS) will be used to screen out patients with significant depressive symptoms. All patients who are taking clozapine must agree to routine blood monitoring (venipuncture for measuring absolute neutrophil count [ANC] – see Appendix 5), with weekly testing (if within 6 months of starting clozapine), bi-weekly testing (if clozapine was started from 6 to 12 months ago), or testing every 4 weeks (if clozapine has been taken for more than 12 months).

Baseline (Day 0)

At the baseline visit (Day 0), the detailed baseline schedule of evaluations outlined in Table 7 will be completed. This will include review of adverse events, updating any change in current medications, assessment of vital signs, completion of the Seizure Checklist, assessment of abnormal movements using the ESRS-A, ECG, the C-SSRS ("Baseline/Screening" version), an alcohol breath test, a urine drug screen, and review of the selection criteria. An additional urine sample will be collected for measuring nicotine and cotinine. Serum and urine 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 surgically sterilized, with the results of the urine testing being used for determining eligibility, and the serum test being used for subsequent confirmation. A serum prolactin level will also be obtained, and a blood sample collected to confirm the patient's compliance with taking their background antipsychotic medication. In addition, an assessment of polymorphisms in cytochrome P450 2D6 (CYP2D6) metabolic capacity, using genotyping, will be done. Hematology, blood chemistry and urinalysis laboratory tests, physical and neurological examinations, and the eye examination do not need to be repeated if previously done within 21 days of baseline. The CDSS will be repeated to assess depressive symptoms. Baseline efficacy evaluations that will be completed include the PANSS, CGI-S, MSQ, and LOF.

Day 1

Upon completion of the baseline pre-dosing safety and efficacy evaluations, patients meeting entry criteria will be randomized and begin Day 1 dosing. In this study, all Day 0 (pre-dose) and Day 1 (post-dose) procedures are expected to be completed on the same day, if possible. After the initial dose of study medication, the post-dose battery of safety evaluations outlined in Table 7 will be completed. These will include an ECG, vital signs, ESRS-A and EEG recording to be conducted near the predicted T_{max} of evenamide, 1-3 hours (60 to 180 min) after dosing with the study drug, and a Seizure Checklist of terms suggestive of potential seizure activity to be performed 4 hours after dosing and assessing the entire 4-hour post-dose period.

Blood samples will be collected to measure plasma levels of evenamide and its major metabolite, (3-butoxy-phenyl)-acetic acid, before dosing (as a blank sample) and 30 min, 60 min, 120 min and 240 min after the initial dose.

If no significant side effects are noted during the 4-hr period of post-first dose safety evaluations, the patient will be discharged and given a supply of study medication for the remainder of the first week's treatment; the patient will be instructed to take the next dose of study drug at his/her residence in the evening of the first day at least 6 hours after the initial dose. Treatment should continue as prescribed until the next scheduled study visit, unless significant tolerability issues arise during the week. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance.

Patients will be proactively contacted by telephone on Day 4 to assess the tolerability of their current dose, and to review the Seizure Checklist and AEs. If any tolerability issue does arise, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work-up.

Day 8

Patients will be asked not to take their study medication before coming to the clinic on Day 8 and will receive their dose in the clinic. The detailed assessment schedule outlined in Table 8 will be followed. If significant safety or tolerability issues are detected during the pre-dose assessments on Day 8, further dosing will be reduced to once daily (*od*) and the patient will remain on *od* dosing for the duration of the study. If the safety or tolerability issues are severe, the study drug should be discontinued.

On Day 8 a pre-dose EEG will be performed and a PK blood sample will be collected to measure steady state trough plasma 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. Post-dose safety assessments will include, an EEG recording to be conducted near the predicted T_{max} of evenamide, 1-3 hours (60 to 180 min) after dosing with the study drug, and a Seizure Checklist of terms suggestive of potential seizure activity to be performed 4 hours after dosing and assessing the entire 4-hour post-dose period.

If no significant safety or tolerability issues are identified in the 4-hour post-dose period during completion of the safety assessments, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on Day 8 in the evening at their residence at least 6 hr after the morning dose.

Patients will be proactively contacted by telephone on Day 11 to assess the tolerability of their current dose and to review the Seizure Checklist and AEs. If significant tolerability issues arise during the week, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 15

Patients will be asked not to take their study medication before coming to the clinic on Day 15, as the dose will be administered in the clinic. The detailed assessment schedule outlined in Table 9 will be followed at

this visit. If significant safety or tolerability issues are detected during the pre-dose assessments, further dosing may be reduced to *od,* and the patient will remain on *od* dosing for the duration of the study. If the safety or tolerability issues are severe the study drug should be discontinued.

Post-dose safety assessments will be performed as outlined in Table 9. Among these, the Seizure Checklist and assessment of adverse events will be performed. If no significant safety or tolerability issues are identified after the 4 hours of post-treatment observation, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on the evening of Day 15 at their residence and continue treatment as prescribed until their next study visit. If significant tolerability issues arise during the week, patients should be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Patients will be proactively contacted by telephone on Day 18 to assess the tolerability of their current dose, and to review the Seizure Checklist and AEs. If significant tolerability issues arise during the week, patients will be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 22

Patients will be asked not to take their study medication before coming to the clinic on Day 22, as the dose will be administered in the clinic. The detailed assessment schedule outlined in Table 10 should be followed. If significant safety or tolerability issues are detected during the pre-dose assessments, further dosing will be reduced to *od*. If the safety or tolerability issues are severe the study drug should be discontinued.

Post-dose safety assessments will also be performed as outlined in Table 10. If no significant safety or tolerability issues are identified after 4 hours of post treatment observation, the patient will receive a supply of study medication and can return to his/her residence. An overnight stay in the hospital should be considered if the patient shows signs of moderate/severe intolerance. Patients should take their second dose of study medication on the evening of Day 22 at their residence and continue treatment as prescribed until their next study visit. If significant tolerability issues arise during the week, patients should be instructed to call the clinic to determine how to proceed. If any severe/serious event is detected, especially CNS or cardiac events, the patient will be brought back to the clinic for a full work up.

Day 29 or Final Visit

The patient will be instructed to take a final dose of study medication in the evening on Day 28, and on Day 29 (or at early discontinuation) the patient will return to the clinic for all final safety and efficacy evaluations. The detailed schedule of evaluations outlined in Table 11 should be followed. In addition, a PK blood sample will be collected to measure trough plasma levels of evenamide and its major metabolite (3-butoxy-phenyl)-acetic acid during this final day of assessment.

Telephone Contacts

Patients will receive a telephone contact from the Investigator/site staff on Days 4, 11 and 18 to inquire about their medication satisfaction, any safety or tolerability issues, and use of concomitant medication. The investigator will evaluate if the patient is experiencing any of the following symptoms and signs suggestive of seizures: seizures, fits, jerks, jerky movements, easy startle, convulsions, absence seizures, gazing, staring, falls, fainting, syncope, auditory/visual auras, myoclonus, automatism, unconsciousness, biting of tongue, through careful open-ended questioning. If the patient reports any of these symptoms the patient will be asked to return to the hospital immediately for an unscheduled visit, an examination of the patient will be performed to determine the presence of symptoms or signs suggestive of seizures, including an EEG. If the EEG shows spike and wave activity suggestive of seizures, dosing will be interrupted, and

the patient kept in the hospital pending a full evaluation. A decision on the patient's continued participation in the trial will be made by the Investigator based on a full review of the patient's history and other safety data collected during the study.

Throughout the study, if the examination of the patient confirms symptoms or signs suggestive of seizures or significant cardiac events, if the EEG detects activity suggestive of seizures, or the ECG shows significant changes, dosing should be interrupted, and the patient kept in the hospital pending a full evaluation. A decision on the patient's further participation in the trial will be made by the Investigator based on a full review of the patient's history and data collected in the study.

Safety Follow-up Evaluation

Patients who discontinue prematurely, as well as those who complete 4 weeks of double-blind treatment, will undergo, a safety follow-up visit one week after their final dose of study medication. During this visit, an assessment of vital signs and adverse events will be performed. Patients who do not return for their 7-day safety follow-up visit must be contacted by the study site to follow up on the occurrence of any adverse events. In addition, the patient will be contacted 30 days after the last dose of study medication to follow up on the occurrence of any Serious Adverse Events (SAEs) within 30 days after the final dose.

Hospitalization

Generally, patients will come to the clinic for scheduled visits, and return to their home or residential care facility after all evaluations are completed. However, if the Investigator feels it is necessary for safety or other reasons, a patient may be hospitalized.

11.2.2 Laboratory and PK Sample Collection and Processing

Blood sampling for laboratory tests

Venous blood samples will be drawn for safety and screening evaluations, comprising hematology, blood chemistry, virology, HbA1c, thyroid function tests, serum prolactin and serum pregnancy test.

The maximum blood volume collected on any day for these tests will be approximately 30 mL. The blood volumes collected for each of the tests may vary between countries/regions (see laboratory manual). Blood samples will be collected for the following laboratory tests during the study:

- routine hematology tests,
- routine blood chemistry tests,
- virology tests (Screening only),
- HbA1c (Screening and last visit),
- thyroid tests (Screening only),
- serum prolactin levels (Baseline and last visit),
- serum pregnancy test (Screening, Baseline and Day 29); this test will be performed 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. If the local laboratory is unable to perform the serum pregnancy test, it can be sent out to another laboratory for analysis.

Clozapine ANC monitoring

All patients who are taking clozapine must agree to routine blood monitoring (venipuncture for measuring absolute neutrophil count [ANC] – see Appendix 5), with weekly testing (if within 6 months of starting

clozapine), bi-weekly testing (if clozapine was started from 6 to 12 months ago), or testing every 4 weeks (if clozapine has been taken for more than 12 months).

Urine collection

The minimal quantity of urine needed for the routine urinalysis and urine drug screen (at screening, baseline and the last visit) is 30 ml. An additional urine sample will be collected at baseline for measurement of nicotine and cotinine. A urine pregnancy test (dipstick) will be performed at Screening and Baseline 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. The urine test will be performed to obtain immediate results for determining eligibility of the patient for randomization. As noted above, a blood sample will also be collected at Baseline for performing a serum pregnancy test for confirmation of the results of the urine test.

Sampling for measurement of plasma levels of evenamide and its main metabolite (3-butoxy-phenyl)-acetic acid

In addition to the blood samples taken for laboratory tests, 5-ml blood samples will be collected for measurement of plasma concentrations of evenamide and its main metabolite (3-butoxy-phenyl)-acetic acid. Blood samples will be taken pre-dose (blank) and 30, 60, 120 and 240 min after dosing on Day 1. A sample for measuring the steady state trough plasma level will be taken prior to the morning dose on Day 8, and additional samples will be taken 30, 60, 120 and 240 min after dosing A blood sample will be collected in the morning on Day 29, after final dose on the prior evening. The exact time of sampling relative to the dose, including the time of the dose of study medication prior to the Day 29 sample (the time of the prior evening dose, based on the report of the patient/caregiver), must be recorded in the CRF.

For each sample time point, 5 mL of whole blood will be collected in standard 5-mL Li-heparinized vacuum tubes, gently inverted several times and centrifuged within 30 minutes at 4°C. After centrifugation (15 minutes at approx. 1500g), the supernatant plasma (2x at least 1 mL) will be immediately pipetted off, transferred into two pre-labeled polypropylene cryo-vials and deep frozen at < -20°C as soon as possible. The tubes will be kept frozen at < -20°C pending shipment for analysis.

Processing of samples

All blood and urine samples collected screening (virology, HbA1c, thyroid tests, drug screen, pregnancy test), baseline (drug screen; nicotine and cotinine; pregnancy test; serum prolactin) and routine safety (hematology/ blood chemistry/ urinalysis) evaluations will be sent to a local laboratory, following the instructions provided by the laboratory.

All plasma samples for each cohort for the assay of systemic concentrations of NW-3509 and its main metabolite, (3-butoxy-phenyl)-acetic acid, will be stored at < -20°C. The samples will then be transferred in bulk on dry ice to LGC Ltd, Fordham, UK, for determination of NW-3509 and metabolite levels using a fully validated bioanalytical assay based upon a liquid chromatography – tandem mass spectrometry (LC-MS/MS) procedure. Samples will only be destroyed or sent where indicated, upon approval/request by the Sponsor.

Measurement of plasma concentrations of concomitant atypical antipsychotics

Blood samples will be collected at Baseline (prior to first dose of study medication) for measurement of plasma levels of the permitted concomitant atypical (second-generation) antipsychotics aripiprazole, clozapine, quetiapine, olanzapine, paliperidone or risperidone). The plasma concentrations of these drugs will be used to confirm adherence with dosing prior to the patient entering the double-blind treatment period. The exact time of sampling, and the time of the prior dose (based on the report of the patient/caregiver), must be recorded in the CRF.

The tubes and procedures to be used for collection and processing of these samples, the sample volume required, and the analysis procedures will be described in separate procedure manuals provided by the laboratory (LGC Ltd, Fordham, UK).

Timing of blood sample collection relative to other assessments

When the time of blood sample collection overlaps with the time of other scheduled safety assessments, e.g. vital signs, ECG, and physical/neurological examinations, these safety assessments should be performed prior to the blood draw.

11.3 Schedule of Evaluations

The study flow-chart with the schedule of evaluations to be performed at each visit in the study is provided in Table 6. Detailed schedule of evaluations for Days 0/1, Day 8, Day 15, Day 22 and Day 29 are provided in Tables 7, 8, 9, 10 and 11, respectively.

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Table 6. 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]										
Pharmacokinetic blood samples for evenamide and (3-butoxy-phenyl)-acetic acid plasma levels		X[F]	X[F]		X[F]					X[N]		

Period	Pre-Treatment		Treatment Phase								Post-Treatment	
Assessment / Visit	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]
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 $\pm$ 5 min for the early post-dose PK samples (30 and 60 minutes), and $\pm$ 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 7. 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 sample (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 8. 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 sample (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 9. 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 10. 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 11. 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.

11.4 Visit schedule and assessments

11.4.1 Screening (Days -21 to -1)

At Screening (minimally 7 days before Baseline), each subject will report to the clinic where the following procedures will be performed to establish eligibility for the study:

a) obtaining written informed consent (before any study procedures)

b) demography and background information (including substance use)

c) psychiatric history

d) medical history and current medical conditions

e) physical examination

f) neurological examination

g) standard eye examination

h) C-SSRS evaluation ('Screening' version)

i) CDSS evaluation

j) laboratory evaluations comprising the following tests:

- hematology - RBC, WBC, hemoglobin, hematocrit, platelets, neutrophils (including ANC for clozapine-treated patients) #, eosinophils, basophils, lymphocytes, monocytes;
- biochemistry - total bilirubin, albumin, AST, ALT, GGT, BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, LDH, alkaline phosphatase, total cholesterol, total protein, HDL, LDL, VLDL, triglycerides, glucose, and CPK;
- virology tests* - hepatitis B antibody (core and surface) and surface antigen, and hepatitis C antibody screens; HIV;
- HbA1c
- thyroid function tests* - TSH, free thyroxine (T4), and free triiodothyronine (T3);
- urinalysis – pH, glucose, ketones, specific gravity, nitrites, protein, bilirubin, hemoglobin, and microscopic RBC, WBC and casts;
- urine drug screen;
- urine and serum pregnancy tests - for women of child-bearing potential, excepting those who are post-menopausal (age 50 or older with confirmed amenorrhea for >12 months) or have had a tubal ligation;

  *screening only

  # blood sampling for measuring ANC in patients receiving clozapine will be repeated minimally at one-week intervals for patients who have been receiving clozapine for 6 months or less, every two weeks for patients who have been treated for 6 to 12 months, and every 4 weeks for patients receiving clozapine treatment for more than 12 months (see Appendix 5);

k) vital signs – body weight, height, temperature, pulse, systolic and diastolic BP, and respiratory rate

l) 12-lead standard ECG

m) EEG (performed two times with approximately one hour in between, if feasible for the patient)

n) prior (previous 1 year) and concomitant medications and therapies

o) adverse events (to be collected from the time of signing the consent form), including symptoms and signs suggestive of seizures (see Seizure Checklist in Appendix 4)

p) PANSS

q) CGI-S

r) subject eligibility and inclusion/exclusion criteria checklist **(all laboratory results must be available before the baseline visit).**

11.4.2 Baseline (Day 0 and Day 1 pre-dose)

The evaluations to be performed at Baseline are shown in Table 7.

11.4.3 Day 1 (post-dose)

The evaluations to be performed on Day 1 after the first dose is administered in the clinic are shown in Table 7.

11.4.4 Days 4, 11 and 18 - Telephone contact

A telephone contact will be made with each patient being treated as an outpatient on the 4th day after the start of dosing (i.e. Day 4) and on Days 11 and 18 to inquire about the occurrence of any adverse events, and to assess the MSQ and use of concomitant medication. In particular, the Investigator will evaluate if the patient is experiencing any symptoms and signs suggestive of seizures through careful open-ended questioning using the Seizure Checklist (Appendix 4). If the patient reports any of these symptoms, the Investigator will determine if a dose reduction is warranted (i.e. decrease to once daily dosing) or if the patient should be asked to return to the hospital for an unscheduled visit.

11.4.5 Day 8

The evaluations to be performed on Day 8 are shown in Table 8.

11.4.6 Day 15

The evaluations to be performed on Day 15 are shown in Table 9.

11.4.7 Day 22

The evaluations to be performed on Day 22 are shown in Table 10.

11.4.8 Day 29 – End of Double-Blind Study (or at early discontinuation)

The last dose of study medication will be taken by the patients at their residence on the evening of Day 28, and the patients will return to the clinic on Day 29 for their final evaluations. The evaluations to be performed on Day 29 are shown in Table 11.

11.4.9 Safety Follow-up (7 ± 2 days after last dose of study medication)

a) vital signs – body weight, temperature, respiratory rate, pulse, systolic and diastolic BP

b) Adverse Events (AEs) – reported by the subject or observed by the Investigator, including symptoms and signs suggestive of seizures.

11.4.10 Follow-up on Serious Adverse Events (30 days after last dose)

A telephone contact will be made with the patient to assess the occurrence of any SAEs within the 30-day period following the last dose of study medication. Any SAEs that are noted will be reported according to the usual procedure.

11.4.11 Visit Windows

A window of ± 1 day will be allowed on scheduled weekly visits on Days 8, 15, 22 and 29, and on the telephone contacts on Days 11 and 18. A window of ± 2 days will be permitted for the safety follow-up visit (7 days after last dose). The last day of dosing for the study medication in the initial 4-week treatment period will be on Day 28 (in the evening at the patient's residence). The final evaluations will be performed on Day 29 (or at early discontinuation); however, if the patient will be delayed by 1 or 2 days in returning for the final evaluations, he/she should continue taking the study medication twice daily through the evening prior to the visit.

11.5 Concomitant Medications

Any medication, in addition to the study medication, that is administered during the study from the start of the screening period through to the final evaluations on Day 29 must be recorded in the CRF (including over-the-counter [OTC] medications). Patients and their caregivers will be instructed to contact the Investigator for approval prior to taking any medications, including OTC medications, while residing at home or in a residential care facility and prior to their final evaluation on Day 29.

Restrictions on concomitant medications being taken upon entry into the screening period and during the treatment period of the study will follow those specified in the Exclusion criteria (Section 9.2.2, *Concomitant Therapy*).

The following psychotropic medications will be allowed for the treatment of insomnia on an 'as needed' basis at the doses specified:

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

In addition, quetiapine, at a maximum dose of 50 mg *hs*, will be permitted as a sedative in patients who have been taking it for at least 4 weeks prior to screening. However, patients will not be allowed to start quetiapine (50 mg *hs*) for sedation post-randomization. Also, valproic acid will be permitted, if used as a prophylaxis of clozapine-induced seizures, and/or maintenance treatment. Drugs that can increase the risk of seizures, e.g. bupropion, should not be administered.

Rescue Medication

If a patient has an exacerbation of his/her schizophrenia while in the treatment period of the study that requires additional pharmacological intervention, the Investigator may increase the dose of the patient's atypical antipsychotic (if not currently at their maximum tolerated dose) or administer any antipsychotic or

other medication required to treat the episode. The need for administering 'rescue medication' to an individual patient will be left to the clinical judgment of the Investigator; however, any of the following changes from baseline in the patient's status should be considered as adequate justification for considering a rescue by making a change in the patient's treatment regimen:

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

If the dose of the patient's current antipsychotic is **increased by more than 25%**, or the rescue medication administered is a drug prohibited by the protocol (e.g. an antipsychotic or a mood stabilizer), and use of the medication is not temporary (5 days or less), all final (Day 29) efficacy evaluations should be performed prior to the start of dosing. Despite this intervention, the patient should continue in the study and return for all scheduled efficacy and safety evaluations.

If the dose of a patient's current antipsychotic is **reduced by more than 25%** for safety/tolerability reasons, all final (Day 29) efficacy evaluations should be performed prior to the dose reduction. Despite this dose reduction, the patient should continue in the study and return for all scheduled efficacy and safety evaluations.

Benzodiazepines

Patients receiving chronic dosing with lorazepam or other benzodiazepine must have been on a stable dose for at least 2 months prior to screening, excluding occasional *prn* dosing. The lowest possible dose should be used, and no dose should be given within 8 hours of a scheduled efficacy assessment.

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

12 EVALUATIONS

12.1 Screening Evaluations

12.1.1 Demographics, and Medical/Psychiatric History

As part of the screening evaluations, demographic information (e.g. age, weight, height, race, ethnicity, gender, education, marital status, employment, housing status, substance use) will be collected and a complete medical and psychiatric history will be obtained for each patient. The psychiatric history will include severity of illness, duration of illness, duration of current episode, number of hospitalizations, family history of schizophrenia, history of other psychiatric disorders, including substance abuse, and prior treatment with psychotropic medication, as well as the patient's response to treatment.

12.1.2 Calgary Depression Scale for Schizophrenia (CDSS)

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

12.2 Safety Assessments

The assessment of safety will be based on the following:

a) Electroencephalogram (EEG) using 10-20 international EEG electrode application procedures

b) laboratory tests (hematology, blood chemistry, and urinalysis; HbA1c; serum prolactin),

c) 12-lead standard ECG

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

e) physical examination,

f) neurological examination,

g) standard eye examination,

h) C-SSRS,

i) ESRS-A,

j) CDSS (see Section 12.1.2),

k) subjective reporting of any AE by the subject,

l) objective observation of any AE by the Investigator

m) Seizure Checklist (see Appendix 4).

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

12.2.1 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 receive 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.

If abnormal epileptiform phenomena (3 per second spike and slow wave discharges) are observed on either of the screening EEGs, the patient will not be eligible for the study. During the double-blind treatment period, if there is evidence of seizure-like activity, e.g. spike and wave, the patient's study medication will be withheld, and appropriate follow-up assessments will be performed.

12.2.2 Physical and Neurological 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). The findings will be entered on the Physical Examination section of the CRF. The physical examination will include an examination of general appearance, skin, neck (including thyroid), eyes and ears, nose, mouth, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system. Genital, urinary tract and rectal examinations will not be done on a routine basis.

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). The findings will be entered on the Neurological Examination section of the CRF. The neurological examination includes the following: evaluation of mental status, cranial nerves, muscle strength and tone, reflexes, the sensory system, coordination and gait.

12.2.3 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 signs 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. On Day 1 and Day 8, vital signs will be repeated at 1 and 4 hr after the first dose of study medication.

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

12.2.4 Electrocardiogram (ECG)

All subjects will have a standard 12-lead ECG performed as specified in the schedule of evaluations (see Table 6 in Section 11.3 Study flow-chart). If the ECG is abnormal at screening, the evaluation can be repeated, and if no clinically significant abnormalities are noted, the patient may be eligible for the study. 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 values should be used in determining eligibility for the study. On Day 1, the ECG will be repeated at 1 and 4 hr after the first dose of study medication. Each ECG should be performed before collecting the scheduled blood samples for PK assessments. Additional ECGs will be performed on Day 8 (pre-dose and 1 hr and 4 hr post-dose) and Day 29.

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

Each ECG tracing must have the following information entered on it:

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

If clinically significant abnormalities are found, the subject's ECG should be repeated at regular intervals until it returns to normal. Any ECG abnormality that requires intervention, leads to a reduction in the dose of the study medication or concomitant antipsychotic, or is symptomatic should be recorded on the Adverse Events CRF.

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

12.2.5 Laboratory Evaluations

Blood and urine samples will be collected at the visits specified in the schedule of evaluations (see Table 6 in Section 11.3 Study flow-chart). Evaluations of the hematology, blood chemistry and urinalysis analytes listed in Table 12 will be performed at all visits, except at baseline, if screening evaluation was performed within 21 days prior, and at Day 22. In addition, virology tests (hepatitis B core and surface antibodies and surface antigen, hepatitis C antibodies, and a HIV test), measurement of HbA1c and tests of thyroid function (TSH, free thyroxine [T_4] and free triiodothyronine [T_3]) will be performed at screening. A serum pregnancy test will be performed at Screening, Baseline and the final visit (Day 29 or early discontinuation) 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. In addition, a urine pregnancy test will be performed at Screening and Baseline to provide an immediate result for determining eligibility of the patient for continuing the screening process or randomization, respectively, and the serum test will be used for confirmation. Serum prolactin will be measured at baseline and at the last visit to assess the effect of the concomitant antipsychotic, as well as any potential effect of evenamide treatment, on prolactin levels. Measurement of HbA1c will be repeated at the final visit.

Table 12. 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.			

Subjects will also undergo a urine drug screen at screening, and both a urine drug screen and an alcohol breath test will be performed upon admittance to the hospital at baseline. A urine drug screen, along with an assessment of substance use, will be performed at the final visit. The following substances will be analyzed in the urine drug screen (performed at the study site): amphetamines, barbiturates, benzodiazepines, THC, cocaine, methylenedioxy-methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene, tricyclic antidepressants). Subjects who are found to have positive urine results for any substances of abuse (except THC) or a positive breath alcohol, measured using a breathalyzer or similar device, will be excluded from the study. In cases where the drug screen is positive at screening but is repeated at baseline and the results are negative, the patient may be eligible for enrollment, dependent on the type of drug and the likelihood of abuse during the study. Patients who test positive for THC will not be excluded from the study; however, the diagnosis of schizophrenia should be confirmed to ensure that they are not experiencing toxic psychosis. These cases should be discussed with the Medical Monitor if the patient is being considered for enrollment. At baseline, an additional urine sample will be collected for measurement of nicotine and its major metabolite cotinine using standard methodology employing HPLC or GC-MS.

The Investigator must review screening laboratory values prior to the first administration of the study agent, to ensure that the subject meets the protocol's inclusion/exclusion criteria. Abnormal tests at screening can be repeated, however, results must be available before baseline to determine if the patient is eligible for the study. The Investigator must review post-dose laboratory values within 24 hours of receipt of the laboratory report. After the review is completed, the Investigator must sign and date each laboratory report.

The laboratory will provide normal reference ranges for the laboratory tests on the laboratory results report. A value is **normal** when it falls on or within the upper and lower limits of the reference range. A value is **abnormal** when it exceeds the upper or lower limit of the reference range. The laboratory will flag all

abnormal and clinically notable values (defined in Appendix 2) on the laboratory report, will provide the normal reference ranges for each parameter, and will verify that the result is not due to pre-analytical problems (e.g., sample taken improperly, sample stored incorrectly, sample labeled incorrectly) or to analytical problems (e.g., machine not accurately calibrated, technical problems with equipment or reagents, or deterioration of analyte).

The Investigator must evaluate any *change of clinical relevance* from pre-dose to post-dose in a laboratory test as to whether it meets the definition of an adverse event, and repeat, if needed, any clinically significant abnormal laboratory test. Any laboratory abnormality that requires intervention, leads to a reduction in the dose of the study medication or concomitant antipsychotic, or is symptomatic should be recorded on the Adverse Events CRF.

Refer to Section 13.0, "Reporting Safety Information" for further directions.

12.2.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2007; Posner et al, 2011) is a standardized suicidal rating system. Its use is recommended by the Food and Drug Administration (FDA). This version collects information on the lifetime history of suicidality, as well as information on 'suicidal ideation' over the past month and 'suicidal behavior' over the past 2 years. At Screening, an assessment of suicidality will be performed using the 'Screening' version of the C-SSRS. At the Baseline visit, upon admission to the clinical unit, the 'Since Last Visit' version of the C-SSRS will be performed. Follow-up assessments will be performed at each scheduled visit on Days 8, 15, and 22, and at the final visit (Day 29 or early discontinuation) using the 'Since Last Visit' version of the C-SSRS. Patients with suicidal ideation (past 6 months) indicated by a "yes" response on the C-SSRS Suicidal Ideation Item 4 (Active suicidal ideation with some intent to act, without specific plan) or Item 5 (Active suicidal ideation with some specific plan and intent), **or** a "yes" response on any of the five C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within the past 6 months, as well as those who have made a suicide attempt within the past 6 months before screening, will be excluded from participating in the trial.

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

The ESRS is a 33-item scale designed to examine changes in motor function associated with pharmacologic treatment (Chouinard et al, 1980; Chouinard and Margolese 2005). It has a 'subjective' part (12 items, 0 - 4 rating) and a part scored 'objectively' on the basis of observation and examination (parkinsonism: eight items, dystonia: two items, dyskinesia: seven items; all scored on a 0 - 6 scale described for each item separately in terms of frequency and severity, some subdivided for body-parts). There are three global scales assessing dyskinesia, parkinsonism and dystonia, and a Hoehn and Yahr stage estimation of parkinsonism. It has been validated in a large number of studies including add-on therapy and drug withdrawal studies for atypical antipsychotics. An abbreviated version of the ESRS, the ESRS-A, will be used in this study and will be performed at Baseline (Day 0), Day 1 (2-4 hr post-dose) and on Day 29 (or at early discontinuation).

12.2.8 Standard Eye Examination

A standard eye examination, comprising assessments of visual acuity (Snellen chart), visual field, eye muscles, pupillary response, fundus (dilated, if feasible), tonometry, and the front part of the eyes (eyelids, cornea, conjunctiva, sclera and iris) 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). The examination should be performed by a physician at the site who has the appropriate experience and training. If a clinically significant abnormality is noted that requires expert follow-up, an Ophthalmologist or Optometrist should be consulted.

12.2.9 Metabolic Syndrome

Most antipsychotics cause significant cardio-metabolic and endocrine side effects, including weight gain, insulin resistance, dyslipidemia, and hypertension (Henderson et al, 2015; Riordan et al, 2011). Up to 50% of patients treated with antipsychotics will develop these complications comprising a metabolic syndrome. Metabolic complications and obesity are commonly found in patients treated with clozapine (Zimbron et al, 2016). Criteria for metabolic syndrome, according to the International Diabetes Federation (2006), include central obesity, plus any 2 of the following 4 factors: elevated triglyceride level, reduced HDL cholesterol, elevated blood pressure, and elevated fasting plasma glucose or previously diagnosed type 2 diabetes. Since all patients enrolled in this study will have an extensive treatment history with other antipsychotics, a number of parameters will be evaluated to assess the presence of metabolic syndrome at screening, and to monitor its progress over the course of the study to assess any potential effects of evenamide. These parameters include HbA1c, in addition to the tests that are part of the routine laboratory panel (e.g. plasma glucose, triglycerides, HDL, LDL), and vital signs (e.g. weight, BMI, blood pressure), measured during the study.

12.3 Efficacy Assessments

To ensure consistency of ratings for key efficacy measures, these assessments should be performed at the approximately the same time relative to the morning dose of study medication during the scheduled clinic visits on Days 8, 15, 22 and 29. Patients/caregivers will be instructed to withhold the morning dose of study medication on the day of each scheduled visit, as it will be administered in the clinic, and the key efficacy assessments, e.g. PANSS and CGI-C/S, should be conducted approximately 2 hours post-dose. Patients should take their concomitant antipsychotic and other medications at their residence according to their usual schedule.

12.3.1 Positive and Negative Syndrome Scale (PANSS)

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

The rater for the PANSS should be an MD, clinical psychologist, or other clinician with extensive training and experience (See Rater Training, Section 12.3.5, for detailed rater qualification requirements) in performing the clinical interview and rating the scale. The PANSS rater should not be the same physician performing the ratings of the CGI-C and CGI-S.

12.3.2 CGI

The CGI (Guy 1976) is the general name for 2 scales: the CGI-Severity (CGI-S) measures global severity of illness at a given point in time, and the CGI-Change (CGI-C) measures change from the baseline state at each post-baseline visit. In this study, the ratings of the CGI-S and CGI-C must be performed by a clinician who is involved in the management of patient care, but is not involved in the rating of the PANSS. The CGI rater will not have access to the PANSS data; however, they will be able to access the results of safety assessments and the ratings on other secondary/tertiary efficacy measures. Whenever possible, the CGI scales must be completed by the same clinician for every assessment; if this is not possible, the rating

clinician should review the subject's presentation (along with review of clinical notes) with the rater who completed the initial evaluation.

The CGI rating scale permits a global evaluation of the subject's improvement over time. At baseline, a CGI-S is performed, in which the investigator rates the severity of a subject's condition on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). At subsequent visits, the investigator assesses the severity of illness using the CGI-S, and the subject's improvement relative to the symptoms at baseline 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).

To ensure that the assessments of the CGI-S and CGI-C are done consistently, the CGI rater should perform a complete assessment of the patient at baseline, including positive and negative symptoms, global psychopathology, functioning and mental state. Investigators will be provided with a guide to ensure that all domains are assessed.

The baseline interview may be audio/video-recorded so that it can be referred to when assessing response at subsequent visits. If it is not possible to perform a video or audio recording, a baseline narrative must be written that covers the dimensions of symptomatology identified above. This recording/narrative will remain at the site and be readily available to the rater(s) for subsequent ratings. The recording/narrative MUST be reviewed prior to completing any future CGI-C rating. At each subsequent visit, the rater should write a brief paragraph describing the justification for the rating on the CGI-S and CGI-C.

12.3.3 Strauss-Carpenter Level of Functioning (LOF) scale

The LOF has been widely used as an instrument to evaluate clinical outcome in patients with schizophrenia (Strauss and Carpenter, 1977). The LOF is a semi-structured, clinician-administered scale containing nine items and requires approximately 15 to 20 minutes for completion. The individual items fall into four domains, with higher scores on a 5-point scale (0 - 4) reflecting better functioning. The subscales are Social Contacts (frequency and quality of social contacts), Work (quantity and quality of useful work), Symptomatology (absence of symptoms and recent hospitalization), and Function (ability to meet basic needs, fullness of life, and overall level of function). Subscale scores 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. Inter-rater reliability has been demonstrated, and the instrument has been shown to be sensitive to subtle changes in functioning and treatment effects over time. The LOF will be conducted at Baseline (Day 0) and on Day 29 (or at early discontinuation).

12.3.4 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 (Vernon et al, 2010). The patient's response to the question "Overall, how satisfied are you with your current antipsychotic medication(s)?" is rated by the clinician as follows: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = somewhat dissatisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat satisfied, 6 = very satisfied, and 7 = extremely satisfied. The scale has been shown to be a reliable and valid instrument for assessing antipsychotic treatment satisfaction. It has been used previously in a large placebo-controlled study comparing antipsychotic treatments in patients with schizophrenia experiencing an acute exacerbation, and was able to show a statistically significant difference between treatment groups in satisfaction with the medication (Potkin et al, 2006). The MSQ 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.

12.3.5 Rater Training

All raters in this study must have demonstrated competence in administering scales used in clinical trials. Raters must be trained and certified for the PANSS and CGI-S/C using the Newron specialized website and its training program. These ratings must be completed by separate raters for individual patients. The same rater must perform all the ratings for a given patient throughout the study; this applies to both the PANSS and CGI raters.

Raters for the PANSS will have a minimum of a Master of Science (MS or equivalent) degree in psychology or psychiatry or Bachelor of Science (BS or equivalent) degree in psychiatric nursing. In addition, they must have experience in working with persons with schizophrenia for at least 2 years, and at least 2 years' experience in rating the PANSS. Raters of the CGI-C/S must be clinicians who have had at least 3 years' experience in treating patients with schizophrenia. New raters must receive in-field training (co-rating with current rater, until he/she shows competence in administering scales on their own) and have been certified as defined by this study.

Certification of PANSS and CGI ratings for this study will involve the following:

- Review and rating of a patient video provided by the Sponsor via the Internet, and following their rating, listening to an expert's review of the patient.
- Review and rating of a video of a second patient, followed by general discussion led by an expert rater that will focus on the purpose, rules for administration, overview of some items, and scoring. This video scored by an expert group will be used for certification.

If a potential rater is not certified initially, remedial training will be given. If the rater does not meet rater qualification criteria, despite this training, the Principal Investigator will be contacted and asked to identify an additional rater at the site. This additional rater will also need to go through the training and qualification process described above. Videotapes will be made available to study sites for improving performance of raters using the Internet, and pre-scored.

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

If a rater is not going to be present to conduct a scheduled assessment, another qualified rater who is familiar with the patient and can be present for the rating at the prior visit should conduct the assessment. For the CGI-S/C, the substitute rater should carefully review the notes from the baseline interview, prior to interviewing and rating the patient.

12.4 Exploratory Measures

12.4.1 Polymorphism in CYP2D6 Metabolism

The debrisoquine hydroxylation polymorphism is the most commonly studied genetic polymorphism of the Cytochrome P450 2D6 enzyme (CYP2D6). The CYP2D6 enzyme is involved in the metabolism of a number of widely used drugs, including antipsychotics, antidepressants and β-blockers. Two debrisoquine hydroxylation phenotypes have been defined, "poor" and "extensive" metabolizers, based on the metabolic ratio, i.e., the ratio of the molar concentration of unchanged debrisoquine to that of the 4-hydroxydebrisoquine metabolite in the urine (Llerena et al, 2009; Zhou 2009).

Recently, genotyping has replaced the debrisoquine assay for identifying metabolic phenotypes for CYP2D6. 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 (Crews et al, 2014; Stingl and Viviani, 2015).

The purpose of including this assessment in the current study 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.

13 REPORTING SAFETY INFORMATION

13.1 Adverse Events

Adverse Event evaluations will be performed during the screening period, at baseline and at each visit of the study. Untoward medical events will be collected, from the time of signing of Informed Consent to the end of the safety follow-up period (7 days after the final dose of study medication). All Adverse Events will be recorded in the CRF. In addition, all subjects will be followed up for 30 days after their last dose of study medication for the occurrence of any Serious AE.

13.1.1 Glossary

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at last a reasonable possibility, i.e., the relationship cannot be ruled out.

Adverse Event (AE)

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

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., an event which, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred (it does not include an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child),
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

In addition, hospitalizations for pre-planned medical procedures identified prior to study entry will not be reported as SAEs. Similarly, hospitalizations for respite care of the patient or other reasons that are unrelated to worsening of symptoms will also not be considered as SAEs. However, extensions of hospital stays due to worsening of symptoms or newly occurring severe adverse events will be reported as SAEs. Symptoms or medically significant laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, should not be considered an adverse event. However, occurrence of new symptoms or laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, are considered adverse events.

If an SAE is identified, appropriate follow-up should be obtained to assist in understanding the event. This would include, but not be limited to 1) a plasma blood level of the study drug obtained as soon as possible after the event, with documentation of time of prior dosing; 2) additional follow-up relevant to the event, e.g., ECG and cardiology consult for a cardiac event, or EEG and neurological consult for a seizure.

Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Non-Serious Adverse Event

A non-serious adverse event is any adverse event that does not meet the criteria listed above for a serious adverse event.

Treatment-Emergent Adverse Events

Adverse events that are newly occurring or worsened in severity after the first administration of the study medication are considered to be treatment-emergent AEs (TEAEs).

13.1.2 Data Collection

For each event, record the following information on the Adverse Event section of the Case Report Form:

- **Classification of the Event:** Classify the event as either serious or non-serious
- **Description of Signs or Symptoms:** Whenever possible, record a specific diagnosis for the event. If a diagnosis cannot be made, then record each sign or symptom separately, e.g., record nausea and vomiting as two events. If multiple episodes of an event occur, separated by an appropriate time interval to justify considering the subsequent episodes as a repeat occurrence, record each episode separately on the Case Report Form.
- **Onset Date and Time:** Record the date and time the event started. If a change from baseline/previous evaluation in a laboratory test is reported as an adverse event, record the start date as the date of collection of the first lab sample that shows the change.

Stop Date and Time: Record the date and time the event resolved. If a change from baseline/previous evaluation in a laboratory test is reported as an adverse event, record the stop date as the date of collection of the first sample that shows a return to the previous level.

Intensity:

1. **Mild:** Event not resulting in disability/incapacity, which resolves without treatment.
2. **Moderate:** Event not resulting in disability/incapacity, which requires treatment.
3. **Severe:** Event resulting in temporary and mild disability/incapacity, which requires treatment.

Relationship to the Study Agent: Every effort should be made to determine the cause of each adverse event. The correlation between the study agent and the adverse event should be classified as follows:

1. **Probable**
   a) The event follows a reasonable temporal sequence from administration of the study agent;
   b) The event follows a known response pattern to the study agent;
   c) The event cannot be reasonably explained by:
      - the known characteristics of subject's clinical state, or
      - by other therapy administered, or
      - by the diagnostic/interventional procedure;
   d) There is evidence of partial or complete disappearance of the event after withdrawal of the product (positive de-challenge)

2. **Possible**
   a) The event follows a reasonable temporal sequence from administration of the study agent;
   b) Causation of the event by the study agent cannot be excluded;
   c) The event follows a known response pattern to the study agent but the event could have been produced by:
      - the subject's clinical state, or
      - other therapy administered, or
      - a diagnostic/interventional procedure.

3. **Unlikely**
   a) The adverse event follows a reasonable temporal sequence from administration of the study agent;
   b) Other reasons are more likely to be the cause of the adverse event, based on the present knowledge of the
      - disease under treatment, or
      - other therapy administered, or
      - study drug;
   c) A causal relationship between the adverse event and the study drug can't be ruled out with certainty.

4. **Not Related**
   The event is either a pre-dose event or is definitely due to causes separate from the administration of the study agent, i.e.,
      - documented pre-existing condition
      - technical and manual procedural problems
      - concomitant medication
      - subject's clinical state.

Action Taken in Relation to the Adverse Event:

i. **None**

ii. **Drug treatment required** (a medication was prescribed or changed; record on the Concomitant Medication section of the Case Report Form)

iii. **Change in dose of concomitant medication**

iv. **Non-drug treatment required** (a non-drug treatment was prescribed or changed, record under "Comments" in the Adverse Event section of the Case Report Form)

v. **Hospitalization or prolonged hospitalization**

vi. **Diagnostic or clinical test(s) conducted** (attach a copy of the results to the Case Report Form)

vii. **Subject discontinued from the study**

Action Taken with the Study Medication:

i. **Study medication dose interruption**

ii. **Study medication dose reduction**

iii. **Study medication discontinuation**

iv. **None**

Subject Outcome:

1. **Recovered without sequelae**
2. **Recovered with sequelae** (describe the sequelae under "Comments" in the Adverse Event section of the Case Report Form)
3. **Not Recovered, event on-going** (follow the subject until a definite outcome can be determined. When follow-up data are collected, report follow-up information under "Comments" in the Adverse Event section of the Case Report Form; if event is serious, fill in a follow-up Serious Adverse Event Report)
4. **Died** (list primary cause of death under "Event Description" of the Adverse Event section of the Case Report Form; if available, attach a copy of the autopsy report to the Case Report Form and send a copy to the Sponsor)

Comments:

Provide other pertinent clinical information and observations under "Comments" in the Adverse Event section of the Case Report Form. For example, record predisposing or contributing conditions, such as previous history, concomitant diseases or medications, and/or procedural risks.

13.1.3 Subject Follow-up

Every attempt should be made to follow the subject until the adverse event has resolved or until the Investigator determines the subject has returned to an acceptable state of health.

13.1.4 Reporting Serious Adverse Events

The Investigator must report **all Serious Adverse Events within 24 hours**, irrespective of the relationship to study medication, to the CRO, by telephone or by fax. The CRO will then forward this information to Newron within 24 hours of receipt. The names of the CRO contact will be communicated to the investigators by the CRO prior to the start of subject enrollment.

The minimum information required for an initial report of a Serious AE is as follows:

- Sender of report (name, address of Investigator, site number),
- Subject identification (subject number),
- Protocol number,
- Reportable event.

In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the CRO, and the Serious AE section of the AE Form completed in the eCRF. If an autopsy is performed, a copy of the autopsy report should be actively sought by the Investigator and sent to the CRO as soon as available. A copy of the autopsy report will be retained on-site.

A follow-up Serious Adverse Event Report will be completed by the Investigator if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow-up form will be sent to the CRO as described above.

If the Investigator becomes aware of any deaths or Serious Adverse Events after the end of the 30-day follow-up window established in the protocol following investigational product administration, they will be reported to the CRO as described above.

13.1.5 Safety Reporting to Investigators, IRBs, ECs and Regulatory Authorities

The Sponsor or their designee will be responsible for reporting all SAEs to regulatory authorities, investigators, Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs), as applicable, in accordance with national regulations. For all active investigators located in the United States, the Sponsor or their designee will prepare an expedited report for all SAEs that are unexpected and potentially related to the study drug, and copies will be distributed according to all applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to their IRB.

Any AE or SAE attributed to another concomitant medication used in this study should be reported to the responsible company by the PI according to the MedWatch or CIOMS procedures customary for that country.

13.1.6 Reporting of Overdose (based on Newron safety reporting standards)

Procedure to be followed in the US

If the investigational site staff administering the study medication, the caregiver, or the subject reports that a subject inadvertently took more than the requisite number of capsules or a higher dose than was assigned, this will be considered an overdose and must be reported immediately to the Investigator. In addition, if the study Pharmacist notes a significant discrepancy, based on pill counting of returned medication (i.e. 2 or more fewer capsules were returned than expected, based on the dosing period), indicating that the patient may have taken more than twice the number of capsules prescribed as an individual dose, the Investigator should attempt to determine the possible cause for the discrepancy. For example, the missing medication may have been lost, damaged, diverted to another patient, or mistakenly discarded. If the cause of the

discrepancy is identified, and is not the result of the patient deliberately taking more capsules than prescribed, the event will not be considered an overdose.

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

Procedure to be followed in India

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

13.1.7 Breaking of the Study Blind by the Investigator

The blind should be broken by the Investigator only in the case of emergency and if knowledge of the administered compound is deemed necessary for the medical treatment of the subject. The Investigator will be able to break the blind through the IWRS. If possible, the Medical Monitor or Sponsor should be contacted before the study drug blind is broken. If the blind is broken, the Investigator must immediately notify the CRO and provide the subject's number. The reason for breaking the blind should be noted on the Adverse Event (or Serious Adverse Event) section of the CRF. Newron will inform the Safety Monitoring Board of the unblinding.

13.1.8 Pregnancy

Women of child-bearing potential, who are not using a contraception method judged to be adequate by their Health Care Provider, will not be eligible for the study. Adequate contraception should be continued until 30 days after stopping study medication. As a further precaution, 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 have had a tubal ligation], at Screening and Baseline, and on Day 29 (or at early discontinuation). The results of the serum test at Screening must be available before Baseline. In addition, urine pregnancy tests will be performed at Screening and Baseline for an immediate result to determine eligibility for the study; the results of the serum test will be used for confirmation. Additional serum or urine pregnancy tests may be performed, as needed, based on local requirements.

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

13.2 Independent Safety Monitoring Board

An independent board of knowledgeable experts appointed by Newron will safeguard subjects participating in evenamide trials by reviewing unblinded safety data on an ongoing basis during the conduct of the new trials (Phases I-III) that constitute the evenamide schizophrenia development program, including the current Study 008. Other trials may be added to meet the needs of the development program. The main reasons for Newron to constitute the formation of this Independent Safety Monitoring Board (ISMB) are 1) the limited human safety data generated to date for evenamide, 2) high base rates of major safety events in the underlying population, and 3) susceptibility of the study population to safety risk because of their underlying diseases.

The ISMB will be comprised of at least 3 voting members. All of these members will be clinicians who have extensive experience in the treatment of patients with mental disorders, and may have participated in other ISMBs. Ravi Anand, MD, Newron's Chief Medical Officer, will serve as the Sponsor's representative and primary contact for the ISMB.

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

Based on their review of the safety data, the ISMB will make a recommendation to Newron to (a) amend the ongoing study (e.g., increase safety monitoring), (b) terminate the study (e.g., the evenamide safety profile is unacceptable), or (c) continue the study as designed. The current study protocol will not be amended or changed (this includes the study design and entry criteria) unless mandated by the emerging (unblinded) safety profile of evenamide. The Sponsor's representative will make the decision to accept or reject the ISMB's recommendation and may request access to unblinded study data in order to make an informed decision.

The ISMB will review data from all patients enrolled at specified intervals throughout the trial. The ISMB will receive unblinded data; however, the blind will be maintained to the investigators, Sponsor, and CRO until after the final analysis has been completed. The CRO and Sponsor will compile subject data by treatment group and provide it to the ISMB at regular intervals. The ISMB will have access to safety data, including adverse events, dropouts, SAEs, clinically significant abnormal laboratory tests, vital signs and ECGs. The ISMB will be regularly notified of the occurrence of any fatal/life threatening event within 24 hours of Newron becoming aware, and other SAEs within 72 hours. The ISMB will also receive detailed information on any adverse dropouts occurring in the study.

The ISMB is empowered to review all of the safety data on an ongoing basis, with special emphasis on SAEs and deaths, in addition to the standard safety parameters. Details of the ISMB charter (separate document) will be submitted to regulatory authorities, and will be available to IECs/IRBs upon request.

14 SUBJECT COMPLETION AND DISCONTINUATION

A subject will be considered to have completed the study when he/she returns for the final evaluation on Day 29, or the safety follow-up assessment on Day 35 (7 days after the last dose of study medication), if the patient completed 28 days of treatment. 'Discontinuation' will refer to any subject who does not complete the full 28-day randomized treatment period of the study, exclusive of missed doses during the period.

In the absence of a medical contraindication or significant protocol violation that puts the subject at risk, every effort should be made by the Investigator to keep the subject in the study; however, should the subject be withdrawn, all efforts will be made to complete and report the observations as thoroughly as possible, including post-treatment evaluation at the time of the subject's withdrawal, with an explanation of why the subject is withdrawing from the study. Dropouts will not be replaced.

The criteria for discharging a subject from the study prior to Day 29 are listed below. A subject should be considered for discontinuation from study participation if:

- the subject experiences any moderate/severe hypersensitivity or allergic reaction, clearly linked to the study medication;
- the subject's schizophrenia symptoms worsen to such an extent that, despite therapeutic measures such as multiple administrations of rescue medication (see Section 11.5) for 7 days or more, the patient continues to worsen, and/or requires hospitalization;
- the subject experiences an AE sufficiently severe, in the opinion of the investigator, that it contraindicates continuing in the study;
- the subject wishes to withdraw; in this instance, a specific reason (e.g. subject is unwilling to attend the scheduled clinic visits) must be recorded by the Investigator;
- the subject is afflicted with a systemic illness, unrelated to the study medication, during the study treatment period, for which a prohibited concomitant medication is required and could put the patient at risk for further participation in the study;
- the subject is not adhering to the protocol requirements, and continued participation poses a significant risk to the subject's health;
- the subject is lost to follow-up, i.e., the subject did not return to the clinic, and attempts to contact the subject were unsuccessful. For the subject to be considered as 'lost to follow-up', the site must have made at least 3 unsuccessful attempts to contact the patient and/or his/her caregiver by registered mail; attempts to contact the subject must be fully documented;
- the Sponsor, Institutional Review Board/Ethics Committee (IRB/EC), or regulatory agency terminates the study.

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

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

14.1 Procedures for handling withdrawals

The Investigator may terminate a subject's study participation at any time during the study if a subject meets the study termination criteria described above in Section 14. In addition, a subject may discontinue his/her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded. An attempt should be made to perform all final (Day 29) assessments on the subject, as well as the safety follow-up evaluation 7 days after the final dose of study medication, and to follow up on any safety issues until resolution.

Subjects who discontinue prematurely, as well as those subjects completing the study, should be followed up for 30 days after the last dose of study medication regarding the occurrence of any Serious Adverse Events (this information can be collected through a telephone contact).

15 PHARMACOKINETIC AND STATISTICAL METHODS

15.1 Pharmacokinetics and Determinants of Pharmacokinetic Variability

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 using a validated LC-MS/MS method (see Section 11.2.2). Appropriate pharmacokinetic parameters for each dose level of evenamide will be calculated using non-compartmental methods, e.g. $C_{max,}$ t_{max}, $t_{1/2}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The derived pharmacokinetic parameters will be listed and plotted by subject/analyte and summarized by treatment.

Additional plasma samples will be collected at Baseline for measurement of plasma levels of the concomitant atypical antipsychotics, which all patients will be taking. These data will be used only to aid in assessing adherence with dosing prior to entering the treatment period of the study, and no pharmacokinetic analyses will be performed.

15.2 Statistical methods

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 7.5 mg and 15 mg, *bid* (15 and 30 mg/day) in outpatients with chronic schizophrenia. The main objective of this study is to evaluate the safety and tolerability (including EEG and ECG effects) of two fixed doses of evenamide of 7.5 mg *bid* and 15 mg *bid* as add-on treatment in patients with established schizophrenia on a stable dose of an atypical antipsychotic. In addition, efficacy endpoints will be evaluated to provide evidence of efficacy for evenamide, compared with placebo.

15.2.1 Sample size and power considerations

Approximately 120 patients with schizophrenia will be included in this study, with approximately 40 patients randomly assigned (1:1:1) to receive evenamide doses of 7.5 or 15 mg *bid,* or matching placebo *bid*. 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.

15.2.2 Populations

The Safety population will consist of all subjects who take at least one dose of study medication. The efficacy analyses will be performed on a modified Intent-to-Treat (mITT) population comprising all patients who have a baseline efficacy assessment, receive at least one dose of the study medication, and have at least one post-baseline efficacy assessment.

15.2.3 Background and demographic characteristics

The background and demographic characteristics (age, race, ethnicity, weight, height, smoking history, education, marital status, employment, housing status, past and current medical conditions, etc.) and disease characteristics (severity of illness, duration of illness, concomitant psychotropic medication, etc.) of enrolled patients will be summarized by treatment group. Continuous variables will be summarized by minimum, maximum, mean, median, and standard deviation, and discrete variables will be summarized using frequencies and percentages.

15.2.4 Study medication

The number of subjects receiving each dose level of evenamide, or placebo, and the number of capsules taken, as well as overall adherence, will be reported.

15.2.5 Concomitant therapy

A listing of concomitant medications administered from the time of the first dose of the study medication through completion of the final (Day 29) evaluations will be summarized by treatment group.

15.2.6 Safety analysis

The safety population will be used for the analysis of all safety variables. All AEs will be summarized by body system and preferred term. The incidence (%) of SAEs, AEs that are newly occurring or worsened after administration of study medication (i.e. treatment-emergent AEs [TEAEs]), and AEs leading to discontinuation (ADOs), will also be summarized; the severity of each AE and relatedness to study medication will be assessed and presented. Changes from baseline at each visit and at endpoint (Day 29 or early discontinuation) in 3 per second EEG spike and slow wave activity (as provided by a trained clinician reviewer), vital signs, ECG and laboratory values, and physical/neurological examination and eye examination findings vital signs, ECG and laboratory values, and physical/neurological examinations and standard eye examination findings will be summarized, with abnormal and clinically notable values/findings being identified. A comparison will be made between the evenamide and placebo groups in the proportion of patients experiencing SAEs, ADOs, TEAEs and any clinically significant abnormalities in other safety parameters. Mean changes from baseline in the total score and sub-scale scores on the ESRS-A will be presented. Descriptive statistics will be provided for the C-SSRS and CDSS.

15.2.7 Efficacy analysis

Descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum) will be provided for all continuous efficacy measures for actual values and changes from baseline at each time-point. For categorical variables, the number and percentage of patients in each category will be presented at each time-point. 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.

If patients show significant worsening, the investigators can take whatever measures they deem necessary, e.g. administration of rescue medication. Investigators will be requested to perform all efficacy assessments prior to the intervention, and these will serve as the final assessments for analysis purposes. Subjects will be allowed to continue treatment with evenamide after the intervention, and all post-intervention efficacy data will be collected, but will be censored in some analyses. Dose adjustments for atypical antipsychotics of 25% or less, upwards or downwards, are permitted for efficacy or safety reasons without triggering these measures. Changes in the dose of the primary antipsychotic drug greater than this will trigger the performance of all final (Day 29) safety and efficacy measures and censoring of subsequent data in selected analyses.

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 15-mg *bid* dose group versus placebo will be analyzed first for the primary and key secondary efficacy endpoints followed by the comparison of the 7.5-mg *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 7.5-mg *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.

Efficacy endpoints

The primary and key secondary efficacy endpoints, mean changes from baseline to endpoint (Day 29 or early discontinuation) on the PANSS total score and the CGI-S score, respectively, will be compared between the evenamide groups and the placebo group 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. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger 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.

A 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. 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. Further details of the imputation methodology will be provided in the Statistical Analysis Plan.

Demonstration of a statistically significant improvement from baseline to endpoint on the PANSS total score for evenamide, compared to placebo, would provide a signal of efficacy and benefit as adjunctive therapy in patients showing inadequate response to a stable dose of a single atypical antipsychotic.

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, patients will be excluded if the Baseline (Day 0) value is a greater than 10% improvement from the Screening value. If the Baseline (Day 0) value is missing, the screening assessment will be used unless it was performed more than 21 days before baseline. If the Baseline (Day 0) value is missing, and the screening score cannot be used, a PANSS assessment performed within one hour of the first dose may be substituted.

Exploratory efficacy endpoints will be analyzed to compare the evenamide and placebo groups, with no adjustment for multiplicity. Mean changes 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). Similar analyses will be performed for the MSQ. The LOF will be analyzed based on comparisons of baseline and last assessment on study drug. 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). In addition, the mean score at endpoint for the CGI-C will be compared using ANOVA. '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 from baseline to endpoint on the PANSS total score and the PANSS Positive Symptoms sub-scale.

The planned efficacy analyses will be described in detail in a separate Statistical Analysis Plan.

15.2.8 Interim analysis

No interim analysis is planned for this study.

16 ETHICS

16.1 Ethical Considerations

The study will be carried out in accordance with the Declaration of Helsinki, as amended by the 64th General Assembly of the World Medical Association, Fortaleza Brazil, 2013 (Appendix 1A). However, where applicable, the principles of the 1996 version of the Declaration of Helsinki will be adhered to (Appendix 1B).

Subject Information and Informed Consent

The Informed Consent Form, as well as the Subject Information Sheet must be approved by the IRB or IEC, together with the Study Protocol, before the start of the study.

All subjects must sign and personally date an approved Informed Consent Form after receiving detailed written and verbal information about the reason, the nature, the required procedures, the intended duration and the possible risks and benefits and any discomfort associated with the study.

He/she should be informed that the subject's participation in the study is voluntary and that he/she may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

The language used in the oral and written information about the trial, including the written Informed Consent Form, should be as non-technical as practical and should be understandable to the subject.

The subject must be given ample time to read and to understand the Subject Information Sheet and opportunity to inquire and ask any clarification about the trial before signing the Informed Consent Form.

No study procedure can be performed (including the screening visit) before the informed consent form has been signed. The informed consent procedure must be done according to the guidelines provided in the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

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

By signing the Investigator Statement (Appendix 3), the Investigator assures Newron Pharmaceuticals that Informed Consent will be obtained.

Original signed Informed Consent Forms will be filed with the Investigator's File.

16.2 Institutional Review Board / Independent Ethics Committee Approval

The protocol, Investigator's Brochure, Subject Information Sheet, Informed Consent Form and any advertisement for the recruitment of subjects must be reviewed and approved by an appropriately constituted IRB/IEC, as required in Chapter 3 of the ICH E6 Guideline. A copy of the Committee's dated approval and a list of the members of the IRB/IEC will be given to the Sponsor for the Sponsor's files. A copy will be also included in the Final Report. Written IRB/IEC approval must be obtained by the Sponsor prior to shipment of study agent or subject enrollment. Any amendments to the protocol, Informed Consent Form or Subject Information Sheet, other than administrative ones, must be approved by this committee.

17 ADMINISTRATIVE CONSIDERATIONS

17.1 Regulatory Requirements–Sponsor/Investigator Obligations

This study will be conducted in accordance with the Declaration of Helsinki and the ICH E6 Guideline (Good Clinical Practice). To ensure compliance, the Investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation, including subjects' hospital files (the source documents), by authorized individuals.

17.2 Curriculum Vitae

The Investigator and any co-Investigator(s) must provide the Sponsor with current copies of their own curriculum vitae.

17.3 Investigators and Study Administrative Structure

The administrative structure of the study (e.g., Investigators, monitoring and evaluation personnel, laboratory facilities, clinical trial supply management) is presented in the Trial Master File.

The listing should include:

a) The Investigators;

b) Any other person(s) carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist or house staff physician.

17.4 Investigator's Statement

This document, signed and dated by the Principal Investigator, describes the Investigator's obligations. The standard text is appended to the protocol (Appendix 3).

17.5 Monitoring Procedures

17.5.1 Study Monitoring

A CRO will be selected by the Sponsor to oversee the conduct of the trial. An appropriate representative of the CRO (Study Monitor) will maintain contact with the Investigator and will visit the study site for the purpose of discussing and/or retrieving data. An initiation (pre-study) visit will be made by the Study Monitor to discuss with the Investigator the protocol and the obligations of both the Sponsor and the Investigator. The Investigator must allow the Study Monitor to perform periodic, interim monitoring visits. The purposes of these visits are:

- To verify that written Informed Consent was obtained prior to each subject's participation in the trial.
- To assess the progress of the study.
- To review the compliance with the study protocol.
- To determine whether all adverse events were appropriately reported.
- To determine whether the Investigator is maintaining the essential documents.
- To discuss any emergent problem.
- To check the Case Report Forms for accuracy and completeness.
- To validate the contents of the Case Report Forms against source documents.
- To assess the status of drug storage, dispensing and retrieval.

The Investigator will make available the source documents for inspection. This information will be considered as confidential. *Violations and deviations to the protocol must be notified to the Study Monitor as soon as possible.*

The Study Monitor will perform a closeout visit at the time when all CRFs have been completed and all queries have been answered.

17.5.2 Case Report Form

All subject data generated during the study will be recorded on the electronic Case Report Form (eCRF). The eCRF must be completed for all subjects who sign Informed Consent. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data. No section of the eCRF is to be left blank without an appropriate explanation by the Investigator, since the lack of such explanation may necessitate discarding an otherwise usable observation.

Paper copies of the eCRFs for the patient rating scales (e.g. PANSS, CGI, LOF, ESRS-A, C-SSRS and CDSS) may be printed and used by the Investigator or designated staff during the assessment of the patient. Data recorded on these paper forms must be transcribed into the eCRF, and the original forms stored in the patient's file as source documents.

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

The eCRFs will only be considered complete when each eCRF has been reviewed and electronically confirmed by the Investigator, indicating his/her assurance of the accuracy of all recorded data. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

17.5.3 Auditing/Inspecting

The Investigator will make all pertinent records available, including source documentation, for inspection by regulatory authorities and for auditing by the Sponsor. This information will be considered as confidential. Audits/Inspections may occur any time from start to after conclusion of the study. When an Investigator signs the protocol, he/she agrees to allow regulatory authorities and Newron auditors to inspect his/her study records.

17.6 Archiving of Records

Copies of the protocol, subject identification codes, Case Report Forms, source data, Informed Consent Forms and other documents pertaining to the study conduct must be kept for the maximum period of time as required by the study center, or local country requirements. This time period must be at least two years after the last approval of the marketing application of the study agent in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the study agent.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Originals of all documentation and copies of outgoing correspondence concerning the study will be stored and retained by the Sponsor in a safe area in the Trial Master File for the lifetime of the product. In particular, the final report must be retained by the Sponsor, or the subsequent owner, for five years beyond the lifetime of the study agent.

17.7 Final Report

The Final Study Report will be written by the CRO, according to specifications to be defined by Newron.

17.8 Study Documentation and Publication of Study Results

Study Documentation

All unpublished documentation (including the protocol, Case Report Form and Investigator's Brochure) given to the Investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person not connected with the study without the prior written authorization of Newron Pharmaceuticals. The submission of these documents to the IRB/IEC is expressly permitted. The involved parties agree that the results of this study will be used in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

All information communicated to the investigator(s) by Newron is the exclusive property of Newron Pharmaceuticals S.p.A. The Principal Investigator will ensure this information shall be kept strictly confidential by him/her or any other person connected with the study and shall not be disclosed to any third party without the prior written consent of Newron.

Publication of Results

Any formal presentation or publication of the data from this trial will be considered as a joint publication by the Investigator(s) and Newron. Authorship will be determined by a Publication Committee consisting of the lead investigator(s) from the trial, representatives from Newron, and an external consultant with expertise in the field. For multi-center studies, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol by a statistician designated by Newron. Investigators participating in this study agree not to present or publish data gathered from a single center or sub-group of centers before the full initial publication, unless agreed to by all other investigators and Newron. Authorship of any publications resulting from pooled data will include members of each of the contributing centers, as well as Newron personnel.

Newron will form a study publication committee to coordinate and develop a publication policy and help in its implementation. The publication committee will be comprised of the Principal Investigator(s), a representative of Newron and an external consultant. Members of the publication committee cannot serve as first authors of more than one primary publication.

Any publication, abstract, or paper of any information or material relating to or arising out of the present clinical study shall be sent to Newron for review at least sixty (60) days before presentation at any congress, or publication of the final form(s) by any journal. Newron will inform the Investigator of any changes or deletions necessary to preserve Newron’s confidential and proprietary technical information. All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights, which arise during the course and/or as a result of the present clinical study or which arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of Newron Pharmaceuticals S.p.A.

17.9 Financial Agreement

A financial agreement (separate from the protocol) will be made and signed by Newron Pharmaceuticals or their designee and by a representative of the Institution where the study will be conducted.

17.10 Termination of the Study

In the event that the Investigator is unable to continue the study, another suitable sub-Investigator at the site will be designated to serve as the Investigator in the interim, until a new Investigator can be identified. This interim Investigator, if approved by the site IRB/IEC will carry out the responsibilities of the Investigator. Documentation testifying to this will be submitted to the Study Monitor within 10 days of the change. Within 6 months of the appointment of the interim Investigator, the new Principal Investigator must be identified and approved by both Newron Pharmaceuticals and the IRB/IEC for the study to continue at the site.

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the Investigator terminates the study, an explanatory letter will be provided to Newron Pharmaceuticals. Should the study be discontinued due to a decision by Newron Pharmaceuticals, the Investigator will be reimbursed for reasonable expenses incurred and for the subjects actually treated according to the study protocol.

17.10.1 Study discontinuation by the Sponsor

The Sponsor may terminate the entire study, or the study at an individual site, at any time, for any of the following reasons:

- failure to enroll subjects;
- protocol violations or deviations;
- inaccurate or incomplete data;
- non GCP compliance;
- completion of enrollment;
- administrative reasons.

17.10.2 Study discontinuation by the Clinical Investigator

The Investigator may terminate his/her participation in the study in consultation with the Sponsor due to the occurrence of significant adverse events and/or adverse drug reactions endangering the health of subjects, which make it ethically unacceptable to continue.

17.11 Insurance Policy

Newron or its designee will provide insurance coverage for damages emerging from the trial and involving the subjects treated with the test compound, provided that the Investigator(s) have adhered to the terms and provisions of the protocol. The principal Investigator will be supplied with all data concerning the insurance company and policy number for a maximum sum insurable.

17.12 Financial Disclosure

The study will be performed under a US IND; therefore, all Investigators/sub-Investigators, contractors, etc., are expected to comply with the obligations for studies conducted with FDA oversight, as specified in the US Code of Federal Regulations (21 CFR parts 312 and 54), including requirements for full Financial Disclosure (Guidance for Clinical Investigators, Industry and FDA Staff: Financial Disclosure by Clinical Investigators, 2013).

The Principal Investigator and sub-Investigators will provide the Sponsor with adequate and accurate financial information to ensure that the Sponsor can make complete and accurate financial certification of disclosure statements to concerned regulatory authorities. It is the duty of the Investigator to promptly update previous information provided to the Sponsor if there are salient changes that occur during the course of the study, and for a period of one year following its completion (last patient last visit).

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19 APPENDICES

19.1 APPENDIX 1: Declaration of Helsinki

Appendix 1A: 2008 Version of Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continual y through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

19. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

20. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

21. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

22. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

24. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

25. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

26. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

30. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

31. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

33. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

34. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

35. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

36. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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Appendix 1B: 1996 Version of Declaration of Helsinki

World Medical Association Declaration of Helsinki:
Recommendations Guiding Medical Doctors in
Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989, and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated the fulfilment of this mission. The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civic and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interest of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH CLINICAL CARE
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

19.2 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	°C	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.

19.3 APPENDIX 3: Investigator Statement

Investigator Statement

Compound:	Evenamide (NW-3509)
Protocol Number:	NW-3509/008/II/2019
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.
Trial Center Number:	
Principle Investigator:	
Address:	
Telephone:	
Fax:	
Email:	

COMMITMENTS

By signing this document, I agree to conduct the trial as outlined in the protocol and in accordance with (as applicable) the Declaration of Helsinki, the ICH GCP Guideline as well as all applicable government regulations.

I declare:

1. I am well qualified by scientific training and experience to conduct investigational studies in the clinical area of the proposed trial and I am affiliated with a recognized medical school or with an independent institution recognized for its excellence.
2. I have received and understood the information about pharmacology, toxicology and possible risks and side effects of the investigational compound (e.g., as described in the Investigator's Brochure).

3. I shall provide information to all staff members involved in the trial about their obligations as described in this document.
4. I shall submit the protocol, Informed Consent form/subject information sheet and other required documentation to the IRB/IEC for review and approval.
5. I shall make no changes to the protocol without formal amendment (prepared in agreement with the Sponsor), except when necessary to protect the safety, the rights or welfare of subjects. In this last case I will inform the Sponsor of the change.
6. I shall require Informed Consent from each subject prior to enrollment into the study. The Informed Consent shall be documented by use of a written consent form approved by the Sponsor and the IRB/IEC.
7. I shall use the investigational compound only in compliance with the trial protocol and I shall be responsible for the security and accountability of clinical study supplies.
8. I shall notify NEWRON immediately or no later than 24 hours by telephone and/or by fax of serious or unexpected adverse events and submit written reports of adverse events, as outlined in the protocol, to NEWRON, the IRB/IEC and to Regulatory Authorities (when appropriate).
9. I shall complete the Sponsor's Case Report Form (CRF) in a timely and legible manner.
10. I shall maintain accurate source records (hospital or other institutional records), which will support the data entered into Case Report Forms and I shall maintain these as specified in the protocol.
11. I shall allow monitoring visits by NEWRON's representatives at predetermined frequency.
12. I shall allow the authorized Sponsor representative and any Regulatory Authorities to inspect the facilities and pertinent records at reasonable times and in a manner which ensure subject confidentiality.
13. I shall maintain confidentiality about all information concerning the investigational compound, such as patent applications, formulas, manufacturing process, basic scientific data and formulation information supplied by the Sponsor and not previously published and I shall not disclose this information to a third party without the written consent of the Sponsor.
14. I shall permit the information developed in the clinical trial to be used by the Sponsor in connection with the development of the compound and may be disclosed to the IRB/IEC and Regulatory Authorities.

Following completion of the study, the data may be considered for reporting at a scientific meeting and/or for publication in a scientific journal. A copy of the manuscript or abstract will be provided to the Sponsor for review before submission to a scientific journal for publication and/or a scientific meeting selection committee for oral or poster presentation. Subgroup or individual Investigator publications must not interfere or compromise publication of the multi-center results of this clinical trial.

_____ _____

Investigator Signature Date

_____

Investigator (Printed Name)

19.4 APPENDIX 4: Symptoms and Signs Suggestive of Seizures

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

- seizure,
- fit,
- jerk,
- jerky movements,
- startle,
- convulsion,
- absence seizure,
- gazing,
- staring,
- fall,
- fainting,
- syncope,
- auditory/visual aura,
- myoclonus,
- automatism,
- unconsciousness,
- biting of tongue.

19.5 APPENDIX 5: Absolute Neutrophil Count (ANC) Monitoring for Patients Taking Clozapine

Severe Neutropenia

Background

Clozapine tablets can cause neutropenia (a low absolute neutrophil count [ANC]), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: ANC equals the Total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil "segs" plus neutrophil "bands"). Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary. Neutropenia may be mild, moderate, or severe (see Table 1 below). To improve and standardize understanding, "severe neutropenia" replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than (<) 500/µL, occurs in a small percentage of patients taking clozapine tablets and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which clozapine tablets cause neutropenia is unknown and is not dose-dependent.

Clozapine Tablets Treatment and Monitoring in the General Patient Population (see Table 1)

Obtain a CBC, including the ANC value, prior to initiating treatment with clozapine tablets to ensure the presence of a normal baseline neutrophil count (equal to or greater than (≥) 1500/µL) and to permit later comparisons. Patients in the general population with an ANC ≥ 1500/µL are considered within normal range (Table 1) and are eligible to initiate treatment with clozapine. However, to participate in the current study (Study 004) patients must have a WBC count of ≥ 3500/µL and an ANC of ≥ 2000/µL.

Weekly ANC monitoring is required for all patients during the first 6 months of clozapine treatment. If a patient's ANC remains equal to or greater than 1500/µL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/µL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Table 1. Clozapine Tablets Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

ANC Level	Clozapine Tablets Treatment Recommendations	ANC Monitoring
Normal range (≥ 1500/µL)	1. Initiate treatment 2. If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient	•Weekly from initiation to 6 months •Every 2 weeks from 6 to 12 months •Monthly (every 4 weeks) after 12 months
	•Discontinuation for reasons other than neutropenia	•See Section 2.4 (Discontinuation of Treatment) of Clozapine Prescribing Information (US)

ANC Level	Clozapine Tablets Treatment Recommendations	ANC Monitoring
Mild Neutropenia (1000 to 1499/µL)*	•Continue treatment	•Three times weekly until ANC ≥ 1500/µL •Once ANC ≥ 1500/µL, return to patient's last "Normal Range" ANC monitoring interval †
Moderate Neutropenia (500 to 999/µL)*	•Recommend hematology consultation •Interrupt treatment for suspected clozapine induced neutropenia •Resume treatment once ANC ≥ 1000/µL	•Daily until ANC ≥ 1000/µL, then •Three times weekly until ANC ≥ 1500/µL •Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval †
Severe Neutropenia (less than 500/µL)*	•Recommend hematology consultation •Interrupt treatment for suspected clozapine-induced neutropenia •Do not rechallenge unless prescriber determines benefits outweigh risks	•Daily until ANC ≥ 1000/µL, then •Three times weekly until ANC ≥ 1500/µL •If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µL

* Confirm all **initial** reports of ANC < 1500/µL with a repeat ANC measurement within 24 hours

† If clinically appropriate

For complete information on the use of clozapine, including ANC monitoring, refer to the full Clozaril® (clozapine) Tablets Prescribing Information (US).