Minerva Neurosciences, Inc.

Clinical Protocol

A Multicenter, Randomized, Double-blind, Parallel-Group, Placebo-Controlled, Monotherapy, 12-Week Study to Evaluate the Efficacy and Safety of 2 Fixed Doses of MIN-101 in Adult Patients with Negative Symptoms of Schizophrenia, Followed by 40-Week Open-Label Extension

Protocol MIN-101C07; Phase 3
AMENDMENT 2

MIN-101

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Original Protocol	03 October 2017
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Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

Title, Protocol Number/Phase

A Multicenter, Randomized, Double-blind, Parallel-Group, Placebo-Controlled, Monotherapy, 12-Week Study to Evaluate the Efficacy and Safety of 2 Fixed Doses of MIN-101 in Adult Patients with Negative Symptoms of Schizophrenia, Followed by 40-Week Open-Label Extension.

MIN-101C07 / Phase 3

Objectives:

Primary

- To evaluate the efficacy of 2 fixed doses (32 mg and 64 mg) of MIN-101 compared to placebo in improving the negative symptoms of schizophrenia as measured by the change in the Positive and Negative Syndrome Scale (PANSS) Marder negative symptoms factor score (NSFS) over 12 weeks of double-blind treatment.

Key Secondary

- To assess the effect of MIN-101 compared to placebo on the Personal and Social Performance (PSP) total score, over 12 weeks of double-blind treatment.

Secondary

To assess the effect of MIN-101 compared to placebo over 12 weeks of double-blind treatment on:

- Clinical Global Impression of Severity (CGI-S).
- Safety and tolerability.

Exploratory

[redacted]

Hypotheses

The primary hypothesis is that after 12 weeks, MIN-101 will be superior to placebo on the change from Baseline in the PANSS Marder negative symptoms factor score.

Study Design

This will be a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study in approximately 501 schizophrenic patients who present with negative symptoms.

Eligible patients will be randomized in equal proportion to receive once daily MIN-101 64 mg, MIN-101 32 mg, or placebo, orally (PO), for 12 weeks. Afterwards, all patients will continue treatment with active drug for an additional 40 weeks. During the 40-week, open-label treatment extension, patients who were initially randomized to MIN-101 64 mg or MIN-101 32 mg will continue treatment with the same dose, while patients who were initially randomized to placebo will crossover to MIN-101 64 mg or MIN-101 32 mg in a 1:1 ratio per the randomization schedule implemented on Day 1 (Visit 4). The Week 12+1 Day onward dose is the extension phase dose.

The 3-phase study will consist of:

Pre-Treatment Phase

- *Screening Period (Visit 1)*, including a Screening visit that should take place no more than 28 days before the first administration of study drug on Day 1 (Visit 4).
- *Washout Period (Visit 2)*, an inpatient washout period starting on Day -2 to allow patients on antipsychotic medications or other psychotropics to be washed out from their previous medications. Patients who did not receive any psychotropics will also be hospitalized on Day -2 before Baseline (Visit 3) in order to standardize study procedures in all patients.
- *Baseline Visit (Visit 3, Day -1),* all inclusion and exclusion criteria will be verified and all assessments will be completed prior to initiation of the double-blind treatment phase.

12-Week Double-Blind Treatment Phase

A double-blind, placebo-controlled treatment phase lasting 12 weeks. On Day 1 (Visit 4), patients will be randomized to treatment (MIN-101 64 mg, MIN-101 32 mg, or placebo) in equal proportions. Patients can be discharged at the discretion of the Investigator from the investigator's site on Day 2, after taking the blinded study medication, and having undergone 3 electrocardiogram (ECG) assessments (in triplicate) performed at pre-dose and at the approximate time of maximum drug concentration (C_{max}) of MIN-101 and its metabolite BFB-520. Hence, patients will be hospitalized for a minimum of 4 days (3 nights). Any authorization to leave the hospital will be done with the help of the Readiness for Discharge Questionnaire (RDQ). On Day 2 (Visit 5), if discharged, the patient will come back for visits at Weeks 1, 2, 3, 4, 8, and 12 for efficacy and/or safety assessments. Hospitalization on Visits 6 and 7 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. The patient (or his/her care provider) will be contacted by phone at Weeks 5, 6, 7, 9, 10, and 11 to verify safety and to make sure the patient is doing well and is compliant with study medication.

In case of early termination during the double-blind phase, the Week 12 (Visit 11) must be completed as soon as possible.

40-Week Open-Label Extension Phase

At the end of the 12-week double-blind treatment period (Visit 11), patients will be immediately enrolled into the 40-week open-label extension phase. Patients will be hospitalized for 2 days after the initiation of treatment with MIN-101 (all patients). Patients who received placebo for 12 weeks during the double-blind phase will start receiving 64 mg or 32 mg of MIN-101 per the randomization schedule implemented on Day 1 (Visit 4). Patients will then be allowed to leave the hospital on Visit 13 (Week 12 + 2 days) at the discretion of the investigator and after drug intake and safety have been ascertained clinically, including having undergone 3 ECG assessments (in triplicate) performed at pre-dose and at the approximate time of C_{max} of MIN-101 and its metabolite BFB-520. However, the Investigator may decide to keep the patient hospitalized as needed. RDQ will be completed prior to any authorization to leave the hospital. Hospitalization on Visits 14 and 15 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. Visits 16 to 26 will be ambulatory.

End-of-study (EOS) (Week 54 / Visit 27) assessments will be performed within 2 weeks following the last treatment visit (Week 52 / Visit 26). In case of early withdrawal, the End of Treatment visit (Week 52/ Visit 26) must be completed as soon as possible. It will be followed ±2 weeks later by the EOS visit (Week 54/Visit 27).

Study Population

Inclusion Criteria

Each potential patient must satisfy all the following criteria to be enrolled in the study:

1. Patient and patient's legal representative, if applicable, provided informed consent prior to the initiation of any study related procedures, and the patient is judged by the investigator as being capable of understanding the study requirements.
2. Male or female patient, 18 to 55 years of age, inclusive, and body mass index (BMI) < 35 kg/m^2 at Screening.
3. Patient meets the diagnostic criteria for schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), as established by a full psychiatric interview in conjunction with the Mini International Neuropsychiatric Interview (MINI)[a].
4. Has a caregiver or family member or health care personnel who can provide information towards assessment and support the patient in terms of compliance with the protocol. The caregiver must have contacts with the patient frequently and is not expected to change during the trial.
5. Documented diagnosis of schizophrenia for at least 1 year before screening into the trial.

[a] Current version for DSM-5.

6. Patient is stable in terms of both positive and negative symptoms of schizophrenia over the last 6 months according to his or her clinician and/or based on documentation in the clinical chart or medical records. Patients with or without positive symptoms are allowed if these symptoms are stable for the last 6 months and the patients do not meet exclusion criterion # 2.
7. Patient is currently an outpatient and has not been hospitalized for the last 6 months for acute exacerbation or symptoms worsening. Patients hospitalized for any time period during the last 6 months for social reasons or are currently hospitalized for social reasons can be included only with Sponsor's Responsible Medical Officer's approval (in addition for Ukraine only, the following criteria must be fulfilled: the patient has permanent place of residence, is legally capable, and has a caregiver [see inclusion criterion # 4]). The social reasons must be documented in the electronic case report form (eCRF).
8. Patient with a score of > 20 on the PANSS negative subscore (the original PANSS scale [Sum of N1+N2+N3+N4+N5+N6+N7]) at Screening (Visit 1) and Baseline (Visit 3) AND < 4 points absolute difference between the 2 visits.
9. Patients can be on any psychotropic before the trial if the psychotropics can be discontinued at the beginning of the washout phase without risking the patient's clinical status or safety.
10. No history of violence against self or others during the last 1 year.
11. Female patient who are not of childbearing potential, defined as women who are post-menopausal (defined as spontaneous amenorrhoea for at least 1 year or spontaneous amenorrhoea for at least 6 months confirmed by follicle stimulating hormone result of ≥ 40 IU/mL) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).
12. Female patient, if of childbearing potential, must test negative for pregnancy and must be using a double barrier contraceptive method.
13. Patient must be extensive (normal) metabolizers for P450 CYP 2D6, defined as a subject that has at least one functional allele (e.g., *1, or *2), as determined by study-specific genotyping test before the first drug dose is administered.
14. Patient and the caregiver are considered by the investigator to be reliable and likely to cooperate with the assessment procedures.

Exclusion Criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the study:

1. Current major depressive disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, or intellectual disability (intellectual developmental disorder diagnosed by age 14).
2. Patient with PANSS item score of > 4 on:
    - P4 Excitement/Hyperactivity

- P6 Suspiciousness/persecution
- P7 Hostility
- G8 Uncooperativeness
- G14 Poor impulse control

3. A CDSS total score > 6.
4. A score of ≥ 2 on any 2 of items 1, 2, or 3, or a score of ≥ 3 on item 4 of the Barnes Akathisia Rating Scale (BARS).
5. Patient's condition is due to direct physiological effects of a substance (e.g., a drug of abuse, or medication) or a general medical condition.
6. Has a current or recent history of serious suicidal behavior within the past 1 year.
7. Patient has a history of substance use disorder within 3 months of the Screening visit (excluding caffeine and cigarette smoking).
8. Positive urine drug screen for drugs of abuse (cocaine, methadone, amphetamines, cannabinoids, opiates, benzodiazepines, and barbiturates), tricyclic antidepressants (TCA), and alcohol (except for prescription benzodiazepines).
9. Patient who cannot be discontinued from psychotropics other than those allowed.
10. Patient who received clozapine within 6 months of the Screening visit except when used for insomnia at doses ≤ 100 mg per day.
11. Patient receiving treatment with long-acting or depot antipsychotic medication unless his/her next scheduled dose will occur during the protocol Screening period and can be omitted to allow for sufficient washout before receiving the study drug.
12. Patient with a history of significant other major or unstable neurological, neurosurgical (e.g., head trauma), metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, metabolic, gastrointestinal, or urological disorder.
13. Patient with a history of seizures (patient with a history of a single childhood febrile seizure may be enrolled in this study).
14. Patient who has had electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), or repetitive trans-cranial magnetic stimulation (r-TMS) within the 6 months prior to the Screening visit or who are scheduled for ECT, VNS, or r-TMS at any time during the study.
15. Patient with clinically significant abnormalities in hematology, blood chemistry, ECG, or physical examination not resolved by the Baseline visit which according to Investigator can interfere with study participation.
16. Current systemic infection (e.g., Hepatitis B, Hepatitis C, human immunodeficiency virus [HIV], tuberculosis). Patients with positive Hepatitis B core antibody test and negative Hepatitis B Surface Antigen (HBsAg) may be included in the study if aminotransferase levels (alanine aminotransferase/ serum glutamic pyruvic transaminase [ALT/SGPT] and aspartate aminotransferase/ serum glutamic

oxaloacetic transaminase [AST/SGOT]) do not exceed 2 times upper limit of normal (ULN).

17. Patient who requires or may require concomitant treatment with any other medication likely to increase QT interval (e.g., paroxetine, fluoxetine, duloxetine, amiodarone).
18. Patient who requires medication inhibiting CYP 2D6 or CYP 3A4.
19. Patient with a clinically significant ECG abnormality that could be a safety issue in the study, including QT interval value corrected for heart rate using the Fridericia's formula (QTcF) > 430 msec for males and > 450 msec for females.
20. Patient with a history of myocardial infarction based on medical history or ECG findings at Screening.
21. Familial or personal history of long QT syndrome or with additional risk factors for Torsade de Pointes.
22. Patient whose safety laboratory results show one or more of the following: potassium < 3.4 mmol/L, or calcium < 2.07 mmol/L, or magnesium < 0.70 mmol/L.
23. Patients with unexplained syncope.
24. Woman of child-bearing potential, or man, who are unwilling or unable to use accepted methods of birth control.
25. Woman with a positive pregnancy test, is lactating, or is planning to become pregnant during the study.
26. Patient who participated in another clinical study within 3 months prior to Screening, or received MIN-101 previously, or has previously participated in > 2 clinical studies with experimental medication within the past 2 years (previous participation in 3 clinical studies with experimental medication will require approval of the sponsor before eligibility is determined).

Treatments

Study Treatments

Patients who meet all of the inclusion and none of the exclusion criteria will start the psychotropic washout period (if applicable), during which, all psychotropics (antidepressants, mood stabilizers, benzodiazepines, antipsychotics) will be stopped. Patients will then be randomized on Day 1 to receive:

- MIN-101 64 mg for the entire study, or
- MIN-101 32 mg for the entire study, or
- Placebo for 12 weeks followed by MIN-101 64 mg dose during the open-label extension phase, or
- Placebo for 12 weeks followed by MIN-101 32 mg dose during the open-label extension phase.

Treatments will be administered PO, once a day in the morning with or without food.

Efficacy Evaluations

Efficacy will be evaluated based on the change from Baseline in PANSS NSFS after 12 weeks of treatment or at early withdrawal. In addition, other efficacy evaluations will be based on the change from Baseline in the score on the PSP, CGI-S [redacted] The PANSS total and subscale scores, the Marder factor scores, CDSS, and cognition (verbal fluency test) will also be used to evaluate efficacy at specific time points as outlined in the Time and Events Schedules.

Pharmacokinetic Evaluations

Plasma levels of MIN-101 and its metabolite(s) will be tabulated. Standard population pharmacokinetic parameters (e.g., area under the concentration-time curve [AUC], PO clearance [CL/F], etc.) will be estimated at specified time-points as outlined in the Time and Events Schedules.

Safety Evaluations

Safety will be evaluated by an analysis of adverse events (AEs), vital signs, ECG, physical examination results, and clinical laboratory tests (including blood and urine analyses), Abnormal Involuntary Movement Scale (AIMS), BARS, Simpson-Angus Scale (SAS) and Sheehan-Suicidality Tracking Scale (Sheehan-STS) scale, at specified time-points during the study as outlined in the Time and Events Schedules.

Statistical Methods

Sample Size Determination

The sample size for this study is based on the assumption of a treatment difference of 3 points in the mean change from Baseline to Week 12 in PANSS negative subscale score based on the Marder negative factor score between any MIN-101 dose group and placebo. A standard deviation of 6.5 in the change in PANSS negative subscale score from Baseline is used. Assuming an equal allocation to placebo and each of the 2 MIN-101 doses, 100 patients in each treatment arm are required to detect the treatment difference of 3 points with a power of 90% at an overall 2-sided significance level of 0.05. When adjusted for a rate of about 40% of patients who will not have either Baseline or at least 1 on-treatment efficacy assessments, the required number of patients becomes 167 in each treatment arm. Therefore, the total number of patients enrolled across the 3 treatment arms will be 501.

Data Set

The intent-to-treat (ITT) analysis set is defined as all randomized patients who receive at least one dose of study drug during the 12-week double-blind treatment phase regardless of any protocol deviation. This analysis set will be used for efficacy analyses of the 12-week double-blind treatment phase. Analyses of change from Baseline will include only patients who have both Baseline and post-Baseline data during the 12-week double-blind treatment phase.

The Safety Population will consist of all patients who took at least 1 dose of the study drug. Patients will be analyzed based on treatment received.

Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy endpoint will be the change in the NSFS from baseline to Week 12 (the double-blind treatment period). This endpoint will be analyzed using mixed-effect model repeated measurement (MMRM) with treatment arm (MIN-101 64 mg, MIN-101 32 mg, and placebo), pooled study center (by country or region based on enrollment), visit, and treatment arm-by-visit interaction as fixed effects, patient nested in treatment as random effect, and Baseline NSFS as covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. These analyses will be performed based on all post-Baseline scores using only the observed cases (OCs) without imputation of missing values. Comparison against placebo will be performed with the MIN-101 64 mg and 32 mg doses.

The overall type I error rate for testing the 2 MIN-101 doses versus placebo for the primary and the key secondary endpoint will be controlled at the 2-sided 0.05 level. The primary family of hypotheses (corresponding to the primary endpoint) and the secondary family of hypotheses (corresponding to the key secondary endpoint, the change from Baseline in PSP Total score) will be tested in a sequential manner with suitable adjustment for multiplicity within the family of primary hypotheses and within the family of the secondary hypotheses. The key secondary endpoint will not be ordered within the family of secondary hypotheses.

The adjustment for multiplicity within the family of primary hypotheses will utilize the Hochberg procedure for the purpose of reporting of results. This procedure will allow the null hypothesis of no treatment difference for both the 64 mg and 32 mg doses versus placebo to be rejected if largest p-value of comparing either of these 2 doses versus placebo is at or below 0.050. Otherwise, the lowest of these 2 p-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

Key Secondary & Exploratory Efficacy Analyses

The change from Baseline in PSP total scores will be analyzed similarly to the primary endpoint with MMRM. The change from Baseline in CGI-S scores and the [redacted] and Baseline CGI-S score as a covariate.

The change from Baseline for the remaining efficacy endpoints will be analysed similarly to primary endpoint.

The cumulative distribution function for the primary and key secondary endpoint will also be evaluated, as appropriate.

Interim Analyses

No formal interim analyses are planned for this study. Data from the double-blind 12-Week phase are the primary focus of this study and will be analyzed once the last patient completes Visit 11 assessments and the database has been locked.

Additionally, an external data safety monitoring board (DSMB) will be established to review the safety data and formulate recommended decisions/actions in accordance with the charter of the DSMB.

Pharmacokinetic Analyses

Individual plasma levels of MIN-101 and its metabolite(s) will be tabulated by MIN-101 dose with the corresponding time related to study drug administration. Descriptive statistics will be summarized by MIN-101 doses.

Population PK analysis of plasma concentration-time data of MIN-101 and its metabolite(s) will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available patient characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and results of the population PK analysis will be presented in a separate report.

Safety Analyses

All patients randomized to treatment who receive at least one dose of double-blind study drug will be included in the safety analyses. Summary statistics will be provided for all safety data using appropriate descriptive statistics adverse events, Sheehan-STS, laboratory tests, ECGs, vital signs, AIMS, BARS, and SAS.

For QTcF, an ANCOVA model by assessment times (visit and timepoint within visit) using the change from baseline (as dependent variable) with treatment arm (MIN-101 32 mg, MIN-101 64 mg, and placebo) as a factor, and Baseline value as covariate. Estimates for the difference at each assessment time for each dose group versus placebo, standard error of the mean, and the upper bound of the 2-sided 90% confidence intervals will be presented.

Pharmacokinetic / Pharmacodynamic Analyses

The effect of coincidentally measured (time-matched) plasma concentrations of MIN-101 and BFB-520 as compared to placebo on QTcF changes from Baseline will be analyzed utilizing the plasma concentration bin method. This analysis will pool all assessment times at which both the QTcF and PK data are available and will treat the bins as separate groups using quartile distribution. Plasma concentration data from placebo-treated patients will be set to 0 (zero). Repeated measures ANCOVA model will be used and will include PK concentration Bin Group and per-protocol assessment times as fixed effects, Baseline QTcF as a covariate, and patient nested in treatment as a random effect.

Furthermore, the analysis will be repeated by using the largest QTcF increase value (worst case) per patient, with the matched plasma concentration level independent of time of assessment, will also be performed using ANCOVA model with PK concentration Bin Group as fixed effects, Baseline QTcF as a covariate, and patient nested in treatment as a random effect. Analysis of the largest time-matched mean difference from Baseline will also be explored, as applicable.

P-value and the least squares means difference, and the corresponding upper bound of the two-sided 90% confidence intervals for the change from baseline versus placebo will be computed for each bin.

These analyses will be performed for MIN-101 plasma concentration and its main metabolites, as separate analyses.

Extension Phase

Patients enrolled in the 40-week open-label extension phase will receive either MIN-101 64 mg or 32 mg. Patients who received placebo in the double-blind 12-week treatment phase will receive one of the 2 MIN-101 doses according to the randomization schedule used at the beginning of the double-blind phase (Day 1). Data from all patients enrolled in the 40-week extension phase will be summarized descriptively, as appropriate, by treatment arm sequence (MIN-101 64 mg, MIN-101 32 mg, placebo to MIN-101 64 mg, placebo to MIN-101 32 mg, overall MIN-101, overall placebo to MIN-101, and overall) as appropriate, and by visit.

DSMB

An external DSMB will be established to review the safety data and formulate recommended decisions/actions in accordance with the charter of the DSMB. The DSMB will consist of 2 clinicians (psychiatrist and cardiologist), and a statistician, one of whom will chair the board. The DSMB will review the outputs from statistical summaries of demographics and safety data prepared by the contract research organization managing the study on behalf of the sponsor who are not otherwise affiliated by the study team.

Further details regarding the safety analysis will be specified in a separate DSMB charter.

TIME AND EVENTS SCHEDULE – DOUBLE-BLIND PHASE

Study Phase	**3- to 4-Week Pre-Treatment Phase**			**Double-Blind Treatment Phase**							
	Screening Period	**Washout Period**	**Baseline**								
Study Day/Week[a]	**Day -28 to Day -2**	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12[m]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Procedures											
Informed consent	X										
Patient demography	X										
Psychiatric and medical history	X										
MINI	X										
Prior medication	X	X									
Urine drug screen	X	X									
Inclusion/exclusion criteria	X	X	X								
Hospitalization[b]		**Continuous**				X[b]	X[b]				X
Randomization				X							
Safety Assessments											
Vital signs[c]	X		X	X	X	X	X	X	X	X	X
Height/weight/waist circumference[d]	X		X						X	X	X
Physical examination	X		X						X		X
12-lead ECG (triplicate)[e]	X		X	X	X	X	X	X	X	X	X
Safety laboratories[f]	X	X							X	X	X
HbA1c laboratory test	X		X								X
Serology (HBsAg, HCV, and HIV)	X										
Urinalysis[g]	X		X						X	X	X
Pregnancy test[h]	X	X							X	X	X
RDQ[i]					X						

Study Phase	3- to 4-Week Pre-Treatment Phase			Double-Blind Treatment Phase							
	Screening Period	Washout Period	Baseline								
Study Day/Week[a]	Day -28 to Day -2	Day -2	Day -1	Day 1	Day 2	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12[m]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
AIMS	X		X						X	X	X
SAS and BARS	X		X			X	X	X	X	X	X
Safety Assessments (Cont'd)											
Sheehan-STS	X		X	X	X	X	X	X	X	X	X
Adverse events	**Continuous**										
Concomitant medication	**Continuous**										
Other Laboratory Assessments											
CYP 2D6 genotyping	X										
Pharmacokinetic and concomitant medications sampling[j]				X	X	X	X	X	X	X	X
Efficacy Assessments											
[redacted]	X		X				X		X	X	X
PSP			X						X	X	X
CGI-S	X		X				X		X	X	X
[redacted]							X		X	X	X
[redacted]			X						X		X
[redacted]	X		X						X	X	X
Study Medication											
Administration				X	X	X	X	X	X	X	X
Dispense study drug[k]					X	X	X	X	X	X	
Study drug accountability[l]						X	X	X	X	X	X

NOTE: Patient's eligibility must be verified, including Baseline laboratory results, before the patient can be randomized.

NOTE: Weeks 2 to 12 (Visits 7 to 13) have ± 2 days window.

NOTE: Patients to be contacted via phone at Weeks 5, 6, 7, 9, 10, and 11 to verify safety and to make sure the patient is doing well and is compliant with study medication.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Scale; [redacted] CGI-S = Clinical Global Impression-Severity Scale; CYP = cytochrome; ECG = electrocardiogram; EOS = end-of-study; HbA1c = hemoglobin A1c; HBsAg = surface antigen of hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MINI = Mini International Neuropsychiatric Interview; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; RDQ = Readiness for Discharge Questionnaire; SAS = Simpson-Angus Scale; STS = Suicidality Tracking Scale.

Footnotes:

[a] Visits 7 to 13 may occur ± 2 days from scheduled visit.

[b] Visits 2-5 hospitalization may be extended at the discretion of the investigator. Hospitalization on Visits 6 and 7 are at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. Hospitalization includes admission to a hospital or the utilization of an inpatient facility.

[c] Vital signs (blood pressure, heart rate, respiratory rate, and oral or aural body temperature) obtained after the patient is resting in supine position for ≥ 5 minutes. Vital signs during hospitalization are assessed pre-dose within 30 minutes of dosing, and at about 4 hours post dosing. All other assessments are at about 4 hours post dosing.

[d] Height only at Screening Visit; Patients will be weighed clothed (lightly) and without shoes at every indicated visit.

[e] Scheduled ECG recordings (in triplicate) should be obtained after the patient is resting in supine position for ≥ 10 minutes. Three triplicate ECG assessments (9 assessments) should be performed on Day -1 to serve as the Baseline value. Scheduled ECG recording during hospitalization (Visits 4 through 7 and Visit 11) should be done prior to the planned PK sample at pre-dose within 30 minutes of dosing, and at the approximate time of maximum plasma concentration of both MIN-101 (6 to 8 hours post dosing) and BFB-520 (9 to 12 hours post dosing). Scheduled ECG recordings on Visits 8 to 10 should be done prior to the planned PK sample 2-4 hours post dosing after all other assessments have been completed.

[f] Safety laboratory tests include haematology, serum chemistry (including serum lipid profile, and fasting blood glucose) and prolactin. Patients must fast for 8 hours before the blood sample is taken. Baseline safety laboratory tests will be performed no later than Day -2 (and not earlier than Day -5) to ensure results are available prior to the first study drug administration.

[g] Dipstick urinalysis will be completed on site at Screening, Baseline, and Weeks 4, 8, 12 (or early termination). Urine specimen will only be sent to the central laboratory for microscopic analysis in the event the dipstick results are abnormal.

[h] All females of childbearing potential will have a serum pregnancy test at Screening and Week 12 / Visit 11 (or in case of early termination); urine samples will be collected at Baseline (Day-2) and Visits 9, 10, and 11. The samples will be tested at the study sites using urine dipstick test. Any patient with a positive or doubtful urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

[i] On Day 2 or prior to any discharge authorization if later than Day 2.

[j] Pre-dose samples (may be done along with the safety laboratory samples, when scheduled) during Visits 4 through 7 and Visit 11 and at the approximate time of maximum plasma concentration of both MIN-101 (6 to 8 hours post dosing) and BFB-520 (9 to 12 hours post dosing). PK samples during Visits 8 to 10 should be done pre-dose and 2-4 hours post dosing. A concomitant medication blood sample should be collected coincidental with the PK sample scheduled at the approximate time of maximum plasma concentration of MIN-101 (6 to 8 hours post dosing) during Visit 4 through 7 and Visit 11, and 2-4 hours after dosing during Visits 8 to 10. PK samples should follow the ECG (in triplicate) assessments, when applicable.

[k] At each visit, when new medication blisters are dispensed, the patient should start taking drug from the new blisters except at Week 12 (Visit 11) where medication from blisters dispensed during Week 8 (Visit 10) should be used.

[l] Patient's drug intake diary should be collected and reviewed, and new diary dispensed with the new medication blisters.

[m] Every attempt must be made to complete Week 12 (Visit 11) in case of early termination during the double-blind phase.

TIME AND EVENTS SCHEDULE – OPEN-LABEL EXTENSION PHASE

Study Phase	**End of Double-Blind Phase**	**Open-Label Treatment Phase**															
Study Week[a]	**Week 12**	**Week 12+1 Day**	**Week 12+2 Days**	**Week 13**	**Week 14**	**Week 15**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[m]**	**EOS/ Week 54[m]**
Visit Number	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Procedures																	
Hospitalization[b]	**Continuous**			X[b]	X[b]												
Safety Assessments																	
Weight and waist circumference[c]	X						X	X	X	X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X						X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratories[g]	X						X	X		X		X		X		X	X
HbA1c laboratory test	X								X			X				X	X
Urinalysis	X						X	X		X		X				X	X
Pregnancy test (urine)	X						X	X	X	X	X	X	X	X	X	X	X
RDQ[h]			X														
AIMS	X						X	X	X	X	X	X	X	X	X	X	X
SAS and BARS	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sheehan-STS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	**Continuous**																
Concomitant medication	**Continuous**																
Other Laboratory Assessments																	

Study Phase	End of Double-Blind Phase	Open-Label Treatment Phase														
Study Week[a]	**Week 12**	**Week 12+1 Day**	**Week 12+2 Days**	**Week 13**	**Week 14**	**Week 15**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[m]**	**EOS/ Week 54[m]**
Visit Number	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Pharmacokinetic and concomitant medications sampling[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																	
PANSS	X				X		X		X		X		X		X	X	X
PSP	X						X		X		X		X		X	X	
CGI-S	X				X		X	X	X	X	X	X	X	X	X	X	X
[redacted]	[redacted]				[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]						[redacted]		[redacted]			[redacted]				[redacted]	
[redacted]	X						X		X			X				X	
Study Medication																	
Administration[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense[k]			X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug accountability[l]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	

NOTE: Patients to be contacted via phone at Weeks 18, 22, 26, 30, 34, 38, 42, 46, and 50 to verify safety and to make sure the patient is doing well and is compliant with study medication.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BARS= Barnes Akathisia Scale; [redacted] CGI-S = Clinical Global Impression-Severity Scale; ECG = electrocardiogram; EOS = end-of-study; HbA1C = hemoglobin A1c; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; RDQ = Readiness Discharge Questionnaire; SAS = Simpson-Angus Scale; STS = Suicidality Tracking Scale.

Footnotes:

[a] Visits 14 – 27 may occur ± 2 days from scheduled visit.

[b] Patients will be hospitalized starting on the morning of the last day of the double-blind treatment phase (Visit 11) up to Visit 13. Hospitalization on Visits 14 and 15 are at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. Hospitalization includes admission to a hospital or the utilization of an inpatient facility.

[c] Patients will be weighed clothed (lightly) and without shoes.

[d] Vital signs (blood pressure, heart rate, respiratory rate, and oral or aural body temperature) obtained after the patient is resting in supine position for ≥ 5 minutes. Vital signs during hospitalization are assessed pre-dose within 30 minutes of dosing, and at about 4 hours post dosing. All other assessments are at about 4 hours post dosing.

[e] Abbreviated physical examinations at Visits 18, 19, 21, 22, 24 and 25.

[f] Scheduled ECG recording on Visits 12 through 15 should be done prior to the planned PK sample at pre-dose within 30 minutes of dosing, and at the approximate time of maximum plasma concentration of both MIN-101 (6 to 8 hours post dosing) and BFB-520 (9 to 12 hours post dosing). Scheduled ECG recordings on Visits 16 through 26 should be done prior to the planned PK sample 2-4 hours post dosing after all other assessments have been completed.

[g] Safety laboratory tests include haematology, serum chemistry (including serum lipid profile, and fasting blood glucose) and prolactin. Patients must fast for 8 hours before the blood sample is taken

[h] On Week 12 + 2 days or prior to discharge authorization if later than Week 12 + 2 days.

[i] Pre-dose samples (may be done along with the safety laboratory samples, when scheduled) during Visits 12 through 15 and at the approximate time of maximum plasma concentration of both MIN-101 (6 to 8 hours post dosing) and BFB-520 (9 to 12 hours post dosing). PK samples during Visits 16 through 26 should be done pre-dose and 2-4 hours post dosing. One sample will be collected at Visit 27 along with the safety laboratory samples. A concomitant medication blood sample should be collected coincidental with the PK sample scheduled at the approximate time of maximum plasma concentration of MIN-101 (6 to 8 hours post dosing) during Visit 12 through 15, and 2-4 hours after dosing during Visits 16 through 26. PK samples should follow the ECG (in triplicate) assessments.

[j] At Week 12 (Visit 11), drug dispensed at Week 8 (Visit 10) must be administered.

[k] At Visits 12 - 25 when new blisters are dispensed, the patient should start taking drug from the new blisters.

[l] Patient's drug intake diary should be collected and reviewed, and new diary dispensed with the new medication blisters.

[m] Every attempt must be made to complete both the Week 52 (Visit 26) and EOS/Week 54 (Visit 27) in case of early termination during the open-label extension phase.

ABBREVIATIONS

5-HT_{2A}	5-hydroxytryptamine-2A
AAA	anhedonia, avolition, and asociality
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BARS	Barnes Akathisia Rating Scale
b.i.d	twice daily
BMI	body mass index
BNSS	Brief Negative Symptom Scale
BUN	blood urea nitrogen
[redacted]	[redacted]
[redacted]	[redacted]
CGI-S	Clinical Global Impression - Severity Scale
CIAS	Cognitive Impairment Associated with Schizophrenia
CL/F	oral clearance
C_{max}	maximum drug concentration (in plasma or serum)
CNS	central nervous system
CO	cross-over
CPK	creatine phosphokinase
CYP	cytochrome
DA	dopamine
DB	double-blind
DOPAC	3,4-dihydroxyphenylacetic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DSMB	data safety monitoring board
ECG	electrocardiogram
eCOA	clinical outcome assessments
eCRF	electronic case report form
ECT	electroconvulsive therapy
ED_{50}	median effective dose
EE	emotional expressivity
EM	extensive metabolizer
EMA	European Medicines Agency
EOS	end-of-study
EPS	extrapyramidal symptoms
F	female
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

HbA1C	hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HIV	Human immunodeficiency virus
HV	healthy volunteer
HVA	homovanillic acid
IC_{50}	half-maximal inhibitory concentration
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IKr	delayed rectifier potassium current
IR	immediate-release
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous, intravenously
IWRS	Interactive Web Response System
JP	Japanese Pharmacopeia
K_i	inhibitory constant
LDH	lactic acid dehydrogenase
LDL	low-density lipoprotein
LOCF	last observation carried forward
M	male
MAP	methamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model Repeated Measures
MoA	mechanism of action
MR	modified release
NF	National Formulary
NMDA	N-methyl-D-aspartic acid
NOAEL	No-observed-adverse-effect level
NSFS	Negative Symptoms Factor Score
OCs	observed cases
OL	open-label
PANSS	Positive and Negative Syndrome Scale
PC	placebo-controlled
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PM	poor metabolizer
PO	oral, by mouth (orally)
PP	per-protocol
PQC	product quality complaint
PRN	*Pro Re Nata* (as needed or rescue medication)
PSP	Personal and Social Performance

QTc	QT interval value corrected for heart rate
QTcB	QT interval value corrected for heart rate using Bazett's formula
QTcF	QT interval value corrected for heart rate using Fridericia's formula
RDQ	Readiness for Discharge Questionnaire
RBC	red blood cells
r-TMS	repetitive trans-cranial magnetic stimulation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
Sheehan-STS	Sheehan-Suicidality Tracking Scale
SMA	spontaneous motor activity
SR	sustained-release
$t_{1/2}$	terminal elimination half-life
TCA	tricyclic antidepressants
TD	tardive dyskinesia
TEAE	treatment-emergent adverse event
T_{max}	time to maximum drug concentration (in plasma or serum)
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USP	United States Pharmacopeia
VLDL	very low-density lipoprotein
VNS	vagal nerve stimulation
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background on the Disease

Schizophrenia is a complex, challenging, and heterogeneous psychiatric condition, affecting up to 0.7% of the world population according to the World Health Organization (WHO 2006). Schizophrenia is characterized by positive symptoms (including delusions and hallucinations), negative symptoms (blunted affect, alogia, asociality, anhedonia, and avolition) and pervasive cognitive deficits, often described as cognitive impairment associated with schizophrenia (CIAS). In addition to these symptoms, some comorbid symptoms might be present, like sleep disorders (insomnia, hypersomnia, deep sleep disorders, and overall biological rhythms dysregulations (Chouinard et al. 2004, Wulff et al. 2012). Much of the morbidity of the illness is related to its negative symptoms and cognitive impairment, which lead to functional impairment and withdrawal from social and occupational activities.

The relative success of currently marketed antipsychotics in treating positive symptoms is limited by the fact that a substantial number of patients are refractory to current medications and by their lack of direct effect on negative and cognitive symptoms, which often determine the level of functional impairment (Buchanan et al. 2005, Hill et al. 2010, Keefe et al. 2007, Kirkpatrick et al. 2006). Another limiting aspect of the currently available antipsychotics is their high incidence of side effects such as sedation, extrapyramidal symptoms (EPS), increased prolactin plasma levels, weight gain, and metabolic disorders or syndrome (Boettger et al. 2015).

All antipsychotics share some common mechanism of action (MoA), characterized by dopamine D_2 postsynaptic partial or complete blockade and serotonin 2A (5-HT_{2A}) blockade. Despite major efforts involving attempts to pharmacologically manipulate N-methyl-D-aspartic acid (NMDA)/glutamate neurotransmission and glycine reuptake, no therapeutic progress has been made. In a recent review updating the MoA of antipsychotics, the authors strongly suggested that new MoA are needed to both improve the side effect profile and to address unmet medical needs, like negative symptoms and cognitive impairment (Correll 2014).

Clinical practice, guidelines and trials indicating that continuous administration of antipsychotics (long-term maintenance) reduces the risk of exacerbation or periodic worsening of psychotic symptoms (Leucht et al. 2012a, Leucht et al. 2012b, Leucht et al. 2017). However, this practice has been criticized on several grounds. First, most of the maintenance trials last 6-12 months which is a relatively short period in a life-long disease. Hence, concluding that patients need life-long antipsychotic treatment based on 6-12 months trials, is not particularly convincing. It is possible that drugs that have been effective for a period of time, subsequently lose their effectiveness (Harrow et al. 2012). Second, the outcomes measurements used to show that maintenance with antipsychotics is superior to placebo remains controversial. Change in PANSS scores, hospitalization, agitation, violence of any degree, and almost any unusual event that removes the patient from the trial, is considered an outcome. Indeed, antipsychotics or as they were initially called *major tranquilizers*, reduce the global magnitude of all events and activities (Moncrieff 2015). However, it is doubtful for example if any

episode of agitation reflects illness worsening or exacerbation rather than an amplified reaction to a routine life event in an individual with questionable social skills. Third, recent research indicates that in a subgroup of schizophrenia patients, symptoms do not worsen despite absence of maintenance antipsychotics for lengthy periods of time (Häfner et al. 2013, Harrow et al. 2012, Harrow et al. 2014, Wunderink et al. 2013, Wils et al. 2016). While the methods of some of these studies have been criticized in the literature, the absolute need for continuous and indefinite antipsychotic maintenance treatment for all non-actively psychotic schizophrenia patients, has also been questioned by academics (Insel 2013) and practicing psychiatrists (Moncrieff 2015). On the negative side, it is not inconceivable that long term continuous administration of antipsychotics is associated with parenchymal brain lesions (Nopoulos et al. 2001) in addition to the metabolic and endocrine adverse effects. Furthermore, one cannot ignore the dissatisfaction of many patients with continuous antipsychotic treatment as evidenced by very poor compliance with medications.

In an attempt to address these and related concerns, a National Institute of Mental Health workshop was held in 2005 on the methodological issues related to the design of trials of pharmacological agents for improving negative symptoms in schizophrenia (Kirkpatrick et al. 2006). Since then, several meetings have taken place, which helped refine the methodology to be used in clinical trials (Marder et al. 2011, Marder et al. 2013) and initiatives have been set up to create new instruments able to capture effects of drugs on negative symptoms and cognitive impairments.

There are currently no drugs approved for the treatment of negative symptoms, with the exception of amisulpride in some European countries. However, the efficacy of amisulpride against negative symptoms is questioned by regulators, investigators, and clinicians and has been supported mostly by post-hoc analysis. A number of investigational pharmacological targets are being (or have been) studied in clinical trials. Among those, glutamatergic and nicotinergic pathways have received most attention. Glycine transporter inhibitors used adjunctively with antipsychotics failed to improve negative symptoms of schizophrenia (Goff 2014).

An adjunctive alpha-7 nicotinic acetylcholine receptor agonist was reported to have some efficacy in 1 study (Hilt 2013), but no efficacy in most other studies on negative and cognitive symptoms. Agents that act at the glycine site of the NMDA glutamatergic receptor (glycine or D-cycloserine) were found not to be effective for the treatment of negative symptoms or cognitive impairments (Buchanan et al. 2007). Minocycline an antibiotic, has improved negative symptoms (Chaudhry et al. 2012) in 1 study but not in most others.

In summary, the idea that second generation antipsychotics (or atypicals) are significantly more effective than first generation antipsychotics or that second generation antipsychotics can benefit primary negative symptoms, cognitive impairment, or social and vocational functioning is not supported by data or hard-core outcome measurements. Hence, there is a need of new pharmacological treatments, using novel mechanisms of action which are inducing less side-effects, are controlling better positive symptoms, and can also improve negative symptoms and CIAS. MIN-101 is currently developed for this purpose.

1.2. Background on the Molecule

MIN-101 is a novel cyclic amido derivative, which has specific affinities for sigma$_2$, 5-HT$_{2A}$ and at lower affinity levels, α1-adrenergic receptors. MIN-101 exhibits very low or no affinity for other receptors including dopaminergic, muscarinic, cholinergic, and histaminergic receptors. In vivo functional studies have established that MIN-101 is an antagonist at both 5-HT$_{2A}$ and sigma$_2$ receptors.

For 5-HT$_{2A}$ receptor antagonists, the most known and described effect is a beneficial effect in reducing EPS occurrence in patients treated with drugs blocking post-synaptic D$_2$ receptors. A recent paper, summarizing the effects of 5-HT$_{2A}$ antagonists on psychotic, positive symptoms, shows that these drugs might also have an antipsychotic effect of their own, as they show superiority to placebo but they are probably less effective than antipsychotics (Ebdrup et al. 2011). Furthermore, some recent data with pimavanserin (a drug targeting 5-HT$_{2A}$ and 5-HT$_{2C}$), show that the drug might be a new treatment for Parkinson's disease-associated psychosis (Meltzer & Roth 2013). Finally, 5-HT$_{2A}$ antagonists are also known to improve sleep, particularly by increasing sleep maintenance parameters and by increasing the amount of deep sleep (Al-Shamma et al. 2010).

Sigma receptors are known to affect several behavioral domains (Skuza 2012) and have potential therapeutic roles in disorders, like anxiety, depression, schizophrenia and drug addiction (Banister & Kassiou 2012). Two subtypes of sigma receptors have been described, and active research effort is going on to further characterize sigma$_2$ subtypes. It is possible that sigma$_2$ receptors are implicated in the modulation of dopaminergic (DA) (Katz et al. 2011, Lever et al. 2014), glutamatergic pathways (Skuza 2012), and calcium neuronal modulation (Vilner & Bonen 2000). Recent literature on sigma receptors also shows new bindings sites, like the progesterone receptor membrane component 1 (Xu et al. 2011). This later hypothesis has been recently challenged, since the sigma$_2$ receptor has been purified from tissue, revealing its identity as TMEM97, an endoplasmic reticulum-resident transmembrane protein that regulates the sterol transporter NPC1 (Alon et al. 2017). Taken together, it might be hypothesized that sigma$_2$ receptors are involved in counteracting dysregulations in key neurotransmitter pathways, like dopamine and glutamate.

Interestingly, some of the pharmacological effects described above are demonstrated with MIN-101 in preclinical models of positive and negative schizophrenia symptoms. For example, DA turnover, DA metabolites such as dihydroxy-phenyl acetic acid and homovanillic acid and prolactin are elevated at high doses of MIN-101, suggesting that the molecule behaves like a weak antagonist at the DA receptor. This effect occurs, despite the fact that there is no direct binding to DA receptors, consistent with an intrinsic antipsychotic effect in addition to the rest of the pharmacological effects. Furthermore, antipsychotic effects (control of positive symptoms) of MIN-101 were supported by behavioral models.

Similar to other antipsychotics, MIN-101 inhibited abnormal behaviors induced by DA agonists such as apomorphine and methamphetamine (please refer to the MIN-101 Investigator's Brochure for detailed results). Finally, MIN-101 improved social interaction impairment induced by phencyclidine and impairment of spontaneous alternation behavior

induced by MK-801, NMDA receptor antagonists. All these preclinical models are believed to be predictive of a therapeutic effect on negative symptoms and possibly on positive symptoms (please refer to the MIN-101 Investigator's Brochure for detailed results). Of note, the effects on the negative symptoms models were observed at lower doses as the ones observed in the positive symptoms models. Depending on the model used, the ratio varies from 3 to 10.

In terms of safety/tolerability pharmacology, MIN-101 produced antipsychotic-related side effects in animals such as catalepsy and prolactin elevation only at considerably high doses, much higher than the doses producing the therapeutic effects in the animal models (positive and negative symptoms equivalents).

In clinical studies in both healthy subjects and schizophrenia patients, MIN-101 was well-tolerated, inducing no sedation, no weight gain, and no increase in prolactin level. The incidence of EPS was also comparable to the placebo groups (see the MIN-101 Investigator's Brochure for detailed results).

Data from last 2 clinical studies (CYR-101C01 and MIN-101C03) demonstrated that MIN-101, given as monotherapy, improves negative symptoms, and possibly cognitive impairment, which constitute an important unmet need. This confirms that the innovative pharmacological profile of MIN-101 might be beneficial for patients suffering from schizophrenia.

1.3. Nonclinical Studies

1.3.1. Pharmacologic Profile

In in vitro receptor binding studies, MIN-101 demonstrated a unique binding profile. MIN-101 bound [redacted]

[redacted]

[redacted]

[redacted] antipsychotics for which increase in prolactin concentrations occurred at lower dose levels.

1.3.2. Pharmacological Effect of MIN-101 in Mice and Rats

The potential of MIN-101 to induce [redacted]

1.3.3. Safety Pharmacology

[redacted]

[redacted]

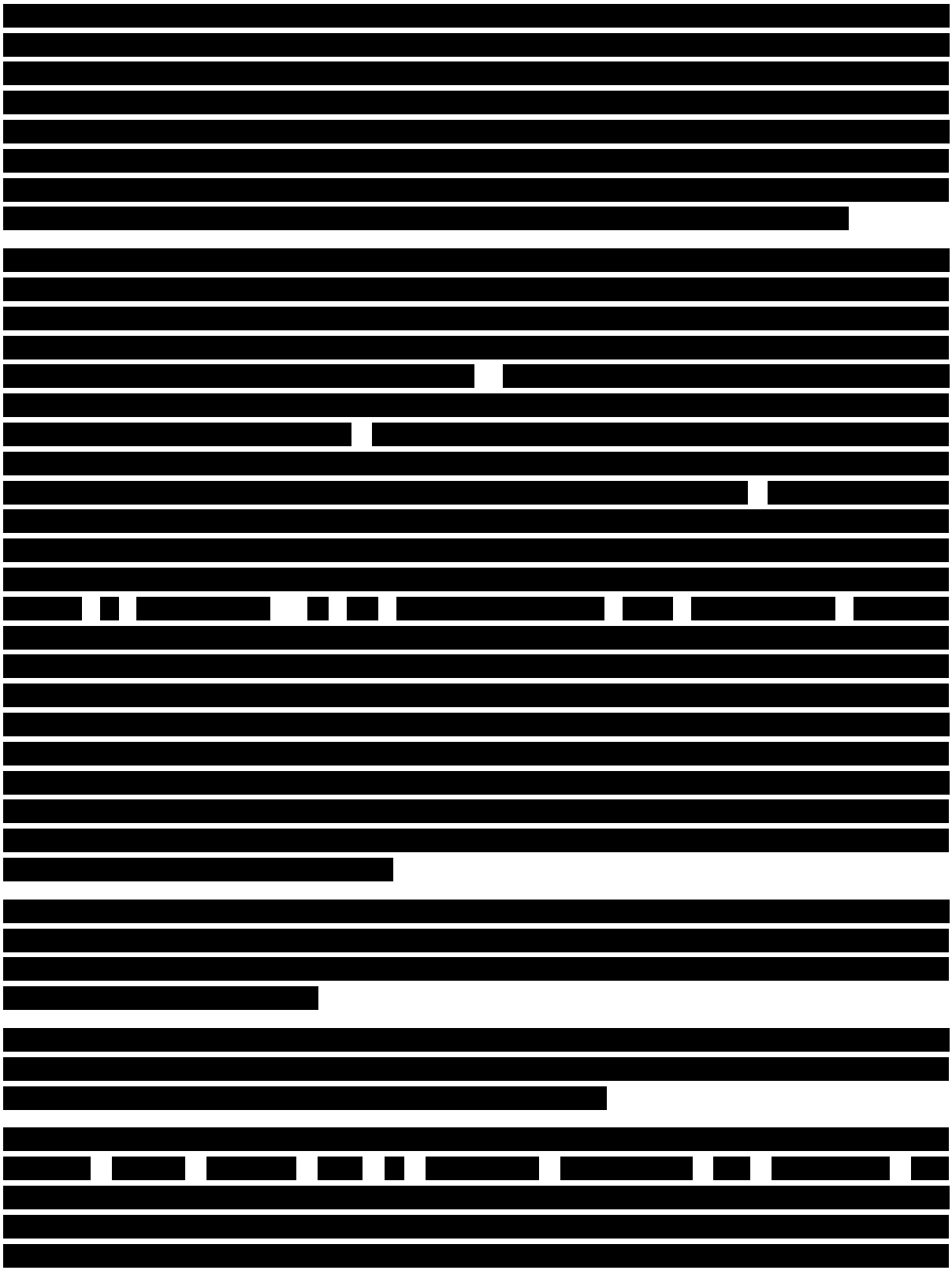
[redacted]

[redacted]

1.3.4. Toxicology

[redacted]

[redacted]



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1.3.5. Pharmacokinetic Profile

[redacted]

[redacted]

[redacted]

[redacted]

1.4. Clinical Studies

1.4.1. Healthy Subject Studies

To date, 6 clinical pharmacology studies (MT-210-E01, MT-210-E02, MT-210-E03, MT-210-E04, MT 210-A01, and MIN-101C02) have been conducted in healthy subjects to evaluate the safety, tolerability, pharmacodynamic (PD), and PK profiles of MIN-101. MIN-101C02 was a reformulation and safety study conducted to support a modified-release tablet, which was used in the Phase 2b study carried out in patients suffering from schizophrenia (MIN-101C03). Three more clinical pharmacology studies (MIN-101C04, MIN-101C05, and MIN-101C06) have completed the subject assessment phases and results are expected by the end of 4Q2017.

An overview of the clinical pharmacology studies is presented in Table 1.

Table 1. Overview of Clinical Pharmacology Studies of MIN-101 in Healthy Subjects

Study / Status	Main Objectives and Design	Drug Doses/Form	Study Population Sex (M/F)	Number of Subjects Enrolled/ Completed
MT-210-E01 Complete	Ascending single-dose study in sequential cohorts. DB, PC, Safety/ Tolerability/PK/PD	Placebo, 0.5 to 32 mg IR	HV 64M	64/64
MT-210-E02 Complete	Single dose administration under fed and fasted conditions. OL, 2x CO, Safety/ Tolerability/PK	24 mg IR	HV 14M	14/13
MT-210-E03 Complete	Group A: Single dose administration under fasted condition. Group B: Single dose administration under fed and fasted conditions. OL, 2x CO, Safety/Tolerability/PK	24 mg Group A IR vs SR Group B SR	HV 29M	29/26
MT-210-E04 Complete	Multiple dose administration DB, PC, Safety/Tolerability/PK/PD	Placebo, 8 mg b.i.d. SR	HV 12M EM	12/12
MT-210-A01 Complete	Single dose administration. OL, Safety/Tolerability/PK	16 mg IR	HV 12M/12F	24/23
MIN-101C02 Complete	Part 1: Single dose administration. OL, Safety/ Tolerability/PK PK; select MR formulation for Part 2 Part 2: Multiple dose administration DB, PC, Safety/ Tolerability/PK, changes in QT/QTc interval	32 and 40 mg MR Placebo, 16 and 32 mg MR	HV 12M EM HV 16M/4F EM	12/10 20/19
MIN-101C04 Ongoing	ADME	16 mg single dose (oral solution)	HV (M) 4-6 EM	6/6
MIN-101C05 Ongoing	Poor versus Extensive Metabolizer PK & Safety	4 mg, 8 mg, 16 mg (oral solution)	HV (M&F) 12 – 16 EM 12 – 16 PM	10/8 PM, 13/12 EM
MIN-101C06 Ongoing	Re-formulation PK & Food Effect	32 mg (tablets)	HV (M&F) 16 EM	14 EM

ADME = absorption, distribution, metabolism, and excretion; b.i.d. = twice daily; CO = cross-over; DB = double-blind; EM = extensive metabolizer; F = females; HV = healthy volunteer; IR = immediate-release formulation; M = males; MR = modified-release formulation; OL = open-label; PC = placebo-controlled; PD = pharmacodynamics; PK = pharmacokinetics; PM = poor metabolizer; SR = sustained-release formulation

1.4.1.1. Pharmacokinetics

The MIN-101 immediate-release (IR) formulation was tested [redacted]

Data obtained from the urine analysis showed that according to the mean renal clearance estimates, the primary mechanism for MIN-101 elimination appeared to be non-renal clearance.

Administration of a standard breakfast delayed the IR MIN-101 absorption by 1 hour and the peak plasma concentration was around half that observed in the fasted condition. Gender differences were tested using the 16 mg dose. The PK of MIN-101 was not different in males and females except for a higher C_{max} of BFB-999 in females.

With single PO dose administration of the sustained-release (SR) MIN-101 formulation, the T_{max} occurred 1.5 hours after PO administration. C_{max} was around 70% lower as compared to IR administration. The estimates suggested a reduction of extent of exposure (AUC_t) for SR formulation compared to IR formulation of 16%. In healthy subjects, the $t_{1/2}$ of MIN-101 in plasma after SR administration was about 5 hours. Administration of a standard meal delayed SR MIN-101 absorption by around 2 hours.

With the slow modified-release (MR) formulation in Part 1 of Study MIN-101C02, C_{max} and AUC_{24} for MIN-101 at 32 and 40 mg doses under fasted condition showed an increase that was slightly more than dose-proportional. Median $t_{1/2}$ ranged from 6.4 to 8.1 hours, for the 32 and 40 mg doses, respectively, and median T_{max} ranged from 2.2 to 2.5 hours, respectively. Similar findings were noted for BFB-520 and BFB-999, with T_{max} occurring at about 2 hours post that of the parent compound (MIN-101).

In using the 32 mg MR formulation, food had a positive effect on C_{max} (increase by 2-fold), T_{max} (increased by almost 3-fold), and $t_{1/2}$ (decreased to 3.2 hours). Food had no noticeable effect on AUC. Similar findings were noted for BFB-520 and BFB-999.

After repeated PO SR MIN-101 administration, mean T_{max} was 2.3 hours. The mean accumulation factor was 1.22. The $t_{1/2}$ of SR MIN-101 was not significantly different after single (7.5 hours) and multiple doses (8.6 hours). The coefficients of variability were high indicating a high inter-individual variability.

A few subjects in the different studies (healthy subjects and patients) showed higher exposure to MIN-101 and BFB-520. These elevated concentrations could be explained by the poor or intermediate metabolizer status of these subjects.

In Part 2 of Study MIN-101C02 where 16 and 32 mg doses were tested under fasted conditions for 7 days in a crossover, randomized, placebo-controlled study design, the 2 doses exhibited dose-proportional PK properties for all exposure parameters, for all 3 analytes. T_{max} was shortest for MIN-101 with BFB-520 and BFB-999 showing a 1-hour lag. Accumulation as

measured by the ratio of AUC_{24} at Day 7 as compared to that of Day 1 was highest for BFB-520 (> 2-fold) and similar for MIN-101 and BFB-999 (< 2-fold). Assessment of pre-dose (trough) levels on Days 3 to 7 suggested steady state was achieved by Day 7.

1.4.1.2. Safety

Single doses of MIN-101 in healthy subjects were generally well tolerated up to 24 mg (IR and SR formulations) and up to 40 mg (MR formulation). No serious adverse events (SAEs) and no deaths were reported. Dose limiting postural hypotensions were reported at the 32 mg dose level with the IR formulation.

In all single-dose studies, ECG evaluation employed single assessment of ECG that was read locally, and QT was corrected in most cases, through Bazett formula. Mild QT prolongations were observed following MIN-101 single-dose administration. No increase from Baseline in QT interval value corrected for heart rate using Bazett's formula (QTcB) or QTcF of ≥ 60 msec was reported with the exception of 1 occurrence in MT-210-E02 (24 mg IR, QTcB). QTcB/QTcF values remained < 480 msec except in 1 female subject in MT-210-A01 (16 mg IR), who had 3 episodes of post-dose QTcF value > 480 msec (max 498 msec 4 hours post dose).

Multiple doses of MIN-101 in healthy subjects were generally well tolerated up to 16 mg (SR formulation) and up to 32 mg (MR formulation). No SAEs and no deaths were reported. No postural hypotension and no significant changes in ECG parameters were reported. No subject had a QTc > 480 msec or an increase from Baseline in QTc ≥ 60 msec. No EPS were observed in healthy subjects. MIN-101 did not seem to induce any relevant change in safety laboratory parameters. Only 2 cases of mild increase (< 3 ULN) in liver enzymes were reported.

1.4.2. Patient Studies

Three clinical studies (MT-210-A02, CYR-101C01, and MIN-101C03) have been conducted in schizophrenia patients. Two different formulations have been used to date, the SR and the MR. The dose ranges tested in these studies were between 16 and 96 mg for MIN-101 SR (8 mg to 48 mg given twice daily [b.i.d.]) and 32 and 64 mg for MIN-101 MR tablet.

An overview of the clinical studies is presented in Table 2.

Table 2. Overview of Clinical Studies of MIN-101 in Schizophrenia Patients

Study / Status	Phase	Main Objectives and Design	Drug Doses/Form	Study Population Sex (M/F)	No. of Subjects Enrolled/ Completed
MT-210-A02 Complete	1	Multiple-dose rising study in sequential cohorts DB, PC, Safety/ Tolerability/ PK/ preliminary efficacy	8 to 48 mg b.i.d. SR for 12 days	Schizophrenia patients 11M/1F	12/5
CYR-101C01 Complete	2a	A Multi-center, Inpatient and Ambulatory, Phase 2, DB, Randomized, PC, Proof of Concept Study of CYR-101 in Patients with DSM-5 Schizophrenia	Dose adjustment period 8, 16 and 32 mg SR b.i.d. for two days each. Then fixed dose-period at the optimal dose, maximum of 32 mg b.i.d.; Placebo	Schizophrenia patients 49M/47F	96/30
MIN-101C03 Complete	2b	Multi-center, DB, Randomized, Parallel-group, PC, Study to Evaluate Efficacy, Tolerability and Safety of MIN-101 in Patients with Persistent, Stable, Predominant Negative Symptoms of Schizophrenia, followed by 24 weeks of open-label extension	Placebo, 32 and 64 mg MR for total of 36 weeks.	Schizophrenia patients 137M/107F	244 (randomized) / 165 (completed double-blind phase*) / 88 (completed 36 weeks)

* Include patients who dropped out after completion of the 12-Week double-blind phase.
b.i.d. = twice daily; DB = double-blind; F = females; M = males; MR = modified-release formulation; PC = placebo controlled; PK = pharmacokinetics; SR = sustained-release formulation.

1.4.2.1. Pharmacokinetics

In the first 2 patient studies, SR MIN-101 was administered using an up-titration dosing regimen. In Study MT-210-A02, 8, 16, 32, and 48 mg were administered b.i.d, 3 days at each dose-level for a total of 12 days. In this study, T_{max} was achieved in approximately 3 hours and the PK profile was dose-proportional through Day 12. One poor metabolizer for CYP 2D6 patient was enrolled by error and showed plasma concentrations of the metabolite BFB-520 that were extremely high.

In Study CYR-101C01, 8, 16, and 32 mg were administered b.i.d, 2 days at each dose level. It was followed by a fixed dose-period at the optimal dose, maximum of 32 mg b.i.d until Day 84 (12 weeks). In this study, during the dose adjustment period (Day 2 to Day 6), mean post-dose plasma concentrations for MIN-101, BFB-520, and BFB-999 increased with dose, while mean pre-dose concentrations did not significantly increase. During the fixed dose period (Day 6 to Day 14), mean post-dose plasma concentrations slightly increased towards a steady-state, which was achieved by Day 14. Mean pre-dose plasma concentrations slightly increased for BFB-520 only but remained almost constant for the MIN-101 metabolite MT-210 and BFB-999.

During the ambulatory period (Day 14 to Day 84), mean post-dose plasma concentrations were similar to steady-state. Pre-dose plasma concentrations increased notably for MIN-101 until Day 56 (pre-dose Day 14 was 3.97 ng/ml; pre-dose Day 56 was 17.4 ng/ml) increased slightly for BFB-999 but remained stable for BFB-520. Coefficients of variability were high indicating a high inter-individual variability.

In Study MIN-101C03, 32 mg and 64 mg MR daily doses were administered for up to 36 months. PK samples were collected during the double-blind and open-label extension period. The PK data analysis is ongoing and is focused on assessing the PK/PD relationship with regards to both efficacy and QT changes using the bin concentration method that utilizes concentration data rather than dose.

Concentration data of MIN-101, BFB-520, and BFB-999 were also summarized by dose and sampling times exhibited dose proportionality for MIN-101 and BFB-520, and slightly more than dose-proportional for BFB-520. Geometric mean values were consistent with the absorption and elimination profile of MIN-101 and its 2 metabolites.

The exposure-response analysis using data from the MIN-101C03 study showed that an exposure-response relationship could be identified, and that arguably, exposure is more important than dose in determining response. This is implied by the fact that there was an overlap in the exposure for the 32 and 64 mg dose cohort. Such conclusion must be evaluated in the context of sparse sampling and intersubject variability with regards to compliance, metabolism, and other intrinsic (body weight, gender, genotype, etc.) and extrinsic (concomitant medication, food intake, etc.) factors.

The population PK QT modeling using data from all studies, as appropriate, of data from revealed the effect of MIN-101 concentration on QTcF was best described by a linear effect model. The effect of BFB-520 concentration on QTcF was best described by an E_{max} model as the linear effect model overestimated the observed QTc data at higher concentrations and underestimated at the lower concentrations, most likely due to the scarcity of the higher concentrations.

1.4.2.2. Efficacy

Study MT-210-A02 was not designed to assess efficacy.

In Study CYR-101C01, there was no statistically significant difference between MIN-101 and

placebo in the PANSS total score after one and three months of treatment although a numerical superiority of MIN-101 over placebo was seen after 3 months of treatment in the per-protocol completers group (point estimates decrease of -17.9, ($p < 0.001$) and -24.1, ($p < 0.001$), for placebo and MIN-101 respectively). PANSS Negative sub-score demonstrated a superiority of MIN-101 over placebo at Day 28, which was further confirmed at Day 84 with a statistical difference in favor of MIN-101 (least squares means decrease of -3.2, [$p = 0.049$] and -7.5, [$p < 0.001$], for placebo and MIN-101, respectively, with statistically significant treatment difference in favor of MIN-101 over placebo [$p = 0.0178$]). Cognitive performances were also better in the MIN-101 group (token motor task, list learning task, and verbal fluency) although the difference between the 2 treatment groups were not statistically significant. Throughout the study, MIN-101 showed greater decreases in the negative scale scores when compared to placebo, and the difference between the 2 groups seemed to increase with treatment duration. Relapse of schizophrenia was twice more frequent with placebo (12 subjects, 25%) compared to MIN-101 (6 subjects, 13%).

In Study MIN-101C03, PANSS negative factor scores improved significantly with MIN-101 beginning at Week 2, and after 8 weeks, both MIN-101 treatment groups showed statistically significant improvements as compared to placebo (at Week 12 MIN-101 32 mg group estimated treatment effect of -1.54, $p \leq 0.0240$; MIN-101 64 mg group estimated treatment effect -1.97, $p \leq 0.0036$) (Davidson et al. 2017). A linear trend of improvement continued during the open-label extension phase for patients of the placebo group who crossed over to MIN-101 treatment as well as for the whole study period in patients treated from the beginning of the study with MIN-101.

Secondary/exploratory efficacy analyses showed statistically significant improvements in the MIN-101 64 mg group compared to placebo after 12 weeks of the double-blind phase for the

[redacted]

1.4.2.3. Safety

MIN-101 was generally well-tolerated. The most common treatment-emergent adverse events (TEAEs) were headache, insomnia, agitation, somnolence, nausea, anxiety, and worsening of schizophrenia symptoms. No postural hypotension was reported. MIN-101 did not induce any

significant change in safety laboratory parameters nor in prolactin levels. The incidence of extrapyramidal symptoms with MIN-101 was low and similar to that observed with placebo. Mean change in body weight was similar with MIN-101 and placebo. No deaths and no instances of Torsade de Pointes, seizures or myocardial ischemia were reported in patient studies

In study MT-210-A02, 50% of patients in the MIN-101 and placebo treatment groups had at least 1 TEAE. Half of the patients who reported TEAEs had events considered possibly or probably related to study drug. The most common TEAEs in the MIN-101 treatment group were headache, dizziness, and nausea. There were no severe TEAEs. A total of 3 patients in the MIN-101 treatment group and 1 patient in the placebo treatment group discontinued due to an AE occurrence. All 3 patients, regardless of treatment, discontinued for mild to moderate prolongation of QTc intervals and/or tachycardia.

In study CYR-101C01, 62.5% of patients receiving placebo and 68.1% of patients receiving MIN-101 reported at least 1 TEAE. Most of the reported TEAEs were classified as unrelated or unlikely related to the study treatment.

The System Organ Class most commonly affected by TEAEs were psychiatric disorders (placebo 45.8% patients; MIN-101: 46.8% patients), followed by gastrointestinal disorders and nervous system disorders. The TEAEs most commonly reported were: nausea, somnolence, agitation, anxiety, insomnia, and schizophrenia.

The majority of TEAEs were mild or moderate in intensity. There were 17 severe TEAEs, 11 of which occurred in the MIN-101 group and 6 in the placebo group. All were classified in the System Organ Class of psychiatric disorders: agitation, anxiety, depression, hostility, negativism, restlessness, schizophrenia, suicide attempt, and tension.

Worsening of schizophrenia was twice as frequent in the placebo group compared to the MIN-101 group. The following symptoms were monitored as extrapyramidal events: muscle rigidity, oculogyric crisis, akathisia, dyskinesia, and tremor. They were observed in 2 patients in the MIN-101 group (muscle rigidity and dyskinesia) and in 3 patients of the placebo group (oculogyric crisis, muscle rigidity, akathisia and tremor). Weight increase was observed in only 1 patient of the MIN-101 group (weight increase of 6.4 kg) and in none of the placebo group.

Overall, 4 SAEs were reported in 3 patients: worsening of psychotic symptoms (placebo), suicide attempt (MIN-101), auditory hallucination, and persecutory delusion (same patient, placebo). Only 1 was judged to be related to MIN-101:

- CYR-101C01: 64 mg SR, 30-year-old female, suicide attempt.

In study MIN-101C03, overall, 62.7% of patients experienced TEAEs, 61.2% of patients who received MIN-101 32 mg, 58.8% of patients who received MIN-101 64 mg, and 43.4% of patients who only received placebo during the double-blind phase. The most commonly reported TEAEs in the double-blind phase (≥ 5% in any treatment group) were schizophrenia, headache, anxiety, asthenia, and insomnia. During the whole study period, headache remained the most common TEAE reported in the MIN-101 groups with a higher incidence compared

to the placebo group (8.8% for total MIN-101 and 3.6% for placebo). However, over the 24 weeks of the extension phase, electrocardiogram QT prolonged was reported by 5.9% of the 64 mg dose of MIN-101 but not by subjects taking either the 32 mg dose or placebo. Insomnia and schizophrenia continued to have a higher incidence for placebo than for MIN-101 subjects.

Most TEAEs were mild or moderate in intensity. Severe TEAEs were reported by 10 (4.1%) patients; 1 patient in the placebo group reported psychotic disorder, 7 patients (psychotic disorder, schizophrenia, agitation, and acute psychosis) in the 32 mg MIN-101 treatment, and 2 patients (psychiatric decompensation, and bradycardia) in the 64 mg MIN-101 group.

A total of 38 patients (15.6%) withdrew from the study due to adverse events (AEs) during the double-blind phase (placebo: 12 patients, 32 mg MIN-101: 13 patients, 64 mg MIN-101: 13 patients). The main reason for withdrawal was psychiatric disorders with the highest incidence with placebo (13.3%) and the lowest incidence with 64 mg MIN-101 (9.6%). A total of 4 patients withdrew due to an AE of cardiac origin: bradycardia, sinus bradycardia, ECG QT prolonged, and ECG T-wave inversion. All the concerned patients received 64 mg MIN-101. TEAEs leading to patient's withdrawal were mild or moderate in intensity except for bradycardia, which was assessed as severe and led to the patient's hospitalization and was therefore reported as a SAE. After completing the double-blind phase, 13 further patients were withdrawn due to TEAEs during the open-label extension phase (8 patients in the MIN-101 32 mg group and 5 patients in the MIN-101 64 mg group), 9 previously treated with MIN-101 and 4 previously treated with placebo. All TEAEs were psychiatric disorders, except one (cholecystitis). They were all mild to moderate in intensity except 2 that were assessed as severe (schizophrenia, 32mg MIN-101)

Overall, 12 SAEs were reported in 12 patients. In all cases the seriousness criterion was the need for (or prolongation of) hospitalization in all cases. Of these, 6 were judged to be related to MIN-101:

- MIN-101C03: placebo, 44-year-old female, schizophrenia.
- MIN-101C03: 64 mg MR, 47-year-old female, abdominal pain and vomiting.
- MIN-101C03: 64 mg MR, 58-year-old female, bradycardia.
- MIN-101C03: 64 mg MR, 27-year-old female, psychiatric decompensation.
- MIN-101C03: 32 mg MR, 30-year-old male, acute psychosis.
- MIN-101C03: 32 mg MR, 53-year-old male, schizophrenia.

Among the TEAEs reported, the following symptoms were identified as possible extrapyramidal symptoms: extrapyramidal disorder, tremor and restlessness. Extrapyramidal disorder was reported in 1 patient in the 32 mg group and none in the placebo and 64 mg groups. Tremor was reported in 1 patient each in the placebo group and in the 32 mg group, and none in the 64 mg group. Restlessness was reported in 1 patient in the placebo group, 4 patients in the 32 mg group and 3 patients in the 64 mg group. All cases were mild in intensity except one, which was assessed as moderate (64 mg group).

Total abnormal involuntary movement scale score was low at baseline and similar across dose groups. No significant change from baseline was observed in any treatment group.

In the patient studies, increases in QTc interval were observed and were related to the dose of MIN 101 administered or to the systemic exposure to the BFB-520 metabolite. Increases in QTcF relative to Baseline were mostly transient and mild. Observed cases of QTc > 480 msec and/or increase > 60 msec from Baseline were exclusively observed at the 64 mg dose level.

One episode of ventricular tachycardia was reported by the central reader in the MT-210-A02 study at the 32 mg dose level (16 mg b.i.d). No record of the ECG tracing is available and the duration of ventricular tachycardia was not provided. No harm was caused to the patient, and the patient was not withdrawn immediately from the study and ventricular tachycardia did not recur either during the residual period at the same dose level (16 mg b.i.d) or at next dose level (32 mg b.i.d).

In Study MT-210-A02 study, there were no patients with QTcB/QTcF values over 480 msec. The mean increase from Baseline in QTc in the MIN-101 SR treatment group was greater at the highest dose level, when the patients were being treated with 48 mg b.i.d. Mean changes from Baseline, on Day 10, Day 11, and Day 12 at dose level 48 mg b.i.d, in QTcB/QTcF were 33.3 msec/19.8 msec, 38.3 msec/25.5 msec, and 17.8 msec/19.6 ms, respectively. The number of patients with QTcB values > 450 msec was greater in the MIN-101 SR group than in the placebo group (50.0% versus 0.0%). Changes in the QTcB > 30 msec were also more common in the MIN-101 SR treatment group than in the placebo treatment group (75.0% versus 25.0%).

In Study CYR-101C01 study, the maximum dose administered was 32 mg twice daily. QTc (B or F) changes from Baseline were higher with MIN-101 at all time-points when compared to placebo, but they were lower than changes in QTc observed in Study A02. The maximum mean change from Baseline in QTcB was +14.1 msec on Day 14 in MIN-101 group, and the maximum mean change from Baseline in QTcF was +11.7 msec on Day 14 with MIN-101. Mean changes from Baseline in QTcB increased from Day 2 to Day 14, and then remained constant until the end of the study. With regards to QTcF, mean changes from Baseline increased from Day 2 to Day 28, and then slightly decreased (mean values always < 10 msec) until the end of study.

Two patients who took the 64 mg dose in the MIN-101C03 study had a significant absolute value in QTcF of > 500 msec and a prolongation > 60 msec from Baseline, 1 of them being symptomatic (syncope, bradycardia). Both QTcF outlier patients had very high exposure to the BFB-520 metabolite. For the patient with syncope this high exposure to the metabolite was observed as early as the second day of treatment, approximately 8 days prior to the reported syncope/SAE.

None of the 78 patients who received the 32 mg dose or the 83 who received placebo exhibited absolute value in QTcF of > 500 msec or prolongation > 60 msec from Baseline of their respective QTcF interval.

1.5. Benefit/Risk Assessment

MIN-101 is being developed for the treatment of schizophrenia and in particular, the negative symptoms of schizophrenia, which are considered as an unmet medical need. After a Phase 2a study (CYR-101-C01) in patients suffering from schizophrenia, which showed promising efficacy signals, a Phase 2b study in schizophrenic patients (MIN-101C03) was conducted. The results were confirmed with MIN-101 showing statistically significant benefit over placebo in improving negative symptoms. The effect was shown for both doses tested: 32 mg dose and 64 mg.

In the present study, patients will receive double-blind treatment for a period of 12 weeks during which active study drug (MIN-101) or placebo will be administered. Patients may not benefit from the study in terms of long-term improvement of their symptoms, however they may benefit from the extensive medical review and disease follow-up during the study.

The main risk of enrolling in this trial is that patients in whom maintenance treatment with antipsychotics has been discontinued, may experience symptomatic worsening and/or display behaviors which may endanger them or others. The immediate benefit of enrolling in the trial is that for some of the patients assigned to placebo it may be revealed that maintenance treatment with antipsychotics is no longer necessary, and hence avoiding the adverse effects of antipsychotics. Furthermore, some patients assigned to experimental drug may experience symptomatic and/or long-term improvement.

To date, a total of 458 subjects have been exposed to MIN-101 in 12 clinical studies.

Thorough review of safety information relevant to the use of MIN-101 indicates that MIN-101 is generally safe and well tolerated, with the most frequently reported TEAEs being headache, anxiety, asthenia, and insomnia in patients with schizophrenia. None of the "classical" side effects generally associated with the currently marketed typical or atypical antipsychotic treatments were observed, such as sedation, prolactin and weight gain increases, or extrapyramidal symptoms. QT prolongation was observed in clinical trials with MIN-101. The risk for QT prolongation is dose related, the main driver for QT prolongation being BFB-520 plasma levels. In the MIN-101C03, 2 patients receiving the highest dose (64 mg) of MIN-101 MR formulation, presented with a significant increase in QTcF. These 2 patients were found to be outliers for BFB-520 levels and were identified within the first 4 weeks of treatment.

To mitigate the risks of antipsychotic discontinuation, patients who entered this trial will be closely followed by the treating/research team by frequent face to face visits and phone calls between visits. This will enable the treatment/research team to intervene promptly as soon as patients experience symptomatic worsening or display behaviors that endanger themselves or others.

To mitigate the risk for QT prolongation, a new formulation will be used in the present study that was developed to specifically avoid the presence of high levels of drug and metabolite concentrations while resulting in the same bioavailability (AUC) observed with the formulation used in the Phase 2b study, which resulted in positive treatment effect.

The following measures have also been implemented in the protocol to further mitigate the risk for QT prolongation:

- Only CYP 2D6 extensive metabolizer patients, will be enrolled.
- Drugs likely to increase QT as well as drugs inhibiting CYP 2D6 and CYP3A4/5 (likely to increase MIN-101 and BFB-520 levels) are not allowed during study participation.
- Exclusion of patients with known personal or familial history of QT prolongation (including congenital long QT syndrome), or with recent acute myocardial infraction, or with uncompensated heart failure.
- Exclusion of patients presenting with risk factors such as hypokalemia, hypomagnesemia, hypocalcemia or bradycardia.
- Close monitoring of the patients, who will be hospitalized during the first 2 days of treatment.
- Close ECG monitoring during the first 2 weeks of treatment with triplicates ECGs performed weekly at the C_{max} of both MIN-101 and the BFB-520 metabolite.
- Stopping rules criteria defined in the protocol in order to exclude patients presenting with abnormal safety finding (notably QTc prolongation) that could put them at risk.
- An external DSMB will be established to review the safety data and formulate recommended decisions/actions in accordance with the charter of the DSMB.

The risk/benefit of MIN-101 is therefore positive and the currently available safety and efficacy data support the proposed MIN-101C07 clinical trial to investigate efficacy of MIN-101 after 12 weeks of once daily dosing in subjects suffering from schizophrenia.

More detailed information about the known and expected benefits and risks of MIN-101 may be found in the latest version of the MIN-101 IB (Version 3.1, 2018).

2. OBJECTIVES

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of 2 fixed doses (32 mg and 64 mg doses) of MIN-101 compared to placebo in improving the negative symptoms of schizophrenia over 12 weeks of double-blind treatment.	• Change from Baseline in the Positive and Negative Syndrome Scale (PANSS) Marder negative symptoms factor score (NSFS)
Key Secondary	
To assess the effect of MIN-101 compared to placebo on the Personal and Social Performance (PSP) over 12 weeks of double-blind treatment	• Change from Baseline in the PSP Total score
Secondary	
To assess the efficacy of MIN-101 compared to placebo on the Clinical Global Impression of Severity (CGI-S) over 12 weeks of double-blind treatment	• Change from Baseline in the CGI-S score
To assess the safety and tolerability of MIN-101 compared to placebo in patients with schizophrenia	• Safety assessments, including adverse events, laboratory values, ECG, vital signs, physical exam, AIMS, BARS SAS, and the Sheehan-STS.

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-S = Clinical Global Impression of Severity; NSFS = Marder negative symptoms factor score; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; SAS=Simpson-Angus Scale; STS = Suicidality Tracking Scale.

In addition, the exploratory objectives are:

[redacted]

- [redacted]

[redacted]

Refer to Section 8, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis is that after 12 weeks, MIN-101 will be superior to placebo on the change from Baseline in the PANSS Marder NSFS.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This will be a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study in approximately 501 schizophrenic patients who present with negative symptoms.

Eligible patients will be randomized in equal proportions to receive once daily MIN-101 64 mg, MIN-101 32 mg, or placebo, PO, for 12 weeks. Afterwards, all patients will continue treatment with active drug for an additional 40 weeks. During the 40-week, open-label treatment extension, patients who were initially randomized to MIN-101 64 mg or MIN-101 32 mg will continue treatment with the same dose, while patients who were initially randomized to placebo will crossover to MIN-101 64 mg or MIN-101 32 mg in a 1:1 ratio per the randomization schedule implemented on Day 1 (Visit 4). The Week 12+1 Day onward dose is the extension phase dose.

This 3-phase study, as depicted in Figure 1, will consist of:

Pre-Treatment Phase:

- *Screening Period (Visit 1)*, including a Screening visit that should take place no more than 28 days before the first administration of study drug on Day 1 (Visit 4).
- *Washout Period (Visit 2)*, an inpatient washout period starting on Day -2 to allow patients on antipsychotic medications or other psychotropics to be washed out from their previous medications. Patients who did not receive any psychotropics will also be hospitalized on Day -2 before Baseline (Visit 3) in order to standardize study procedures in all patients.
- *Baseline Visit (Visit 3, Day -1),* all inclusion and exclusion criteria will be verified and all assessments will be completed prior to initiation of the double-blind treatment phase.

12-Week Double-Blind Treatment Phase:

A double-blind, placebo-controlled treatment phase lasting 12 weeks. On Day 1 (Visit 4), patients will be randomized to treatment (MIN-101 64 mg, MIN-101 32 mg, or placebo) in equal proportions. Patients can be discharged at the discretion of the Investigator from the

investigator's site on Day 2, after taking the blinded study medication, and having undergone 3 ECG assessments (in triplicate) performed at pre-dose and at the approximate time of C_{max} of MIN-101 and its metabolite BFB-520. Hence, patients will be hospitalized for a minimum of 4 days (3 nights). Any authorization to leave the hospital will be done with the help of the Readiness for Discharge Questionnaire (RDQ, Attachment 2). On Day 2 (Visit 5), if discharged, the patient will come back for visits at Weeks 1, 2, 3, 4, 8, and 12 for efficacy and/or safety assessments. Hospitalization on Visits 6 and 7 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. The patient (or his/her care provider) will be contacted by phone at Weeks 5, 6, 7, 9, 10, and 11 to verify safety and to make sure the patient is doing well and is compliant with study medication.

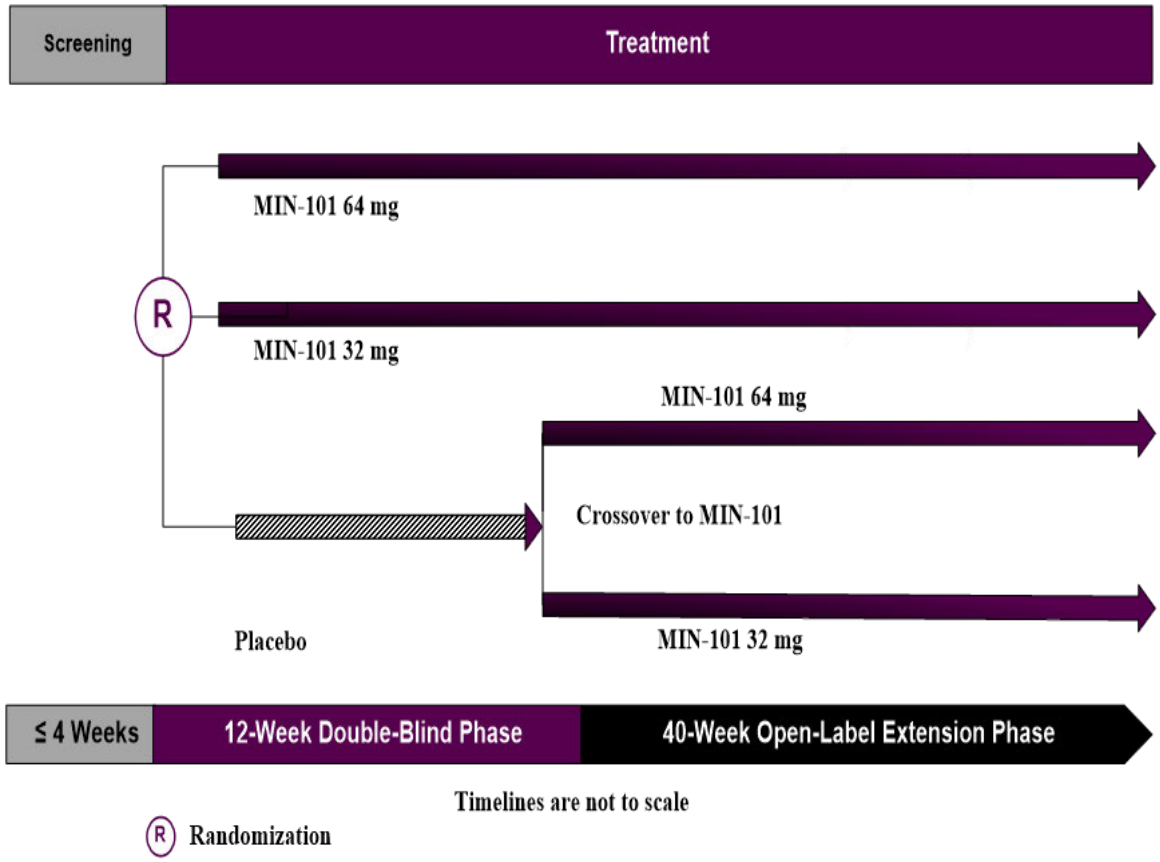
In case of early termination during the double-blind phase, the Week 12 (Visit 11) must be completed as soon as possible.

40-Week Open-Label Extension Phase:

At the end of the 12-Week double-blind treatment period (Visit 11), patients will be immediately enrolled into the 40-week open-label extension phase. Patients will be hospitalized for 2 days after the initiation of treatment with MIN-101 (all patients). Patients who received placebo for 12 weeks during the double-blind phase will start receiving 64 mg or 32 mg of MIN-101 per the randomization schedule implemented on Day 1 (Visit 4). Patients will then be allowed to leave the hospital on Visit 13 (Week 12 + 2 days) at the discretion of the investigator and after drug intake and safety have been ascertained clinically, including having undergone 3 ECG assessments (in triplicate) performed at pre-dose and at the approximate time of C_{max} of MIN-101 and its metabolite BFB-520. However, the Investigator may decide to keep the patient hospitalized as needed. RDQ will be completed prior to any authorization to leave the hospital. Hospitalization on Visits 14 and 15 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done. Visits 16 to 26 will be ambulatory.

EOS (Week 54 / Visit 27) assessments will be performed within 2 weeks following the last treatment visit (Week 52 / Visit 26). In case of early withdrawal, the End of Treatment visit (Week 52/ Visit 26) must be completed as soon as possible. It will be followed ±2 weeks later by the EOS visit (Week 54/Visit 27).

Figure 1. Study Design Diagram



Study Evaluations

All study-specific assessments including efficacy, safety, will be performed as outlined in the Time and Events Schedules that appear after the synopsis.

Efficacy will be evaluated based on the change from Baseline to Week 12 (or at early withdrawal) in the PANSS NSFS. Additionally, the changes from Baseline in PSP total score and subscale (socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors) scores, CGI-S, [redacted]

Safety will be evaluated by monitoring the frequency, severity, and timing of AEs, clinical laboratory test results, 12-lead triplicate ECGs, vital signs measurements, body weight, waist circumference, physical examinations, and pregnancy testing for women of childbearing potential. Laboratory assessments will be monitored throughout the study. For each ECG (performed in triplicate), the QTcF will be measured and evaluated. Specific rating scales also used in the study include the AIMS, BARS, and SAS to assess the extrapyramidal symptoms, and Sheehan-STS to assess suicidal ideation/behavior.

Blood samples (4 mL) for assessing MIN-101 concentration in plasma will be obtained throughout the study with extensive monitoring during the first 4 weeks of both the double-blind and the open-label phases at pre-dose and approximate time of T_{max} of the MIN-101 and BFB-520 plasma levels. Additional samples will be taken during the study to evaluate the presence of prohibited concomitant medications. These samples may be assayed to aid with the interpretation of any ECG abnormalities detected during the visit.

3.2. Study Design Rationale

This Phase 3 study is intended to extend and replicate the results obtained in the previous Phase 2b study of MIN-101, with a schizophrenia patient population that is generalizable to patients seen in clinical practice. Consequently, patients with negative symptoms and without severe symptoms of suspiciousness, agitation, hostility, or impulsivity will be recruited for participation in this study. This will ensure that relatively stable yet symptomatic patients in terms of negative symptoms will be included. Interestingly, recent literature and the experience with the MIN-101 recently completed Phase 2b study show that such a design with the eligibility criteria proposed in this study might be the best approach to achieve the primary and secondary objectives, yet it will also be representative of the real patient population to be treated when the drug will be used in clinical practice (Dunayevich et al. 2014).

Negative, positive, and global PANSS scores will be assessed, as well as functioning and cognition. The Marder NSFS, derived from the administration of the complete PANSS test will be the primary endpoint after 12 weeks of double-blind treatment. Personal and social performance will constitute the key secondary endpoint. [redacted]

MIN-101 will be administered during 12 weeks in a double-blind, placebo-controlled manner. Because additional MIN-101 benefits seem to build up over time, patients who complete the 12-Week double-blind treatment phase will be given the opportunity to participate in a 40-week, open-label treatment extension, in which all patients will receive active drug (32 mg or 64 mg). This will also provide data on the persistence of the therapeutic effect as well as long-term safety.

Two doses of MIN-101 and placebo will be assessed over the first 12 weeks. Both doses (daily 32 and 64 mg) of the newly formulated MIN-101 tablets, with gastro-resistant coating, expected to be equivalent to the ones investigated in the Phase 2b study with regards to AUC, but with a lower C_{max}, will be investigated.

The study is intended to extend and replicate results from the previous placebo-controlled studies of MIN-101 where a statistically significant improvement in negative symptoms was observed as early as 2 weeks that persisted through the primary objective time point at Week 12. In the present study, schizophrenic patients with negative symptoms will be included as they are likely to benefit from the treatment with MIN-101.

Although the primary objective of this study is the effect of MIN-101 on negative symptoms, it remains unclear whether there are common neurobiological mechanisms that underlie cognitive deficits and negative symptoms of schizophrenia (Buchanan et al. 2010). In the previous patient study, MIN-101 showed a trend to an improvement in cognition in parallel to the improvement in negative symptoms; therefore, verbal fluency will be assessed in the present study.

Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown patient attributes (e.g., demographic and Baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Parallel-group design rather than cross-over design has been chosen to avoid ambiguous interpretation of results due to carryover effects. Blinding of the investigators and the patients to actual treatment reduces bias that would otherwise be introduced.

The use of an open-label extension phase allows patients initially randomized to placebo to gain exposure to MIN-101, and for the extended exposure of patients to MIN-101 who may be benefiting from the treatment. It also allows for the assessment of the persistence of effect beyond the 12-week double-blind phase, albeit in an open-label fashion.

Study Population

The study population will consist of adult men and women (aged 18 to 55 years, inclusive) with a diagnosis of schizophrenia as defined in DSM-5, established by a full psychiatric interview in conjunction with the MINI. The threshold for negative symptoms will be defined by PANSS negative subscore (N1+N2+N3+N4+N5+N6+N7) of > 20. Additionally, to ascertain patients' cooperation with the study, stability and safety, patients must have PANSS item score of ≤ 4 on items P4 (excitement/hyperactivity), P6 (suspiciousness), P7 (hostility), G8 (uncooperativeness), and G14 (Poor impulse control).

Choice of Control Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints (efficacy and safety) that may occur in the absence of active treatment. No active control group can be included since there are currently no approved treatments that could serve as positive control.

Most schizophrenia studies have demonstrated that simply participating in a study produces a certain improvement in symptoms. This improvement is probably related to the nursing care and attention awarded by the clinicians and investigators, the patients' altruistic pride of contributing to science, and many other non-specific factors.

The following observations also favor the use of a placebo comparator in this study:

- The trend to improve on placebo has slowly but progressively increased in studies carried out over the last 20 years (Kemp et al. 2010). The Phase 2b study with MIN-101 confirms

this tendency because some patients who received placebo completed the 12-week treatment duration with some improvement on the efficacy measures.

- In studies recruiting chronically ill patients and using an active control in addition to placebo, the active control (verifiably effective drugs) has not been more effective than placebo (i.e., all groups showed significant improvement compared to Baseline (Kinon et al. 2011).
- Currently, there are no objective biological outcome measurements for treatment effect, and despite the best investigator training, outcome measurements remain partially subjective. Therefore, demonstrating symptom improvement in an investigational medication group relative to Baseline without a placebo group would be meaningless and would expose patients to an investigational medication without any scientific benefit.
- Consistent with The Declaration of Helsinki, studies may be ethically acceptable even if proven therapies are available (which is not the case for negative symptoms in patients suffering from schizophrenia) under 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.
- The use of placebo is also recommended by the European Medicines Agency (EMA) to allow for an accurate analysis of the data. In the "Guideline for investigation of medicinal products, including depot preparations in the treatment of schizophrenia" (EMA/CHMP/40072/2010 Rev.1 2012), EMA states that "…assay sensitivity cannot be guaranteed even in well designed and conducted trials if a placebo arm is not included…a placebo control…is also highly desirable so that the 'absolute' effects (both therapeutic and adverse) of a product can be ascertained".
- Findings from short-term, placebo-controlled studies also suggest that there is no higher risk of death, suicide, or suicide attempts among patients treated with placebo for short durations (Isaac & Koch 2010, Storosum et al. 2003).
- Finally, to minimize the risk of patients receiving placebo, only one-third of the patients will receive placebo during the 12-week, double-blind, placebo-controlled, treatment phase.

Washout and Monotherapy

In any trial of a new drug there is a risk in removing regular medications and starting an investigational compound. To minimize the risks, patients will undergo a Screening period, including hospitalization during the Washout Period and at least during the first 2 days of the

new treatment (Washout Period from Day -2; Baseline assessment on Day -1, and treatment on Days 1 and 2). Patients will be allowed to leave the hospital on Day 2, after the administration of the second dose of treatment and after completion of the RDQ and safety check. However, the investigator may decide to keep the patient hospitalized as needed. Patients will then be seen weekly for the first 4 weeks of the double-blind phase, with the first visit occurring within 5 days after being discharged. Additional hospitalization on Visits 6 and 7 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done.

The same procedures will apply after the completion of the double-blind treatment phase. This approach will apply to all participating patients to ensure patients previously treated with placebo and are exposed to MIN-101 for the first time undergo extensive safety monitoring. As such, all patients will be hospitalized at Week 12 (Visit 11) through the start of the open-label treatment period. Patients will be allowed to leave the hospital on Day 2 (Visit 13), after the administration of the second dose of treatment and after completion of the RDQ and safety check. However, the investigator may decide to keep the patient hospitalized as needed. Patients will then be seen weekly for the first 4 weeks of the open-label phase, with the first visit occurring within 5 days after being discharged. Additional hospitalization on Visits 14 and 15 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done.

Also, when antipsychotic medication is discontinued, some patients manifest less avolition and sedation, as well as no EPS or metabolic adverse events. Some of the patients from whom antipsychotic medication is discontinued might have symptomatic worsening. However, this is also true for some patients maintained on medication. Antipsychotic maintenance treatment only reduces the risk of symptomatic worsening, but it does not prevent it as many patients' symptoms worsen and are exacerbated while on medication (Leucht et al. 2012a). Also, many chronically ill but stable patients who in the first years of illness might have benefited from antipsychotics cease to benefit after 5 to 10 years of use (Harrow et al. 2014).

MIN-101 monotherapy has been selected for this study based on efficacy and safety data from the previous Phase 2a and 2b studies which also used a monotherapy design. The possibility of conducting an add-on study in which all patients would be given an antipsychotic treatment followed by MIN-101 or placebo was considered and ruled out. In an add-on design, in order to obtain the necessary statistical power, many thousands of patients will have to be exposed to the investigational medication instead of a few hundred patients in a classic monotherapy design. Furthermore, it is possible that the interference of the dopamine blocking antipsychotics with the dopamine mediated pleasure circuits obliterate the possibility of improvement in negative symptoms due to pharmacological intervention.

Because MIN-101 likely has antipsychotic effects, the effects of MIN-101 would be difficult to ascertain if all patients were treated with an antipsychotic drug. Moreover, antipsychotic drugs induce negative symptoms (e.g., secondary negative symptoms which are hardly distinguishable from primary negative symptoms). Treating all patients with antipsychotic drugs would confound the potential effects of MIN-101 on primary negative symptoms.

Furthermore, attempts to improve negative symptoms and/or CIAS in add-on designs have been unsuccessful to date (Goff 2014).

Study Duration

Study drug will be administered during 12 weeks in a double-blind, placebo-controlled treatment phase, which is consistent with the treatment duration of the previous Phase 2b study with the same patients. Although several patients prematurely dropped out of the 12-week treatment period, significant benefits were observed in the MIN-101-treated patients after 12 weeks.

Twelve weeks of treatment was also used in a previous study exploring the effects of amisulpride, with a primary emphasis on effects on negative symptoms (Boyer et al. 1995, Loo et al. 1997, Danion et al. 1999). Based on the fact that long-term data may be required, an extension phase of 40 weeks is planned in this study. In this open-label extension phase, all patients who successfully completed the 12-week, double-blind treatment phase, will be randomized to receive either MIN-101 32 mg/day or 64 mg/day in the 40-week, open-label treatment extension.

Dose Selection and Dose Administration

The daily doses in this study are 64 mg and 32 mg. Both doses are equivalent to the doses which were given to patients in the previous Phase 2b study and proved to be efficacious. The newly formulated 32-mg tablet was tested in clinical Study MIN-101C06 along with the previously used MR tablet (reference formulation) of the same strength in a crossover design. The MIN-101 AUC_{inf} ratio (test to reference) was 0.98 (90% CI: 0.81, 1.19), and the BFB-520 AUC_{inf} ratio was 0.96 (90% CI: 0.86, 1.07), consistent with the reformulation design specification. Furthermore, the C_{max} data for both MIN-101 and BFB-520 were also consistent with the reformulation specifications that targeted achieving a reduction in the maximum concentration levels: test to reference ratio of 0.66 (90% CI: 0.53, 0.83) for MIN-101, and 0.74 (90% CI: 0.60, 0.92) for BFB-520.

Both doses (daily 32 and 64 mg) have now been reformulated with gastro-resistant coating. By giving these 2 doses in this well powered study, it is expected that their therapeutic effects will be confirmed. Furthermore, using 2 doses may allow for determination of a dose-response effect. Therefore, the planned dose range for this study (32 mg and 64 mg) was selected based on anticipated efficacious dose levels and plasma exposure.

Drug administration will be in the morning, with or without food. This will be a deviation from the dose administration implemented in the Phase 2b study which required dosing in the fasted state. The newly formulated tablets have been tested in study MIN-101C06 under both fasted and fed conditions and the results of the AUC_{inf} and C_{max} comparison suggest food intake will have minimal, but acceptable differences that are within the reformulation design specifications.

Measurement Tools

Primary Efficacy Measure

Marder NSFS: For the effects of MIN-101 on negative symptoms, the Marder NSFS will be used. The NSFS has been the most frequently used scale in schizophrenia clinical studies focusing on negative symptoms since it was published in 1997 (Marder et al. 1997). The NSFS consists of the sum of the PANSS items N1, N2, N3, N4, N6, G7, and G16, and the primary duration of assessment is over 12 weeks of treatment. The PANSS scale is the most frequently used scale in schizophrenia clinical studies worldwide, and is available in many languages. The NSFS is psychometrically robust, reliable, with well documented construct and content validity, inter-rater reliability, sensitivity, and specificity (Edgar et al. 2014).

Secondary Efficacy Measures

PSP: Social functioning will be evaluated using the PSP scale, which is one of most used scales to evaluate the effect of treatment with antipsychotic drugs on functional performance. The PSP was derived from the Social and Occupational Functioning Assessment Scale in 2000, and is available in several languages. The PSP is easy to administer and measures 4 areas of functioning and its anchors only take into consideration the functioning of the individual, independently of symptomatology. The PSP considers 4 areas of social and individual performance (socially useful activities, including work and study; personal and social relationships; self-care; disturbing and aggressive behaviors). For filling it, the clinician must assign an initial six-degree of severity to each area (absent, mild, manifest, marked, severe or very severe). Then, in a table with levels of score set the correspondent decimal (e.g., 21-30), according to the observed performance and, within the decimal range, the assigned unit to determine the final score (e.g., within the range 21-30, the performance corresponds to the score 24). The resulting final value is a single measurement from zero to 100% of functioning. This single value will be the key secondary endpoint for this study.

[redacted]

CGI-S and [redacted] The CGI-S [redacted] will be used as an anchor-based approach of the global impression of the clinician, and to assist in the interpretation of the changes in the NSFS and PSP total score. The 2 CGI measures are also widely used in psychiatric clinical trials and

have shown robust construct and content validity, inter-rater reliability, sensitivity, and specificity.

Cognitive Assessment: Cognitive performance will be assessed since it is possible that there are common neurobiological mechanisms that underlie cognitive deficits and negative symptoms in schizophrenia (Buchanan et al. 2010). Verbal fluency test will be used to represent cognitive performance. This is an established test, simple to administer and perform, and addresses improvement in attention, abstract thinking and categorization, and is available in many languages.

[redacted]

Pharmacokinetic Assessments

A population PK analysis using PK data from a selection of Phase 1 and Phase 2 studies will be performed at the completion of the study. The purpose of the planned population PK analysis will be to assess the PK of MIN-101 and the metabolite BFB-520 in the target patient population, and the potential impact of covariates. PK collection will also enable the evaluation of the relationship between parent drug concentration and metabolites, and the exploration of the correlation of exposure to efficacy or safety measures. These analyses will be helpful in identifying optimal exposure to evaluate in subsequent studies.

Safety Evaluations

Standard safety evaluations including collection of adverse events with special focus on adverse events of special interest, and concomitant medications, physical examination, body weight, waist circumference, vital signs, 12-lead ECG, pregnancy testing, and clinical laboratory tests will be performed to monitor subject safety throughout the study.

Drug-induced EPS will be monitored using the clinician-administered AIMS, BARS, and SAS. The AIMS measures involuntary movements or tardive dyskinesia (TD). TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The SAS measure drug-induced extrapyramidal syndromes. Extrapyramidal syndromes are any of a group of clinical disorders marked by abnormal involuntary movements, alterations in muscle tone, and postural disturbances; the group includes parkinsonism, chorea, athetosis. The BARS evaluates the severity of drug-induced akathisia. The scale includes objective, subjective, and global items such as the level of the patient's restlessness.

Emergence of suicidal ideation will be assessed using the Sheehan-STS. The Sheehan-STS has been used frequently in clinical studies and it is a standard measure for suicidal ideation assessment; its use is in accordance with Food and Drug Administration guidance.

4. STUDY POPULATION

Patient eligibility per all the inclusion and exclusion criteria must be met and assumes the investigators exercised their best judgment in reaching the decision to include or exclude any one patient.

The inclusion and exclusion criteria for enrolling patient in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a patient in the study. Exceptional and limited re-testing of abnormal screening values, including laboratory values, vital signs, and ECGs that potentially lead to exclusion are allowed using an unscheduled visit during the screening period to reassess eligibility.

If a patient does not meet all inclusion and exclusion criteria at initial screening visit (e.g., a screen failure), but in the future is expected to meet the eligibility criteria, the patient may be rescreened on one occasion only. This should be discussed with and approved by the sponsor's medical monitor prior to re-screening. Patients cannot be rescreened if they failed screening on DSM-5 criteria for schizophrenia, or PANSS negative symptom score. Patients who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

4.1. Inclusion Criteria

Each potential patient must satisfy all the following criteria to be enrolled in the study:

1. Patient and patient's legal representative, if applicable, provided informed consent prior to the initiation of any study related procedures, and the patient is judged by the investigator as being capable of understanding the study requirements.
2. Male or female patient, 18 to 55 years of age, inclusive, and BMI< 35 kg/m^2 at Screening.
3. Patient meets the diagnostic criteria for schizophrenia as defined in the DSM-5, as established by a full psychiatric interview in conjunction with the MINI.[a]
4. Has a caregiver or family member or health care personnel who can provide information towards assessment and support the patient in terms of compliance with the protocol. The caregiver must have contacts with the patient frequently and is not expected to change during the trial.
5. Documented diagnosis of schizophrenia for at least 1 year before screening into the trial.
6. Patient is stable in terms of both positive and negative symptoms of schizophrenia over the last 6 months according to his or her treating clinician and/or based on documentation in the clinical chart or medical record. Patients with or without positive symptoms are allowed if these symptoms are stable for the last 6 months and the patients do not meet exclusion criterion # 2.

[a] Current version for DSM-5.

7. Patient is currently an outpatient and has not been hospitalized for the last 6 months for acute exacerbation or symptoms worsening. Patients hospitalized for any time period during the last 6 months for social reasons or are currently hospitalized for social reasons can be included only with Sponsor's Responsible Medical Officer's approval (in addition for Ukraine only, the following criteria must be fulfilled: the patient has permanent place of residence, is legally capable, and has a caregiver [see inclusion criterion # 4]). The social reasons must be documented in the eCRF.
8. Patient with a score of > 20 on the PANSS negative subscore (the original PANSS scale [Sum of N1+N2+N3+N4+N5+N6+N7]) at Screening (Visit 1) and Baseline (Visit 3) AND < 4 points absolute difference between the 2 visits.
9. Patients can be on any psychotropic before the trial if the psychotropics can be discontinued at the beginning of the washout phase without risking the patient's clinical status or safety.
10. No history of violence against self or others during the last 1 year.
11. Female patient who are not of childbearing potential, defined as women who are post-menopausal (defined as spontaneous amenorrhoea for at least 1 year or spontaneous amenorrhoea for at least 6 months confirmed by follicle stimulating hormone result of ≥ 40 IU/mL) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).
12. Female patient, if of childbearing potential, must test negative for pregnancy and must be using a double barrier contraceptive method.
13. Patient must be extensive (normal) metabolizers for P450 CYP 2D6, defined as a subject that has at least one functional allele (e.g., *1, or *2), as determined by study-specific genotyping test before the first drug dose is administered.
14. Patient and the caregiver are considered by the investigator to be reliable and likely to cooperate with the assessment procedures.

4.2. Exclusion Criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the study:

1. Current major depressive disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, or intellectual disability (intellectual developmental disorder diagnosed by age 14).
2. Patient with PANSS item score of > 4 on:
    - P4 Excitement/hyperactivity
    - P6 Suspiciousness/persecution
    - P7 Hostility
    - G8 Uncooperativeness

- G14 Poor impulse control.

3. A CDSS total score > 6.
4. A score of ≥ 2 on any 2 of items 1, 2, or 3, or a score of ≥ 3 on item 4 of the BARS.
5. Patient's condition is due to direct physiological effects of a substance (e.g., a drug of abuse, or medication) or a general medical condition.
6. Has a current or recent history of serious suicidal behavior within the past 1 year.
7. Patient has a history of substance use disorder within 3 months of the Screening visit (excluding caffeine and cigarette smoking).
8. Positive urine drug screen for drugs of abuse (cocaine, methadone, amphetamines, cannabinoids, opiates, benzodiazepines, and barbiturates), TCA, and alcohol (except for prescription benzodiazepines).
9. Patient who cannot be discontinued from psychotropics other than those allowed.
10. Patient who received clozapine within 6 months of the Screening visit except when used for insomnia at doses ≤ 100 mg per day.
11. Patient receiving treatment with long-acting or depot antipsychotic medication unless his/her next scheduled dose will occur during the protocol Screening period and can be omitted to allow for sufficient washout before receiving the study drug.
12. Patient with a history of significant other major or unstable neurological, neurosurgical (e.g., head trauma), metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, metabolic, gastrointestinal, or urological disorder.
13. Patient with a history of seizures (patient with a history of a single childhood febrile seizure may be enrolled in this study).
14. Patient who has had ECT, VNS, or r-TMS within the 6 months prior to the Screening visit or who are scheduled for ECT, VNS, or r-TMS at any time during the study.
15. Patient with clinically significant abnormalities in hematology, blood chemistry, ECG, or physical examination not resolved by the Baseline visit which according to Investigator can interfere with study participation.
16. Current systemic infection (e.g., Hepatitis B, Hepatitis C, HIV, tuberculosis). Patients with positive Hepatitis B core antibody test and negative HBsAg may be included in the study if aminotransferase levels (ALT/SGPT and AST/SGOT do not exceed 2 times ULN.
17. Patient who requires or may require concomitant treatment with any other medication likely to increase QT interval (e.g., paroxetine, fluoxetine, duloxetine, amiodarone).
18. Patient who requires medication inhibiting CYP 2D6 or CYP 3A4.
19. Patient with a clinically significant ECG abnormality that could be a safety issue in the study, including QT interval value corrected for heart rate using QTcF > 430 msec for males and > 450 msec for females.

20. Patient with a history of myocardial infarction based on medical history or ECG findings at Screening.
21. Familial or personal history of long QT syndrome or with additional risk factors for Torsade de Pointes.
22. Patient whose safety laboratory results show one or more of the following: potassium < 3.4 mmol/L, or calcium < 2.07 mmol/L, or magnesium < 0.70 mmol/L.
23. Patients with unexplained syncope.
24. Woman of child-bearing potential, or man, who are unwilling or unable to use accepted methods of birth control.
25. Woman with a positive pregnancy test, is lactating, or is planning to become pregnant during the study.
26. Patient who participated in another clinical study within 3 months prior to Screening, or received MIN-101 previously, or has previously participated in > 2 clinical studies with experimental medication within the past 2 years (previous participation in 3 clinical studies with experimental medication will require approval of the sponsor before eligibility is determined).

4.3. Prohibitions and Restrictions

In general, concomitant medications with primary CNS activity, as well as CYP 2D6 and CYP 3A4/5 inhibitors and concomitant medications likely to increase QT interval are not allowed in this study (refer to Attachment 1). The following are examples of prohibited medications/therapies during the study:

- Oral or injectable antipsychotic medications other than study drug medication
- Depot antipsychotic medication
- Clozapine
- ECT
- VNS
- r-TMS
- Antidepressants
- Lithium

Patients should be discontinued from the study if any of the above prohibited medications are used during the study (the Sponsor's Responsible Medical Officer can allow exceptions).

For a complete list of prohibited therapies, please refer to Attachment 1 (Allowed and Prohibited Concomitant Medications). Of note, grapefruit and Seville oranges (and their juices) are CYP 3A4 inhibitors and must not be consumed during the study.

Additional restrictions include female patients of childbearing potential, and men, who are unwilling to use an accepted method of contraception during the course of the study.

4.4. Prior and Concomitant Therapy

4.4.1. Prior Therapy

Any medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) that the patient is receiving at the time of Screening, or receives during the study, must be recorded on the appropriate eCRF along with the reason for use, dates of administration, and dosages.

An attempt will be made to gather information on any previous antipsychotics used to treat schizophrenia during the last 1 year and these will be recorded at the Screening Visit. Information on the dose, date of last administration, length of time on medication will be collected in the source documents and appropriate eCRF pages.

4.4.2. Concomitant Therapy

All medications, including anticholinergics and other anti-EPS, except study drug, administered to a patient during the study (post-randomization), should be documented in the eCRF as concomitant medications.

The following rescue medications, not exceeding the doses allowed by the local approvals, will be allowed for the treatment of the following conditions and must be documented on the appropriate eCRFs. After symptoms have resolved, the *Pro Re Nata* (as needed, rescue) (PRN) dosage should be reduced as much as possible, and discontinued as soon as possible:

Episodic insomnia, agitation, anxiety, and restlessness complaints

- zolpidem
- zolpidem CR
- zaleplon
- zopiclone
- lorazepam (PO or IM) or equivalent benzodiazepine

Extrapyramidal Symptoms

Anticholinergic medication should be discontinued no later than at the Baseline visit (Visit 3). If treatment for EPS is clinically indicated afterwards, allowed anticholinergics may be given at the approved dose range throughout the study as needed.

The use of anticholinergic medication as prophylaxis for extrapyramidal symptoms is prohibited.

Allowed medications for treatment of EPS include:

- anticholinergics,
- benztropine mesylate,
- biperiden,
- procyclidine, and

- trihexyphenidyl (benzhexol)

Contraception

Patients who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of investigational medicinal product administration until 90 days after the last dose of investigational medicinal product.

The following are considered as highly effective contraception methods:

- Surgical sterilization (i.e., bilateral tubal ligation/salpingectomy, hysterectomy for female patients or partners; vasectomy for male patients or partners).
- Placement of an intrauterine device or intrauterine system.
- Hormonal contraception (implantable, patch, oral, injectable).
- Barrier methods.
  - for male patients, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]
  - for female patients, either their partner's use of a condom or the patient's use of an occlusive cap [diaphragm or cervical/vault caps]

5. TREATMENT ALLOCATION AND BLINDING

5.1. Randomization

Central randomization will be implemented in this study. Patients will be randomized based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by region (United States, all other countries). The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the patient.

Patients will be randomized at Baseline to 1 of 4 treatment arms in a 2:2:1:1 ratio as follows:

- MIN-101 64 mg for the entire study, or
- MIN-101 32 mg for the entire study, or
- Placebo for 12 weeks followed by MIN-101 64 mg dose during the open-label extension phase, or
- Placebo for 12 weeks followed by MIN-101 32 mg dose during the open-label extension phase.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual patient, if needed.

5.2. Blinding

Under normal circumstances, the blind should not be broken until all patients have completed the double-blind phase of study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment the patient is receiving. In such cases, the investigator may in an emergency determine the identity of the treatment by IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week.

In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the investigator, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the patient's source documents in a secure manner (e.g., sealed envelope) so as not to unblind the treatment assignment to the study site, sponsor/contract research organization personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

6. DOSAGE AND ADMINISTRATION

On Day 1 (Visit 4) of the double-blind treatment phase, patients will be randomized to receive once daily MIN-101 32 mg or 64 mg doses, or placebo for 12 weeks, followed by a 40-week open-label treatment extension phase when all patients will receive MIN-101 (Table 3).

Study drug will be packaged using a double-blind design. Drug supplies of the study drug will be packaged using blister card each containing 9 tablets, the equivalent of 1 week of treatment plus 2 tablets (security margin). The patients will receive sufficient medication at the scheduled visits per the Time and Events Schedule. Daily dosing will consist of 1 tablet each containing the intended dose. Placebo and MIN-101 tablets are identically matched in appearance and the MIN-101 tablets are available in 32 mg and 64 mg strength.

Table 3. Characteristics of the Treatment and Dosage per Fully Compliant Patient

Treatment/ daily dosage	Tablet Strength		Total Number of Tablets		
	MIN-101 (mg)	No. of placebo tablets	During 12-week Double-blind Phase	MIN-101 Tablets During 40-week Open-label Phase	Total MIN-101 Tablets Administered
Placebo then 32 mg	0 mg	1	84 (0 mg)	280 (32 mg)	280 (32 mg)
Placebo then 64 mg	0 mg	1	84 (0 mg)	280 (64 mg)	280 (64 mg)
32 mg	32 mg	0	84 (32 mg)	280 (32 mg)	364 (32 mg)
64 mg	64 mg	0	84 (64 mg)	280 (64 mg)	364 (64 mg)

The study drug should be administered in a single dose in the morning at approximately the same time each day, with or without food and no later than 2 PM (local time). Tablets should be swallowed whole with water and not divided, crushed, chewed, or placed in water. Patients who are fully compliant will take up to 84 tablets during the double-blind phase, and a total of up to 364 tablets for the whole study, including the 40-week extension phase. If a patient misses a dose, the dose can be taken up to 2 PM (local time) on the day of dosing. Otherwise the dose must be skipped. The next dose will be taken on the next morning. The patient must not take 2 doses in any one day.

Patients (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and excluded concomitant medications (e.g., QT active drugs).

7. TREATMENT COMPLIANCE

On Days 1 and 2, patients will receive their first dose of study drug after an overnight stay at the hospital. While out-patient, the drug will be self-administered by the patient at their residence.

The number of study drug tablets dispensed for self-administration by patients will be recorded and compared with the number returned during each scheduled visit. Patients are required to record the administration of study drug in diaries and record the time of drug intake. The diaries will be checked and verified against the pill counts and the patients will be counseled regarding compliance at every scheduled visit.

The investigator or designated study center personnel will maintain a log of all study drug dispensed and returned during the study. Patients who have < 75% compliance by Week 8 (Visit 10) may be discontinued from the study following consultation with the study medical monitor.

8. STUDY EVALUATIONS

8.1. Study Procedures

8.1.1. Overview

The Time and Events Schedule that follows the Synopsis summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study.

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local law or regulation, to establish the absence of pregnancy throughout the study.

During the 12-week double-blind phase, the total blood volume to be collected from each patient will be 226.5 mL: 110.5 mL for safety laboratory tests, 84 mL for PK, and 32 mL for concomitant medications.

During the 40-week open-label phase, an additional 334 mL of blood will be collected: 134 mL for safety laboratory tests, 140 mL for PK, and 60 mL for concomitant medications.

These estimates are for required blood samples and do not include additional blood samples that may be collected at the investigator's discretion for drug level monitoring or other clinical laboratory tests deemed necessary for appropriate patient care in case of occurrence of AEs (Table 4).

Table 4. Estimated Blood Volume Drawn[a]

Phase: Type of Sample	Volume per Sample (mL)	No. of Samples per Patient	Total Volume of Blood (mL)[b]
12-Week Double-Blind Treatment Phase:			
Safety:			
Hematology	2	5	10
Chemistry + hormones	16	5	80
HbA1c	2	3	6
Serology[c]	8.5	1	8.5
Genotype	6	1	6
Concomitant Medication Evaluation	4	8	32
Pharmacokinetic	4	21	84
Subtotal		44	226.5
40-Week Open-Label Extension Phase:			
Safety (including end-of-study evaluations):			
Hematology	2	7	14
Chemistry + hormones	16	7	112
HbA1c	2	4	8
Concomitant Medication Evaluation	4	15	60
Pharmacokinetic	4	35	140
Subtotal		68	334
Total		112	560.5

[a]Estimates are based on maximum amount of blood drawn for protocol-specific procedures.
[b]Calculated as number of samples multiplied by amount of blood per sample.
[c]Includes HBsAg, anti-HCV, and anti-HIV.

8.1.2. Pre-Treatment Phase

The pretreatment phase should not exceed 28 days but can be as short as 1 week.

8.1.2.1. Screening Period (Visit 1)

At the Screening visit, a signed informed consent form for study participation will be obtained. Informed consent must be freely given by the patient and the patient's legal representative (if applicable) and documented by signature before any procedures are performed. Screening procedures will be performed as outlined in the Time and Events Schedule that follows the Synopsis.

Screening procedures should be performed within 28 days before study drug is administered on Day 1.

Psychiatric history and diagnosis of schizophrenia will be made using the MINI and the DSM-5 Diagnostic Criteria. Patients will have a physical examination and specific laboratory tests as outlined in the Time and Events Schedules. All Screening procedures/scales should be completed and laboratory results, including genotyping, should be available prior to the Baseline visit (Visit 3).

If a patient does not meet all inclusion and exclusion criteria at initial screening visit (e.g., a screen failure), but in the future is expected to meet the eligibility criteria, the patient may be rescreened on one occasion only, as described in Section 4.

8.1.2.2. Hospitalization Period: Washout (Visit 2) and Baseline (Visits 3)

All inclusion and exclusion criteria will be reviewed prior to patients entering the washout phase of the study. Eligible patients will be hospitalized during the washout period and the first 2 days of treatment (washout period for 2 full days starting on Day -2; Baseline assessment on Day -1; and study Day 1 and Day 2). On Day -2 (and no earlier than Day-5), baseline safety laboratory assessments including urine drug screen and pregnancy test will be sampled. On Day -1 (Baseline or Visit 3), efficacy and the remaining safety assessments will be performed as outlined in the Time and Events Schedule. Eligibility criteria will be verified before randomization on Day 1. The results of the safety laboratory assessments including the urine drug screen as well as the analysis of the baseline ECGs by the central reader must be reviewed by the site prior to randomization. The randomization must be postponed if these results are not available for review.

8.1.3. Double-Blind Treatment Phase

8.1.3.1. Day 1/Randomization (Visit 4)

While remaining hospitalized on Day 1 (Visit 4), all patients will be randomized to 1 of 3 treatment groups: MIN-101 64 mg, MIN-101 32 mg, or placebo and will receive the first dose of study drug. Pharmacokinetic blood samples will be drawn as per the Time and Events Schedule.

8.1.3.2. Day 2 (Visit 5) to Week 8 (Visit 10)

Patients will be allowed to leave the hospital on Day 2, after the administration of the second dose of treatment, and after having undergone 3 ECG assessments (in triplicate) and PK evaluation performed at pre-dose and at the approximate time of C_{max} of MIN-101 and its metabolite BFB-520, and after completion of the RDQ. However, the Investigator may decide to keep the patient hospitalized as needed. RDQ will be completed prior to any authorization to leave the hospital on Day 2 or prior to any discharge authorization if later than Day 2. If discharged, patients will come back for visits at Week 1, 2, 3, 4, 8, and 12 for efficacy and safety assessments. Hospitalization on Visits 6 and 7 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done.

8.1.3.3. Telephone Contacts

Participating patients or their caregivers will be contacted by phone weekly when the patients are not scheduled for site visits to inquire about the patients' well-being, compliance with treatment, and to remind them of the scheduled site visits, as appropriate. These phone calls

should occur on Weeks 5, 6, 7, 9, 10, and 11, and will utilize structured questions for that purpose.

8.1.3.4. Week 12 (Visit 11)

This is the last visit of the double-blind phase. Patients should be administered their last dose of the double-blind medication at this visit (i.e., study drug medication from the blister they received at Week 8). Any patient who terminates early from the study will undergo Week 12 (Visit 11) procedures. Also, patients with ongoing adverse events at the time of the EOS visit (Visit 11) will be followed until all significant changes have resolved or become medically stable.

8.1.4. Open-label Extension Phase

8.1.4.1. Hospitalization Period Following Week 12 (Visits 12 and 13)

The 40-week, open-label extension phase commences with a required overnight hospitalization (i.e., Week 12 or Visit 11) for all patients for 2 nights. Patients will be allowed to leave the hospital on Day 2 (Week 12 + 2 days or Visit 13) of the extension phase after drug administration and after safety has been ascertained clinically and including 3 ECG assessments (in triplicate) and PK evaluation performed at pre-dose and at the approximate time of C_{max} of MIN-101 and its metabolite BFB-520, and with the help of the RDQ. The RDQ will be completed prior to any authorization to leave the hospital.

8.1.4.2. 40-Week Open-Label Treatment Phase

Patients who received MIN-101 during the double-blind treatment phase will continue to receive the same treatment and dose. Patients who previously received placebo will receive 1 of the 2 MIN-101 doses in 1:1 ratio per the randomization at Visit 4 (at the start of the double-blind phase). As such, the descriptor "open-label" is being used loosely to inform that all patients are receiving MIN-101 without knowledge of the dose given or the treatment received during the double-blind phase.

Hospitalization on Visits 14 and 15 will be at the discretion of the investigator to ensure per-protocol ECG assessment and PK sampling are done.

Participating patients and/or their caregivers will be contacted by phone weekly when the patients are not scheduled for site visits to inquire about the patients' well-being, compliance with treatment, and to remind them of the scheduled site visits, as appropriate. These phone calls should occur on Weeks 18, 22, 26, 30, 34, 38, 42, 46, and 50, and will utilize structured questions for that purpose.

Any patient who terminates early from this phase, and therefore from the study, will undergo the End of Treatment visit (Week 52/ Visit 26) as soon as possible. It will be followed ±2 weeks later by the EOS visit (Week 54/Visit 27). If any of the laboratory results indicate an abnormality that warrants repeating the test, the patient should be fasting for the repeat

assessment. Patients with ongoing adverse events at the time of the EOS visit will be followed until all significant changes have resolved or become medically stable.

8.2. Efficacy

8.2.1. Assessments

The following efficacy assessments will be performed at the time points indicated in the Time and Events Schedule. Every effort should be made to ensure that all clinician reported objective measurements are completed by the same individual who made the initial Baseline determinations.

[redacted]

Personal and Social Performance (PSP) Scale is a validated clinician-rated scale that measures personal and social functioning in 4 domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. PSP is a hundred-item scale, divided in 10 similar intervals. The score is based on the assessment of a patient's performance in the 4 domains. It is a reliable, quick measure of personal and social functioning of patients with schizophrenia and can be used on patients in the acute and stable stage. See Attachment 6 for an example of this scale.

Clinical Global Impression- Severity [redacted] – The CGI-S is a clinician-rated scale that is designed to rate the severity of the patient's illness at the time of assessment, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function relative to the clinician's past experience with patients who have the same diagnosis and improvement with treatment. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating, according to: normal (not at all ill) = 1; borderline mentally ill = 2; mildly ill = 3; moderately ill = 4; markedly ill = 5; severely ill = 6; or extremely ill = 7. [redacted]

Cognitive Testing has been widely used in clinical trials with intended features of brief administration and scoring time, portability, repeatability, and availability of alternate forms. The verbal fluency test is such a test. The test is fully portable, and is designed to be easily administered by a variety of testers, including study coordinators, psychologists, psychiatrists, neurologists, social workers, and other mental health workers. It is designed to require about 5 minutes of testing time with minimal extra time for scoring and minimal training demands (Attachment 9).

[redacted]

This study will use electronic clinical outcome assessments (eCOA) to capture questionnaire data. The data will be transmitted electronically to a centralized database at the eCOA vendor. Data may be reviewed by site staff via secure access. eCOA data will be collected using a device provided by the eCOA vendor. The device is designed for entry of data in a way that is compliant with regulations for electronic records.

8.2.2. Efficacy Evaluations

Efficacy will be evaluated based on the change from Baseline in PANSS negative subscale score after 12 weeks of treatment or at early withdrawal. In addition, other efficacy evaluations will be based on the change from Baseline in the scores on the PSP, and CGI-S Scales, cognitive assessment, CDSS, [redacted]

The following efficacy evaluations will be performed at the scheduled visits in the following order and in the morning (between 8:00 a.m. to 1:00 p.m.) during the 12-week, double-blind treatment phase, and as applicable, during the 40-week, open-label extension phase:

- [redacted] at Screening, Baseline, and Weeks 2, 4, 8, 12, and at Weeks 14, 16, 24, 32, 40, 48, 52, and 54 (EOS, or early withdrawal).
- PSP at Baseline and Weeks 4, 8, 12, and at Weeks 16, 24, 32, 40, 48, and 52 (or early withdrawal).
- CGI-S at Screening, Baseline, and Weeks 2, 4, 8, 12, and at Weeks 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 54 (EOS, or early withdrawal).
- [redacted] at Weeks 2, 4, 8, 12, and at Weeks 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 54 (EOS, or early withdrawal).
- Cognitive assessments at Baseline and Weeks 4, 12, and at Weeks 16, 24, 36, and 52 (or early withdrawal).
- [redacted] at Screening, Baseline, and Weeks 4, 8, 12, and at Weeks 16, 24, 36, and 52 (or early withdrawal).

8.3. Pharmacokinetic Evaluations

8.3.1. Sample Collection and Handling

Blood sample (4 mL) will be collected for assessing MIN-101 plasma and its metabolites BFB-520 and BFB-999 concentration during the double-blind and open-label extension phases at every visit per the Time and Events Schedule. Additionally, 1 sample to test for any prohibited concomitant medications will be collected at the at the approximate time of maximum plasma concentration of MIN-101 (6 to 8 hours post dosing) or 2-4 hours post dosing per the Time and Events Schedule. Actual time and date of blood drawn must be accurately recorded on Lab Requisition Form and eCRF.

8.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of MIN-101 and its metabolite(s) using validated, specific, and sensitive liquid chromatography-mass spectrometry methods under the supervision of the sponsor's bioanalytical facility or designee. Similar methodology will be utilized for assessing the prohibited concomitant medication levels.

Plasma samples will be disposed after the clinical study report is finalized.

8.3.3. Pharmacokinetic Evaluations

Plasma levels of MIN-101 and its metabolite(s) will be tabulated.

Population PK analyses will be performed on the data of this study in combination with data pooled from other studies. An objective of these analyses is to continue and refine the existing population PK model for the potential effects of covariates, such as demographics and concomitant drugs, on the pharmacokinetics of MIN-101. An integrated population pharmacokinetic model for MIN-101 will be used combining the data sets of Phase 1 and 2 studies. Standard population pharmacokinetic parameters (e.g., AUC, CL/F, etc.) will be estimated. The effects of demographic characteristics, concomitant medications, laboratory

values, and other covariates on MIN-101 PK will be evaluated. Results of the population PK analysis will be presented in a separate report.

Additionally, the data from this study will also be used to amend the datasets already used for exposure QTcF modeling to continue to investigate the effect of MIN-101 and BFB-520 on the QTcF interval.

8.4. Safety Evaluations

The collection of adverse events and concomitant medications will start after the informed consent has been signed and will continue until the follow-up visit. All safety assessments listed below will be performed as specified in the Time and Events Schedule.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legal representative) for the duration of the study. AEs will be followed by the investigator as specified in Section 11, AE Reporting.

Adverse Events of Special Interest

The following AEs are considered to be of special interest in this study:

- Episodes of palpitations or abnormal heart rhythms
- Episode of dizziness or syncope
- Episode of seizure

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported, the investigator will be required to complete a detailed summary of the event and its clinical course utilizing the eCRF page as soon as information on the outcome (recovered, resolving, or ongoing) is available. Note: If the event meets the seriousness criteria (see Section 11.1.1), the SAE Form must also be completed according to the SAEs reporting timeline described in Section 11.3.2, i.e., within 24 hours of having become aware of the event, even if all details are not available.

Clinical Laboratory Tests

Blood samples for serum chemistry (collected after an overnight fast), prolactin and hematology and urine samples for urinalysis will be collected according to the Time and Events Schedules. In addition, a urine sample for drug and alcohol testing and urine samples from

women of childbearing potential for pregnancy testing will be collected (refer to the Time and Events Schedules). The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The following tests will be performed by the central laboratory.

- ***Hematology:***
  - hemoglobin
  - hematocrit
  - white blood cell (WBC) count with differential
  - platelet count
  - red blood cell (RBC) count
- ***Serum Chemistry:***
  - sodium
  - potassium
  - chloride
  - magnesium
  - blood urea nitrogen (BUN)
  - creatinine
  - glucose[a] (fasting)
  - AST
  - ALT
  - total bilirubin
  - alkaline phosphatase
  - HbA1c
  - gamma-glutamyl transferase (GGT)
  - prolactin
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - bicarbonate (HCO_3-)
  - calcium
  - phosphorous (inorganic)
  - albumin
  - total protein
  - cholesterol (total)
  - triglycerides
  - high-density lipoprotein (HDL)
  - low-density lipoprotein (LDL)
  - very low-density lipoprotein (VLDL)
  - thyroid stimulating hormone[b] (TSH)
- ***Urinalysis***

  Dipstick
  - specific gravity
  - pH
  - glucose
  - protein
  - blood
  - ketones
  - bilirubin
  - urobilinogen
  - nitrite
  - leukocyte esterase

  Sediment (if dipstick result is abnormal)
  - RBC
  - WBC
  - epithelial cells
  - crystals
  - casts
  - bacteria

[a] Fasting glucose can be completed anytime during the Screening period.
[b] Only at Screening visit.

If dipstick result is abnormal, the sediment will be examined microscopically.

Other clinical laboratory tests include:

- CYP 2D6 genotype
- Serum pregnancy test at Screening and Week 12 / Visit 11 (or in case of early termination)

- Urine pregnancy testing for women of childbearing potential only: Pregnancy will be tested at study sites with urine dipstick test according to the Time and Events Schedules. In the case of positive urine pregnancy test result, the serum pregnancy assessment will be performed centrally. If result of the urine pregnancy test is positive, the patient must stop taking the study medication pending the results of the serum pregnancy test. It the serum pregnancy test is doubtful or positive, the patient will be excluded or withdrawn from the study. If the serum pregnancy test is negative, the study drug administration may be resumed.
- Serology (HIV antibody, HBsAg, and HCV antibody)
- Urine drug screen and urine alcohol: Potential patients will be tested for drugs of abuse (cocaine, methadone, amphetamines, cannabinoids, opiates, benzodiazepines, and barbiturates), TCA, and alcohol at Screening and Day -2 according to the Time and Events Schedules. Additionally, urine drug screen will be tested at the study sites with dipstick tests on Day -2. If the results of the urine drug screen (except for prescription benzodiazepines) or the urine alcohol test are positive at Screening or Day -2 (by laboratory or dipstick testing), the patient will not be enrolled (but may be rescreened one time, as described in Section 4) or will be discontinued. Also, if the screen is positive for cannabinoids, they will be excluded (no rescreen authorized).

Electrocardiogram (ECG)

Three 12-lead digitalized ECGs will be recorded 1 minute apart (and to be completed within a 5-minute timeframe) while the patient is supine for at least 10 minutes according to the Time and Events Schedules.

Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. Computer-generated interpretations of ECGs should be reviewed for data integrity and reasonableness.

A central ECG reader will measure the following intervals: HR, RR, PR, QRS, and QT. Electrocardiogram monitoring will include the evaluation of lengthening of the QTc interval using QTcF.

Vital Signs

Vital signs will include PO/aural temperature, respiratory rate, pulse, and blood pressure.

Three consecutive blood pressure and pulse readings will be taken at each assessment per the Time and Events Schedules. Blood pressure and pulse should be taken in the arm with the

highest pressure, using the same arm for each reading and for all visits. An appropriately sized arm cuff will be used, and the size of the cuff should remain constant for all visits.

Blood pressure and pulse will be taken after the patient has been resting in supine position for 5 minutes.

Physical Examination

Complete and abbreviated physical examinations (including anthropomorphic measurements [height, weight, and waist circumference]) will be performed at the times specified in the Time and Events Schedules.

Any abnormalities present at Baseline, or subsequent changes, will be documented in the appropriate sections of the eCRF. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Abnormal Involuntary Movement Scale (AIMS) is rating scale that was designed in the 1970s to measure TD will be performed at the times specified in the Time and Events Schedules. TD is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications. The AIMS test is used not only to detect TD but also to follow the severity of a patient's TD over time. The AIMS test is usually given every 3 to 6 months to monitor the patient for the development of TD. For most patients, TD develops 3 months after the initiation of neuroleptic therapy; in elderly patients, however, TD can develop after as little as one month. The entire test can be completed in about 10 minutes. The AIMS test has a total of 12 items rating involuntary movements of various areas of the patient's body. These items are rated on a 5-point scale of severity from 0–4. The scale is rated from 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe. Two of the 12 items refer to dental care. The patient must be calm and sitting in a firm chair that doesn't have arms, and the patient cannot have anything in his or her mouth. The clinician asks the patient about the condition of his or her teeth and dentures, or if he or she is having any pain or discomfort from dentures.

The remaining 10 items refer to body movements themselves. The clinician or rater asks the patient about body movements. The rater also looks at the patient in order to note any unusual movements first hand. The patient is asked if he or she has noticed any unusual movements of the mouth, face, hands or feet. If the patient says yes, the clinician then asks if the movements annoy the patient or interfere with daily activities. Next, the patient is observed for any movements while sitting in the chair with feet flat on the floor, knees separated slightly with the hands on the knees. The patient is asked to open his or her mouth and stick out the tongue twice while the rater watches. The patient is then asked to tap his or her thumb with each finger very rapidly for 10–15 seconds, the right hand first and then the left hand. Again, the rater observes the patient's face and legs for any abnormal movements.

After the face and hands have been tested, the patient is then asked to flex (bend) and extend one arm at a time. The patient is then asked to stand up so that the rater can observe the entire body for movements. Next, the patient is asked to extend both arms in front of the body with

the palms facing downward. The trunk, legs and mouth are again observed for signs of TD. The patient then walks a few paces, while his or her gait and hands are observed by the rater twice.

See Attachment 3 for an example of the AIMS.

Barnes Akathisia Rating Scale (BARS) is a multiple-choice questionnaire that clinicians may use to provide an assessment of akathisia will be performed at the times specified in the Time and Events Schedules. Akathisia is a state of motor restlessness, sometimes produced by neuroleptic medication that ranges from a feeling of inner distress to an inability to sit still. The clinician or rater is instructed to observe the subject while standing and while sitting, at least 2 minutes each (total of at least 4 minutes in total). There are 4 areas where the subject is to be evaluated, 1 of these is objective, 2 are subjective, and the final is a global assessment. This scale was generated in 1989 (Barnes 1989), and was derived from the findings of studies exploring the clinical features of antipsychotic-induced akathisia both in acute psychiatric admissions and schizophrenic out-patients on maintenance medication. Subsequently, its validity and reliability have been established, and it has been used extensively in clinical studies worldwide.

See Attachment 4 for an example of the BARS.

Simpson-Angus Scale (SAS) is an established reliable and valid rating scale that measures drug-induced extrapyramidal syndromes using 10 items rated from 0= not present to 4 = extremely severe (Simpson & Angus 1970). It consists of one item measuring gait (hypokinesia), six items measuring rigidity (arm dropping, shoulder shacking, elbow rigidity, wrist rigidity, leg pendulousness, and head dropping) and three items measuring glabella tap, tremor and salivation**.** As such, the range of scores is 0 to 40, with increased scores indicate increased severity.

See Attachment 12 for an example of the SAS.

Sheehan Suicidality Tracking Scale (Sheehan-STS) is a prospective rating scale that tracks both treatment-emergent suicidal ideation and behaviors will be performed at the times specified in the Time and Events Schedules. The Sheehan-STS is a scale that can be administered by the clinician or the patient through self-report. Each item is scored on a 5-point Likert scale (0 = not at all, 1 = a little, 2 = moderately, 3 = very, and 4 = extremely). Data from the Sheehan-STS can be analyzed as individual item scores, and total score (calculated by add scores from Questions 1a (only if 1b is coded YES), + 2 through 11 + [the highest of 12 or any row of 16] + [the highest of 14 or any row of 15] + 17 + 20. The Sheehan-STS was adapted from the Suicidality Module of the MINI Structured Diagnostic Interview for DSM-5 (Coric et al. 2009).

See Attachment 11 for an example of this scale.

Pharmacokinetic and Concomitant Medication Samples Associated with Safety Signals

Every reasonable effort should be made to collect additional PK and concomitant medication samples as closely to the onset of any untoward safety signal (e.g., AE of special interest, SAE,

QTc prolongation, etc.) as possible, to aid with the interpretation of the causality of such signals, including the use of prohibited concomitant medications. This procedure is also applicable should a patient is withdrawn due to safety reasons.

9. PATIENT COMPLETION/WITHDRAWAL

9.1. Completion

A patient will be considered to have completed the study if he or she has completed all scheduled assessments through Week 12. Patients who prematurely discontinue study treatment for any reason before completion of all scheduled assessments will not be considered to have completed the study. The investigational drug will not be available after the completion of the study, unless required under local law or regulation and approved by the sponsor.

9.2. Withdrawal from the Study

Throughout the study, patients will be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Failure to use an acceptable method of birth control
- The patient becomes pregnant
- Repeated non-adherence to protocol procedures
- Discretion of the investigator

If a patient discontinues treatment before the double-blind phase ends, attempts to obtain Week 12 (Visit 11) assessments must be made. In case a patient is lost to follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented. When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw will not be replaced.

9.3. Stopping Rules

In addition, specific stopping rule criteria for a patient's withdrawal are described below:

1. Increase from Baseline in PANSS total score of 25% and an increase of 3 points or more on the hallucinations, suspiciousness/paranoia, hostility, delusions, or uncooperativeness PANSS items.
2. CGI-S worsening of more than 2 points.
3. Suicidal ideations or behavior.
4. Occurrence of an AE, which may jeopardize the patient's health as per investigator opinion.

5. Worsening of psychotic symptoms or occurrence of any dangerous behavior against self or others as per investigator opinion.
6. Patient with significant increase in ALT (i.e., > 5 ULN).
7. Patient with abnormal laboratory results with simultaneous increases of total bilirubin (> 2 ULN), ALT or AST (> 3 ULN) with alkaline phosphatases (< 1.5 ULN).
8. Patient with sustained mean QTcF value > 500 msec (confirmed by a second ECG under strict resting position and at minimum at ½ hour [30 minutes] duration from the first measurement). Patient's treatment must be discontinued until mean QTcF values are obtained from the ECG central-reader. If values are confirmed, the patient must be discontinued from the study, else treatment is restarted at the discretion of the investigator.
9. Patient with sustained mean increase of > 60 msec in the QTcF compared to Baseline (confirmed by a second ECG under strict resting position and at minimum at ½ hour [30 minutes] duration from the first measurement). Patient's treatment must be discontinued until mean QTcF values are obtained from the ECG central-reader. If values are confirmed, the patient must be discontinued from the study, else treatment is restarted at the discretion of the investigator.
10. If the patient for any reason requires treatment with another therapeutic agent that has been demonstrated to increase the QT interval or inhibit CYP 2D6 or CYP 3A4. In this case, discontinuation from the study occurs prior to introduction of the new agent.
11. If the patient experiences a syncope or dizziness not explained by other known causes, such as documented orthostatic hypotension, Ménière disease, etc.
12. Patient has an overt seizure or reports seizure-like activity (loss of consciousness, uncontrollable tremor not due to EPS). A seizure or seizure like activity will be followed-up on-site using SAE follow-up forms, neurological examination, and EEG monitoring.

If a patient is withdrawn from the study for safety reason, a PK sample and a concomitant medication sample and a blood sample for biochemistry analysis should be drawn as soon as possible together with any relevant safety assessment, prior to the EOS visit if applicable.

10. STATISTICAL METHODS

Statistical analysis will be performed by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

Specific details will be provided in the Statistical Analysis Plan (SAP).

10.1. Sample Size Determination

The sample size for this study is based on the assumption of a treatment difference of 3 points in the mean change from Baseline to Week 12 in PANSS negative subscale score based on the Marder negative factor score between any MIN-101 dose group and placebo. A standard

deviation of 6.5 in the change in PANSS negative subscale score from Baseline is used. Assuming an equal allocation to placebo and each of the 2 MIN-101 doses, 100 patients in each treatment arm are required to detect the treatment difference of 3 points with a power of 90% at an overall 2-sided significance level of 0.05. When adjusted for a rate of about 40% of patients who will not have either Baseline or at least 1 on-treatment efficacy assessments, the required number of patients becomes 167 in each treatment arm. Therefore, the total number of patients enrolled across the 3 treatment arms will be 501.

10.2. Data Sets

Three populations will be considered in the statistical analysis of the study:

Intent-to-treat (ITT): This population will consist of all patients who were randomly assigned to study drug and received at least 1 dose of study drug.

Safety: This population will consist of all patients who were randomly assigned to study drug and received at least 1 dose of study drug. The safety analysis set is the same as the ITT.

Per-protocol (PP): This population will include all patients in the ITT Population who do not present major protocol violations, i.e., violations thought to interfere with efficacy results such as erroneous diagnosis, insufficient compliance (< 80%), or intake of prohibited concomitant medication. Major protocol violations will be identified before breaking the randomisation code.

Patients' assignment to analysis sets will be performed during the pre-analysis review meeting while the data remain blinded.

Taking into account the nature of this Phase 3 study, all efficacy analyses will be performed on both the ITT and PP sets, and eventual discrepancies between the results obtained in both sets will be discussed.

10.3. Patient Information

For all patients who received at least 1 dose of study drug, descriptive statistics by treatment arm, MIN-101 dose group, totaled over all MIN-101 dose groups, and as appropriate, totaled over all treatment arms, will be provided for age, BMI, weight in kilograms, and height in centimeters. Gender will be tabulated by dose group and overall. The BMI will be calculated and presented using the following formula: BMI = weight in kg/height in meters^2.

The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment arm and pooled across treatment arms for the Safety Population. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the eCRFs will be summarized (number and percentage) by treatment arm for the Safety Population. The percentage of premature discontinuations will be compared overall and for each discontinuation reason between treatment groups using the Fisher exact test.

The number and percent of patients with a current or historical presence of abnormal finding in medical history will be summarized by dose group and totaled over all dose groups.

10.4. Extent of Exposure and Treatment Compliance

Investigational Product

Exposure to double-blind treatment for the Safety Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind treatment taken to the date of the last dose taken, inclusive, for the double-blind treatment period. Descriptive statistics will be presented by treatment group.

Prior and Concomitant Medications

Prior medications are defined as any medication taken before the date of the first dose of double-blind treatment. Concomitant medications are defined as any medication taken on or after the date of the first dose of double-blind treatment.

Both prior medication use and concomitant medication use (during the double-blind treatment period) will be presented in data listings, and only concomitant medication will be summarized by the number and proportion of patients in each treatment arm receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a patient will only be counted once.

Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of tablets actually taken by a patient during that period divided by the number of tablets prescribed during the same period multiplied by 100. The total number of tablets actually taken will be calculated from the study medication record. The number of tablets prescribed for a specific treatment period will be calculated by multiplying the number of days in that period by the number of tablets prescribed per day. Descriptive statistics for treatment compliance will be presented by treatment arm for each period between 2 consecutive visits when medication dispensation occurred, as well as for the entire double-blind treatment period.

10.5. Efficacy Analyses

Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 3 components:

Population: stable patients with schizophrenia with a predefined minimum PANSS negative symptom score.

Endpoint: change in PANSS Marder NSFS from baseline to the end of Week 12.

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all patients remained on their treatment throughout the double-blind phase.

The primary efficacy analysis will be based on the ITT Population. Baseline for efficacy is defined as values recorded at Visit 3 (Baseline).

Analyses of change from baseline will include only subjects who have both baseline and post-baseline data during the 12-week double-blind period.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Additionally, by-visit analyses will be done for all efficacy parameters using the MMRM and last observation carried forward (LOCF) approaches (described in Section 10.5.1), unless stated otherwise.

10.5.1. Primary Endpoint

The primary efficacy endpoint will be the change in the NSFS from baseline to Week 12 (the double-blind treatment period). This endpoint will be analyzed using MMRM with treatment arm (MIN-101 64 mg, MIN-101 32 mg, and placebo), pooled study center (by country or region based on enrollment), visit, and treatment arm-by-visit interaction as fixed effects, patient nested in treatment as random effect, and Baseline NSFS as covariate. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward & Roger 1997) will be used to estimate denominator degrees of freedom. These analyses will be performed based on all post-Baseline scores using only the observed cases without imputation of missing values. Comparison against placebo will be performed with the MIN-101 64 mg and 32 mg doses.

The adjustment for multiplicity within the family of primary hypotheses will utilize the conventional Hochberg procedure for the purpose of reporting of results. This procedure will allow the null hypothesis of no treatment difference for both the 64 mg and 32 mg doses versus placebo to be rejected if largest p-value of comparing either of these 2 doses versus placebo is at or below 0.050. Otherwise, the lowest of these 2 p-values must be at or below 0.025 to allow for rejecting the null hypothesis for the representative dose.

The overall type I error rate for testing the 2 MIN-101 doses versus placebo for the primary and the key secondary endpoint will be controlled at the 2-sided 0.05 level. The primary family of hypotheses (corresponding to the primary endpoint) and the secondary family of hypotheses (corresponding to the key secondary endpoint, the change from Baseline in PSP Total score) will be tested in a sequential manner with suitable adjustment for multiplicity within the family of primary hypotheses and within the family of the secondary hypotheses such that a MIN-101 dose versus placebo null hypothesis contrast testing within the secondary family can be evaluated only when the same null hypothesis contrast in the primary family was rejected.

Sensitivity analyses of the primary endpoint will also be performed and will be detailed further in the SAP. These may include an ANCOVA model with factors for treatment and region and Baseline NSFS as a covariate. In this analysis, subjects without a NSFS at Week 12 will have an earlier postbaseline score imputed using the LOCF method. Other sensitivity analyses may also be performed to investigate the robustness of treatment estimates to the observed pattern of, and/or reason for, early withdrawals.

Additional details will be provided in the SAP, including pre-specified sensitivity analyses under "non-ignorable" missing data mechanisms to assess the potential impact of the incorrect missing data assumption made for the primary analysis.

10.5.2. Secondary and Exploratory Endpoints

The change from Baseline in PSP total scores will be analyzed similarly to the primary endpoint with MMRM. The change from Baseline in CGI-S scores and [redacted] will be analyzed by means of an ANCOVA of ranked data, with treatment (MIN-101 64 mg, 32 mg, and placebo) as a factor, and Baseline CGI-S score as a covariate.

The change from Baseline for the remaining efficacy endpoints will be analysed similarly to primary endpoint.

The cumulative distribution function for the primary and key secondary endpoint will also be evaluated, as appropriate.

10.6. Interim Analyses

No formal interim analyses are planned for this study. Data from the double-blind 12-week phase are the primary focus of this study and will be analyzed once the last patient completes Visit 11 assessments and the database has been locked.

Additionally, an external DSMB will be established to review the safety data and formulate recommended decisions/actions in accordance with the charter of the DSMB.

10.7. Pharmacokinetics

Individual plasma levels of MIN-101 and its metabolite(s) will be tabulated by MIN-101 dose with the corresponding day and time point. Descriptive statistics will be summarized by MIN-101 doses.

Population PK analysis of plasma concentration-time data of MIN-101 and its metabolite(s) will be performed using nonlinear mixed-effects modeling. Data will be combined with ongoing modeling dataset. Available patient characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. Post-hoc Bayesian individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis.

Details will be given in a population PK analysis plan and results of the population pharmacokinetic analysis will be presented in a separate report.

10.8. Safety Analyses

The safety analysis will be performed for the double-blind treatment period and double-blind period using the Safety Population. Safety variables include AEs, clinical laboratory parameters, physical examination, vital signs, and ECG parameters.

For each safety parameter, the last assessment made before the first dose of double-blind treatment, or in case of ECG, the mean of the 3 triplicates (9 assessments) performed on Day -1, will be used as the baseline for all analyses of that safety parameter.

10.8.1. Adverse Events

The verbatim terms used in the eCRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the 12-week double-blind period (i.e., TEAE) will be included in the analysis. For each AE, the percentage of patients who experienced at least one occurrence of the given event will be summarized by treatment group.

Special attention will be given to those patients who died, or who discontinued treatment due to an AE, or who experienced an SAE (e.g., summaries, listings, and narrative preparation may be provided, as appropriate).

Adverse events of special interest are episodes of palpitations or abnormal heart rhythms episode of dizziness or syncope, and episode of seizure. Subjects with AEs of special interest may be presented separately.

An AE that occurs > 14 days after the date of the last dose of treatment will not be considered TEAE, but will be included in the patient data listings but not the summary tables.

10.8.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at Baseline and at each scheduled time point. Changes from Baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of patients with any laboratory results outside the reference ranges will be provided. A listing of patients with any markedly abnormal laboratory results will also be provided.

10.8.3. Vital Signs

Descriptive statistics of body temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) values and changes from Baseline will be summarized at each scheduled time point. The percentage of patients with values beyond clinically important limits will be summarized. Clinically important limits will be defined in the SAP.

10.8.4. Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from Baseline values (mean of Day -1 ECG assessments will be used as Baseline) to allow detection of clinically relevant changes in individuals.

The ECG variables that will be analyzed are HR, RR, PR interval, QRS interval, QT interval, and QTcF interval. QTcF values will be tabulated for their absolute values and also tabulated relative to Baseline measurements in order to detect individual QTcF changes (ICH 2005).

Descriptive statistics of QTcF intervals and changes from Baseline will be summarized at each scheduled time point. The percent of patients with QTc interval > 450 msec, > 480 msec, or > 500 msec will be summarized as will the percent of patients with QTcF interval increases from Baseline of > 30 to 60 msec or > 60 msec.

For QTcF, an ANCOVA model by assessment times (visit and timepoint within visit) using the change from baseline (as dependent variable) with treatment arm (MIN-101 32 mg, MIN-101 64 mg, and placebo) as a factor, and Baseline value as covariate. Estimates for the difference at each assessment time for each dose group versus placebo, standard error of the mean, and the upper bound of the 2-sided 90% confidence intervals will be presented.

All important abnormalities in ECG waveform that are changes from the Baseline readings will be reported (e.g., changes in T-wave morphology or the occurrence of U-waves).

10.8.5. Physical Examination

Physical examination abnormalities will be listed. Observed and change from Baseline values of weight and waist circumference will be summarized descriptively.

10.8.6. Other Safety Parameters

Observed and changes from Baseline in AIMS, BARS, and SAS values will be summarized in tabular format showing descriptive statistics.

10.8.6.1. Sheehan Suicidality Tracking Scale

On the basis of the data collected using the Sheehan-STS, potential suicide-related events will be categorized by the investigator using the event report (page 2 of the scale).

Descriptive statistics of score values and changes from Baseline will be summarized at each scheduled time point. The endpoint of interest will be the proportion of patients with a suicide-related outcome.

10.9. Pharmacokinetic / Pharmacodynamic Analyses

The effect of coincidentally measured (time-matched) plasma concentrations of MIN-101 and BFB-520 as compared to placebo on QTcF changes from Baseline will be analyzed utilizing the plasma concentration bin method. This analysis will pool all assessment times at which both the QTcF and PK data are available and will treat the bins as separate groups using quartile distribution. Plasma concentration data from placebo-treated patients will be set to 0 (zero). Repeated measures ANCOVA model will be used and will include PK concentration Bin Group and assessment times as fixed effects, Baseline QTcF as a covariate, and patient nested in treatment as a random effect.

Furthermore, the analysis will be repeated by using the largest QTcF increase value (worst case) per patient, with the matched plasma concentration level independent of time of assessment, will also be performed using ANCOVA model with PK concentration Bin Group as fixed effects, Baseline QTcF as a covariate, and patient nested in treatment as a random effect. Analysis of the largest time-matched mean difference from Baseline will also be explored, as applicable.

P-value and the least squares means difference, and the corresponding upper bound of the two-sided 90% confidence intervals for the change from baseline versus placebo will be computed for each Bin.

These analyses will be performed for MIN-101 plasma concentration and its main metabolites, as separate analyses.

10.10. Extension Phase

Patients enrolled in the 40-week open-label extension phase will receive either MIN-101 64 mg or 32 mg. Patients who received placebo in the double-blind 12-week treatment phase will be randomized on Day 1 (Visit 4) to receive one of the two MIN-101 doses. Data from all patients enrolled in the 40-week extension phase will be summarized descriptively, as appropriate, by treatment arm sequence (MIN-101 64 mg, MIN-101 32 mg, placebo to MIN-101 64 mg, placebo to MIN-101 32 mg, overall MIN-101, overall placebo to MIN-101, and overall) as appropriate, and by visit.

All data from the 40-week extension phase will be analyzed separately upon last patient enrolled in this study has Visit 27 assessments. Change from Baseline data for the patients treated with placebo and crossed-over to MIN-101 doses will be presented twice, based on Baseline being defined as the original study Baseline (Visit 3) and as the last assessment on placebo at Week 12 (Visit 11), as appropriate.

10.11. Data Safety Monitoring Board

An external DSMB will be established to review the safety data and formulate recommended decisions/actions in accordance with the charter of the DSMB. The DSMB will consist of 2 clinicians (psychiatrist and cardiologist), and a statistician, one of whom will chair the board. The DSMB will review the outputs from statistical summaries of demographics and safety data prepared by the contract research organization managing the study on behalf of the sponsor who are not otherwise affiliated by the study team.

Further details regarding the safety analysis will be specified in a separate DSMB charter.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per International Council on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the Baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 11.3.1, all Adverse Events for time of last AE recording).

Serious Adverse Event

An SAE is defined as any AE that results in any of the following:

- **Death**: The patient died as the result of the event.
- **Life-threatening event**: Any AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.
- **Required or prolonged inpatient hospitalization**: The AE resulted in hospitalization or prolonged an existing hospitalization. Since hospitalization may be part of the study, only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations.
- **Persistent or significant disability/incapacity**: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the IP.
- **Important medical events**: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in

the definition above (e.g., suspected transmission of an infectious agent by a medicinal product is considered an SAE). Any AE is considered a SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An unlisted AE, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Events Associated with the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or definitely by the definitions listed in Section 11.1.2.

11.1.2. Attribution Definitions

- **Unrelated:** An AE that is not related to the use of the drug.
- **Possibly/probably related:** An AE that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive or unlikely. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- **Definitely:** An AE that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

11.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

- **Mild:** Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** Sufficient discomfort is present to cause interference with normal activity.
- **Severe:** Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the patient (e.g., laboratory abnormalities).

11.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug, defined as 3 x daily dose within any 24-hour period.
- Suspected abuse/misuse of a sponsor study drug.

- Accidental or occupational exposure to a sponsor study drug.
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion).
- Exposure to a sponsor study drug during pregnancy or breastfeeding.

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

11.3. Procedures

11.3.1. All Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure (may include contact for follow-up of safety). SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Patients (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

11.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported by the investigational staff within 24 hours of their knowledge of the event via the following email: [redacted]

In the event that transmission is unsuccessful, the following back up fax numbers are available:

- For the US/Canada cases: [redacted]
- For Europe/Rest of the world cases: [redacted]

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to Baseline, if a Baseline value is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a patient's participation in a clinical study must be reported as a SAE, except hospitalizations for the following:

- Extended hospitalization beyond Day 2 after randomization for continued monitoring of a patient.
- Social reasons in absence of an AE.
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).
- Hospitalization for the purpose of assessing ECG and collecting PK samples during the first 4 weeks of the double-blind and open-label phases as required by the protocol.
- Hospitalization at the end of the double-blind phase and the initiation of the open-label treatment phase as required by the protocol.

Suspected transmission of an infectious agent by a medicinal product should be reported as a SAE.

The cause of death of a patient in the study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a SAE.

11.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE Form. Any patient who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male patients included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

12. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, and reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Procedures

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with an SAE, the investigational staff must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 11.3.2, SAEs). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

12.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

13. STUDY DRUG INFORMATION

13.1. Physical Description of Study Drug(s)

[redacted]

13.2. Packaging

The study drug will be packaged in individual patient kits containing child resistant blister cards with sufficient medication, with overage, for 1 week of treatment.

13.3. Labeling

The kits of MIN-101 tablets will have a product and study-specific label containing information that meets the applicable regulatory requirements. The study dispensing labels will contain dosing instructions, quantity of product dispensed, and spaces to record patient number, visit number, date dispensed and investigator's name.

13.4. Preparation, Handling, and Storage

All study drugs must be stored in a controlled environment at room temperature (i.e., 15 - 25 degrees Celsius), with excursions permitted up to 40 °C (inclusive).

13.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the patient, and the return of study drug from the patient (if applicable), must be documented on the drug accountability form. Patients will be instructed to return all original containers, whether empty or containing study drug. They will also be asked to fill a daily drug administration diary to record the time of drug intake and time of first food intake. Study drug returned by study patients will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the patient (if applicable), must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be

documented on the Drug Return Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to patients participating in the study. Returned study drug must not be dispensed again, even to the same patient. Returned study drug may not be relabeled or reassigned for use by other patients. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

14. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- eCRF and infrastructure, including tablets that will be used to capture all efficacy assessments.
- Forms and questionnaires for special assessments.
- PK and prohibited concomitant medication blood sampling supplies.
- Safety laboratory blood sampling supplies.
- Urine dipsticks and urine pregnancy kits.
- Patient education material.
- ECG devices.

15. ETHICAL ASPECTS

15.1. Study-Specific Design Considerations

Clinical Trial in Schizophrenia

Schizophrenia is a severe, chronic and often life-threatening illness. It is a major cause of disability worldwide (WHO 2006). There is a clear need to develop novel and improved therapeutics for schizophrenia.

MIN-101 has shown anti-schizophrenia-like effects in animal models and has unique mechanism of action and good tolerability. These characteristics make MIN-101 an attractive compound to test for efficacy in schizophrenia.

Selection of Patients

The primary aim of the study is to evaluate the efficacy, safety and tolerability of MIN-101 for the treatment of negative symptoms in schizophrenia. Thus, the study cannot be completed in healthy subjects. Patients selected in the study will have adequate capacity to give consent for participation in the study (and via their legal representative, if applicable).

Justification for Using Placebo

Assessing the potential efficacy of a new compound for the treatment of schizophrenia requires adequate and well-controlled clinical studies. For a new compound, this can be achieved either through a placebo-controlled study or through a study comparing it to an active comparator through a non-inferiority design. For non-inferiority studies, previous placebo-controlled studies have shown consistently the superiority of the active standard drug to placebo. A large proportion of studies with antipsychotics fail even with previously proven antipsychotics, making assay sensitivity difficult to establish and thus, a non-inferiority design invalid (Laughren 2001). Furthermore, non-inferiority trials require much larger sample sizes compared to placebo-controlled trials hence, exposing a larger number of patients to an experimental drug of yet unproven efficacy. Therefore, randomized, controlled studies that rely on comparison with standard antipsychotic alone may generate unreliable results with limited assay sensitivity.

Though some continue to consider it unethical to do placebo-controlled studies due to the potential risk of irreversible harm (Rothman & Michels 1994), the use of a placebo-controlled study design remains the gold standard for assessment of efficacy of new compound to allow for scientifically meaningful results. Placebo-controlled studies in schizophrenia are ethically and scientifically justifiable (Temple & Ellenberg 2000, Laughren 2001).

Precautions to Ensure Patient Safety in the Study

Patients may participate in the study only if they (and their legal representative, if applicable) have adequate capacity to give consent and after fully understanding the potential risks and giving an informed consent. Patients may discontinue the study at any time. The probability of receiving placebo and the concept of random assignment will be explained to the patient. The duration of the study is short, minimizing the time on placebo. Potential disadvantages and AEs of participating in the study and alternative treatment options will be discussed. Patients at high risk of suicide or self-harm will be excluded from participating. Patients who do not improve during the study may drop out during the study and clinical care will be provided according to local standards of care.

Compensation for any study requirements or procedure will be fair per local standards and approved by the participating sites IRB in order to not offer any undue incentive to participate in the study.

Specific entry criteria, including exclusion of patients with clinically apparent laboratory abnormalities, and other medically unstable systemic diseases test results at Screening, will further ensure the appropriate selection and safety of patients who enter the study.

Only highly qualified and experienced investigators will be participating in the study.

15.2. Regulatory Ethics Compliance

15.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible.

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

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments.
- Sponsor-approved informed consent form (and any other written materials to be provided to the patients).
- Investigator's Brochure (or equivalent information) and amendments.
- Sponsor-approved patient recruiting materials.
- Information on compensation for study-related injuries or payment to patients for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for patients.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments.

- Revision(s) to informed consent form and any other written materials to be provided to patients.
- If applicable, new or revised patient recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable.
- Investigator's Brochure amendments or new edition(s).
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted, unexpected, and associated with the investigational drug.
- New information that may adversely affect the safety of the patients or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients.
- Report of deaths of patients under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Annual Safety Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

15.2.3. Informed Consent

Each patient (and a legal representative, if applicable) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential patients (or their legal representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed

that choosing not to participate will not affect the care the patient will receive for the treatment of his or her disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating their confidentiality, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient (or legal representative) is authorizing such access, and agrees to allow his or her study physician to re-contact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The patient (or legal representative) will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the patient's or his or her legal representative's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

If the patient (and legal representative, if applicable) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the patient (and legal representative) is obtained.

Written assent should be obtained from patients who are able to write. After having obtained the assent, a copy of the assent form must be given to the patient, and the patient's legal representative.

15.2.4. Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel or designee whose responsibilities require access to personal data agree to keep the identity of study patients confidential.

The informed consent obtained from the patient (and legal representative, if applicable) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable

steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

15.2.5. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 15.1, Study-Specific Design Considerations.

16. ADMINISTRATIVE REQUIREMENTS

16.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

16.2. Regulatory Documentation

16.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, as applicable. A study may not be initiated until all local regulatory requirements are met.

16.2.2. Required Pre-Study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator.

- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Documentation of investigator qualifications (e.g., curriculum vitae).
- Completed investigator financial disclosure form from the investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first patient:

- Documentation of subinvestigator(s) qualifications (e.g., curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests.
- Local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

16.3. Patient Identification, Enrollment, and Screening Logs

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by initials and assigned number only.

The investigator must also complete a patient-screening log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

16.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: patient identification, eligibility, and study identification; study discussion and date

of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Complete medical and psychiatric history and / or discharge summaries or
- Documentation of a telephone call with the treating clinician or letter from the treating clinician if full records are unavailable

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (e.g., electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If electronic source is utilized, references made to the eCRF in the protocol include the electronic source system, but information collected through electronic source may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

16.5. Case Report Form Completion

Case report forms are provided in the eCRF for each patient who was randomized and received at least one dose of study drug. Screen failures will not be entered.

Data must be entered into eCRFs in English. The investigator must verify that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

16.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor or designee will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

16.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

Local laws and regulations regarding record retention policies will be followed.

16.8. Monitoring

The sponsor or designee will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible (but no later than 2 weeks) after

enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRF and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

16.9. Study Completion/Termination

16.9.1. Study Completion

The study is considered completed with the last visit of the last patient participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final patient visit at that site. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

16.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study termination. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended closure.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the investigator.
- Discontinuation of further drug development.

16.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

16.11. Use of Information and Publication

All information, including but not limited to information regarding MIN-101 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of MIN-101, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report generated by the sponsor and will contain eCRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator, if needed. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory

compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, results may need to be published in a given sequence (e.g., substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

16.12. Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: ALLOWED/PROHIBITED CONCOMITANT MEDICATIONS

Drug Class	As Needed	Chronic Use	Restrictions
Analgesics	Y	N	Only non-opiate analgesics are allowed.
Anorexics	N	N	
Antacids	Y	Y	H2 antagonists and proton pump inhibitors not allowed,
Antianginal Agents	N	N	
Antiarrhythmics	N	N	
Antiasthma Agents	Y	Y	Inhaled agents only.
Antibiotics	Y	N	Some macrolides, quinolones and other antibiotics not allowed.(refer to the next table)
Anticholinergics	N	N	Only rescue medications are allowed (refer to protocol)
Anticoagulants	N	Y	Only aspirin (max. 325 mg/day) is allowed as chronic anti-platelet treatment.
Anticonvulsants	N	N	
Antidepressants	N	N	
Antidiarrheal Preparations	Y	N	
Antifungal Agents:			
- Systemic	N	N	
- Topical	Y	Y	
Antihistamines	Y	N	Only fexofenadine, loratadine, cetirizine are allowed.
Antihypertensives (*)	N	Y	Calcium channel blockers and ACE inhibitors allowed. Isradipine and nicardipine not authorized.
Anti-inflammatory Drugs	Y	Y	Systemic corticosteroids are not allowed.
Antinauseants	Y	N	Domperidone, droperidol, odansetron
Antineoplastics	N	N	
Antiobesity	N	N	
Antipsychotics	N	N	
Anxiolytics	N	N	Only rescue medication are allowed; see Section 4.4.2
Cough/Cold Preparations	Y	N	Use of cough and cold preparations containing pseudoephedrine or phenylpropanolamine is not permitted. Decongestants containing narcotics are not permitted. Dextrometorphan and codeine are not authorized
Diuretics	N	Y	Allowed if stable dose 1 month before enrollment. Furosemide, HCTZ not allowed (refer to next table)
H2-Blockers	N	N	
Hormones	N	Y	Only thyroid hormone replacement, oral contraceptives and estrogen replacement therapy are allowed.
Hypoglycemic Agents	N	N	
Hypolipidemics	N	Y	
Insulin	N	N	
Muscle Relaxants	N	N	
Psychotropic drugs not otherwise specified (including herbal products)	N	N	No drugs with psychomotor effects or with anxiolytic, stimulant, antipsychotic, or sedative properties are allowed.
Sedatives/Hypnotics	N	N	Zolpidem, zopiclone and zaleplon allowed

Note: All antihypertensives must be at stable dose >3 months prior to enrollment and must be continued at the same dose during the study.

Key:

Red: known risk of TdP;
Blue-bold: possible risk of TdP;
Black: conditional risk of TdP: e.g., in case of overdose, DDI or electrolytes imbalance.

Drugs inducing QT prolongation	CYP 2D6 inhibitors	CYP 3A4 inhibitors
Anesthetic	**Anti-infectives**	**Anti-infectives**
Sevoflurane	Chloroquine	Chloramphenicol
Propofol	Quinacrine	Clarythromycin
	Cardiovascular	Ciprofloxacin
Anticonvulsivants	Amiodarone	Erythromycin
Ezogabine (retigabine)	Aprindine	Norfloxacin
Felbamate	Mibefradil	Telithromycin
	Propafenone	
Anti-histamines	Labetalol	**Anti-Viral**
Diphenhydramine	Quinidine	Boceprevir
Hydroxyzine		Delvirdine
	Antidepressants	Indinavir
Anti-infectives	Amitriptyline	Nelfinavir
Amantadine	Citalopram	Ritonavir
Artenimol+ piperaquine	Clomipramine	Saquinavir
Azithromycin	Doxepin	Telaprevir
Bedaquiline	Duloxetine	
Chloroquine	Escitalopram	**Antifungal**
Ciprofloxacin	Fluoxetine	Fluconazole
Clarithromycin	Fluvoxamine	Itraconazole
Delamanid	Paroxetine	Ketoconazole
Erythromycin	Sertraline	Voriconazole
Fingolimod		
Garenoxacin	**Antipsychotics**	**Antidepressants**
Gemifloxacin	Chlorpromazine	Fluvoxamine
Halofantrine	Fluphenazine	Nefazodone
hydrochloroquine	Haloperidol	Norfluoxetine
Levofloxacin	Levomepromazine	
norfloxacin	Perphenazine	**Others**
Metronidazole	Promethazine	Amiodarone
Moxifloxacin	Risperidone (weak)	Aprepitant
Ofloxacin	Sertindole	Cimentidine
Quinine	Thioridazine	Diltiazem
Roxithromycin		Gestodene
Telavancin	**Others**	Grapefruit juice
Telithromycin	Bupropion	Imatinib
	Celecoxib	Mibefradil
Antifungal	Cinacalcet	Mifepristone
Amphotericin B	Chlorpheniramine	Suboxone
Fluconazole	Cimetidine	Verapamil
Itraconazole	Clemastine	
Ketoconazole	cocaine	
Pentamidine	Codeine	
Posaconazole	Delavirdine	
Voriconazole	Dextropopoxyphene	
Antiviral	Diltiazem	

atazanavir **Efavirenz** Nelfinavir Ritonavir **Saquinavir** Telaprevir Voriconazole **Cardiovascular:** **Antianginal** Ivabradine Ranolazine **Antiarrhythmics** Amiodarone Disopyramide Dofetilide Dronedarone Flecainide Ibutilide **Pilsicainide** Procainamide Quinidine Sotalol **Calcium Channel Blockers** **Isradipine** **Nicardipine** **Diuretics** Bendorflumethiazide Furosemide Hydrochlorothiazide Indapamide Torasemide **Anti HTA** **ketanserin Moexipril/HCTZ** **Cholinesterase inhibitor** Donepezil Galantamine **Psychotropics:** **Antidepressants**	Diphenhydramine Doxorubicin Entacapone (high doses) Halofantrine Hydroxyzine Indinavir Imatinib Lobelin Lomustine Methadone Moclobemide Metoclopramide Midodrine Moclobemide Nortuloxeline Ranitidine Ritonavir Ticlopidine Tripelennamine Vinblastine Vincristine Vinorelbine Yohimbine	

Amitriptyline Citalopram/escitalopram **Clomipramine** **cyamepromazine** **Desipramine** Doxepin **Imipramine** Fluoxetine Fluvoxamine **Mirtazapine** **Nortriptyline** Paroxetine Sertraline Trazodone **Trimipramine** **Venlafaxine** **Antipsychotics** **Aripiprazole** **Asenapine** Chlorpromazine **Clozapine** **Flupentixol** Haloperidol **Iloperidone** levosulpride **Melperone** Olanzapine **paliperidone** **Pimavanserin** **Pipamperone** Pimozide **Promethazine** **Prothipendyl** **Perphenazine** Quetiapine **Risperidone** **Sertindole** Sulpiride sultopride Thioridazine ziprasidone **Zotepine** **Antimanic** **Lithium**		

Sedative, hypnotics Choral hydrate **Dexmedetomidine** **Antiemetics** Domperidone Droperidol Ondansetron **Granisetron**/ **Dolasetron, Tropisetron** Metoclopramide **Others:** *Phospho-diesterase 3 inhibitor*: Anagrelide cilostazol *Protein kinase inhibitors*: **Lapatinib**, **Sunitinib, Bosutinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Lenvatinib, Nilotinib, Osimertinib, Pazopanib, Ribociclib, Sorafenib** **Apomorphine** **Alfuzosin** **Atomoxetine** **Capecitabine** Cocaine **Degarelix** Esomeprazole **Eribulin** **Famotidine** **Hydrocodone** Ibogaine Lanzoprazole **Leuprolide** Levomethadyl Loperamide Methadone **Mifepristone** **Mirabegron** **Necitumumab** **Nusinersen** Omeprazole **Oxytocin** Pantoprazole **Panobinostat** Papaverine		

Pasireotide **Romidepsin** Solifenacin **Tacrolimus** **Tamoxifen** Terlipressin Terolidine **Tetrabenazine** **Tiapride** **Tizanidine** **Tolterodine** **Toremifene** Vandetanib **Vardenafil** **Vemurafenib** **Vorinostat**		

ATTACHMENT 2: READINESS FOR DISCHARGE QUESTIONNAIRE

This tool is to be used for research purposes only and should not be utilized in determining actual eligibility for discharge			
Note: The items below should be rated independently of social or economic factors.			
Please circle your response to each question:			
1) The subject is **not** actively suicidal or homicidal.			
Strongly Agree	Agree	Disagree	Strongly Disagree
2) The subject has adequate control over aggression and impulsivity.			
Strongly Agree	Agree	Disagree	Strongly Disagree
3) The subject has the ability to carry out basic ADLs (Activities of daily living).			
Strongly Agree	Agree	Disagree	Strongly Disagree
4) The subject has the ability to take medicine independently (from the hospital/medical staff).			
Strongly Agree	Agree	Disagree	Strongly Disagree
5) The subject's delusions and hallucinations do not significantly interfere with functioning.			
Strongly Agree	Agree	Disagree	Strongly Disagree
6) Does the subject have a CGI-Severity of ≤ **4**? (see below)			
Yes	No		
• Rate the patient's CGI-Severity. Considering your total clinical experience with this population, how mentally ill is the patient at this time?			
0 = Not assessed		4 = Moderately ill	
1 = Normal, not mentally ill		5 = Markedly ill	
2 = Borderline Mentally ill		6 = Severely ill	
3 = Mildly ill		7 = Among the most extremely ill patients	
• Using the above items <u>as a guide only,</u> please answer the following:			
Based on your clinical judgment of symptomatic improvement, and independent of social or economic factors, is this subject ready for discharge?			

This tool is to be used for research purposes only and should not be utilized in determining actual eligibility for discharge			
Note: The items below should be rated independently of social or economic factors.			
Please circle your response to each question:			
Yes	**No**		

ATTACHMENT 3: ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service

Alcohol, Drug Abuse, and Mental Health Administration

National Institute of Mental Health

NAME: _____

DATE: _____

Prescribing Practitioner: _____

CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.)
before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies		RATER Date	RATER Date	RATER Date
Facial and Oral Movements	1. **Muscles of Facial Expression** e.g., movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. **Jaw** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Extremity Movements	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures?**	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes

	13. Edentia?	No	Yes	No	Yes	No	Yes
	14. Do movements disappear in sleep?	No	Yes	No	Yes	No	Yes

Final: 9/2000

ATTACHMENT 4: BARNES AKATHISIA RATING SCALE (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs

1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed

2 Observed phenomena, as described in (1) above, which are present for at least half the observation period

3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0 Absence of inner restlessness

1 Non-specific sense of inner restlessness

2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still

3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress

1 Mild

2 Moderate

3 Severe

Global Clinical Assessment of Akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable.* Non-specific inner tension and fidgety movements.

2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.

3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing.

4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.

5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Scoring the Barnes Akathisia Rating Scale

The Barnes Akathisia Rating Scale is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

ATTACHMENT 5: POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) RATING CRITERIA

GENERAL RATING INSTRUCTIONS

Data gathered from this assessment procedure are applied to the PANSS ratings. Each of the 30 items is accompanied by a specific definition, as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology, as follows:

1 – absent
2 – minimal
3 – mild
4 – moderate
5 – moderate severe
6 – severe
7 – extreme

In assigning ratings, one first considers whether an item is at all present, as judging by its definition. If the item is absent, it is scored 1, whereas if it is present, one must determine its severity by reference to the particular criteria from the achorning points. The highest applicable rating point is always assigned, even if the patient meets criteria for lower points as well. In judging the level of severity, the rater must utilise a holistic perspective in deciding which anchoring point best characterises the patient's functioning and rate accordingly, whether or not all elements of the description are observed.

The rating points of 2 to 7 correspond to incremental levels of symptom severity:

- A rating of 2 (minimal) denotes questionable or subtle or suspected pathology, or it also may allude to the extreme end of the normal range.

- A rating of 3 (mild) is indicative of a symptom whose presence is clearly established but not pronounced and interferes little in day-to-day functioning.

- A rating of 4 (moderate) characterises a symptom which, though representing a serious problem, either occurs only occasionally or intrudes on daily life only to a moderate extent.

- A rating of 5 (moderate severe) indicates marked manifestations that distinctly impact on one's functioning but are not all-consuming and usually can be contained at will.

- A rating of 6 (severe) represents gross pathology that is present very frequently, proves highly disruptive to one's life, and often calls for direct supervision.

- A rating of 7 (extreme) refers to the most serious level of psychopathology, whereby the manifestations drastically interfere in most or all major life functions, typically necessitating close supervision and assistance in many areas.

Each item is rated in consultation with the definitions and criteria provided in this manual. The ratings are rendered on the PANSS rating form overleaf by encircling the appropriate number following each dimension.

PANSS RATING FORM

		Absent	Minimal	Mild	Moderate	Moderate severe	Severe	Extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgment & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

SCORING INSTRUCTIONS

Of the 30 items included in the PANSS, 7 constitute a Positive Scale, 7 a Negative Scale, and the remaining 16 a General Psychopathology Scale. The scores for these scales are arrived at by summaries of ratings across component items. Therefore, the potential ranges are 7 to 49 for the Positive and Negative Scales, and 16 to 112 for the General Psychopathology Scale. In addition to these measures, a Composite Scale is scored by subtracting the negative score from the positive score. This yields a bipolar index that ranges from -42 to +42, which is essentially a difference score reflecting the degree of predominance of one syndrome in relation to the other.

POSITIVE SCALE (P)

P1. **DELUSIONS** – Beliefs which are unfounded, unrealistic, and idiosyncratic.

Basis for rating – Thought content expressed in the interview and its influence on social relations and behaviour.

1 **Absent** – Definition does not apply

2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Presence of one or two delusions which are vague, uncrystallised and not tenaciously held. Delusions do not interfere with thinking, social relations or behaviour.

4 **Moderate** – Presence of either a kaleidoscopic array of poorly formed, unstable delusions or a few well-formed delusions that occasionally interfere with thinking, social relations or behaviour.

5 **Moderate Severe** – Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations and behaviour.

6 **Severe** – Presence of a stable set of delusions which are crystallised, poss bly systematized, tenaciously held and clearly interfere with thinking, social relations and behaviour.

7 **Extreme** – Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardise the safety of the patient or others.

P2. **CONCEPTUAL DISORGANISATION** – Disorganised process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, loose associations, tangentiality, gross illogicality or thought block.

Basis for rating – Cognitive-verbal processes observed during the course of interview.

1 **Absent** – Definition does not apply

2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Thinking is circumstantial, tangential or paralogical. There is some difficulty in directing thoughts towards a goal, and some loosening of associations may be evidenced under pressure.

4 **Moderate** – Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.

5 **Moderate Severe** – Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevancies, disconnectedness or loosening of associations even when not under pressure.

6 **Severe** – Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.

7 **Extreme** – Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which result in total failure of communication, e.g., "word salad" or mutism.

P3. **HALLUCINATORY BEHAVIOR** – Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms.

Basis for rating – Verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour.

4 **Moderate** – Hallucinations occur frequently but not continuously, and the patient's thinking and behaviour are only affected to a minor extent.

5 **Moderate Severe** – Hallucinations occur frequently, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behaviour. Patient may have a delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.

6 **Severe** – Hallucinations are present almost continuously, causing major disruption of thinking and behaviour. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.

7 **Extreme** – Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behaviour. Hallucinations are provided a rigid interpretation and provoke verbal and behavioural responses, including obedience to command hallucinations.

P4. **EXCITEMENT** – Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance or excessive mood lability.

Basis for rating – Behavioural manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Tends to be slightly agitated, hypervigilant or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.

4 **Moderate** – Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.

5 **Moderate Severe** – Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.

6 **Severe** – Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating or sleeping.

7 **Extreme** – Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

P5. **GRANDIOSITY** – Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power and moral righteousness.

Basis for rating – Thought content expressed in the interview and its influence on behaviour.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.

4 **Moderate** – Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.

5 **Moderate Severe** – Clear-cut delusions concerning remarkable abilities, status or power are expressed and influence attitude but not behaviour.

6 **Severe** – Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions and may be acted upon.

7 **Extreme** – Thinking interactions and behaviour are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power and/or moral stature, which may take on a bizarre quality.

P6. **SUSPICIOUSNESS/PERSECUTION** – Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, and distrustful attitude, suspicious hypervigilance or frank delusions that others mean harm.

Basis for rating – Thought content expressed in the interview and its influence on behaviour.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Presents a guarded or even openly distrustful attitude, but thoughts, interactions and behaviour are minimally affected.
4 **Moderate** – Distrustfulness is clearly evident and intrudes on the interview and/or behaviour, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.
5 **Moderate Severe** – Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behaviour.
6 **Severe** – Clear-cut pervasive delusions of persecution which may be systematized and significantly interfere in interpersonal relations.
7 **Extreme** – A network of systematized persecutory delusions dominates the patient's thinking, social relations and behaviour.

P7. **HOSTILITY** – Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse and assaultiveness.

Basis for rating – Interpersonal behaviour observed during the course of interview and reports by primary care workers or family.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions and occasional irritability.
4 **Moderate** – Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.
5 **Moderate Severe** – Patient is highly irritable and occasionally verbally abusive or threatening.
6 **Severe** – Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive towards them.
7 **Extreme** – Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault towards others.

NEGATIVE SCALE (N)

N1. **BLUNTED AFFECT** – Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings and communicative gestures.

Basis for rating – Observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Changes in facial expression and communicative gestures seem to be stilted, forced, artificial or lacking in modulation.
4 **Moderate** – Reduced range of facial expression and few expressive gestures result in a dull appearance.
5 **Moderate Severe** – Affect is generally 'flat' with only occasional changes in facial expression and a paucity of communicative gestures.
6 **Severe** – Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage or inappropriate uncontrolled laughter.
7 **Extreme** – Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or 'wooden' expression.

N2. **EMOTIONAL WITHDRAWAL** – Lack of interest in, involvement with, and affective commitment to life's events.

Basis for rating – Reports of functioning from primary care workers or family and observation of interpersonal behaviour during the course of the interview.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Usually lack initiative and occasionally may show deficient interest in surrounding events.
4 **Moderate** – Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.
5 **Moderate Severe** – Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts of engagement. Patient appears distant, docile, and purposeless, but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.
6 **Severe** – Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent and frequent neglect of personal functions, for which the patient requires supervision.
7 **Extreme** – Patient is almost totally withdrawn, uncommunicative and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

N3. **POOR RAPPORT** – Lack of interpersonal empathy, openness in conversation and sense of closeness, interest or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication.

Basis for rating – Interpersonal behaviour during the course of interview.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Conversation is characterized by a stilted, strained or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.
4 **Moderate** – Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored or express disinterest.
5 **Moderate Severe** – Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.
6 **Severe** – Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.
7 **Extreme** – Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

N4. **PASSIVE/APATHETIC SOCIAL WITHDRAWAL** – Diminished interest and initiative in social interactions due to passivity, apathy, anergy or avolition. This leads to reduced interpersonal involvements and neglect of activities or daily living.

Basis for rating – Reports on social behaviour from primary care workers or family.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.
4 **Moderate** – Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.
5 **Moderate Severe** – Passively participates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.
6 **Severe** – Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.
7 **Extreme** – Profoundly apathetic, socially isolated and personally neglectful.

N5. **DIFFICULTY IN ABSTRACT THINKING** – Impairment in the use of abstract-symbolic mode of thinking, as evidence by difficulty in classification, forming generalisations and proceeding beyond concrete or egocentric thinking in problem-solving tasks.

Basis for rating – Responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

1 **Absent** – Definition does not apply

2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.

4 **Moderate** – Often utilizes a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.

5 **Moderate Severe** – Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.

6 **Severe** – Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features and idiosyncratic interpretations.

7 **Extreme** – Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

N6. **LACK OF SPONTANEITY AND FLOW OF CONVERSATION** – Reduction in the normal flow of communication associated with apathy, avolition, defensiveness or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal interactional process.

Basis for rating – Cognitive-verbal processes observed during the course of interview.

1 **Absent** – Definition does not apply

2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.

4 **Moderate** – Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.

5 **Moderate Severe** – Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.

6 **Severe** – Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (e.g., "I don't know", "I'm not at liberty to say"). Conversation is seriously impaired as a result and the interview is highly unproductive.

7 **Extreme** – Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.

N7. **STEREOTYPED THINKING** – Decreased fluidity, spontaneity and flexibility of thinking, as evidenced in rigid, repetitious or barren thought content.

Basis for rating – Cognitive-verbal processes observed during the interview.

1 **Absent** – Definition does not apply

2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Some rigidity shown in attitude or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.

4 **Moderate** – Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.

5 **Moderate Severe** – Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.

6 **Severe** – Uncontrolled repetition of demands, statements, ideas or questions which severely impairs conversation.

7 **Extreme** – Thinking, behaviour and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness and restrictiveness of patient's communication.

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1. **SOMATIC CONCERN** – Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease.

Basis for rating – Thought content expressed in the interview.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Distinctly concerned about health or bodily malfunction, but there is no delusional conviction and overconcern can be allayed by reassurance.
4 **Moderate** – Complaints about poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.
5 **Moderate Severe** – Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.
6 **Severe** – Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.
7 **Extreme** – Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect or thinking.

G2. **ANXIETY** – Subjective experience of nervousness, worry, apprehension or restlessness, ranging from excessive concern about the present or future to feelings of panic.

Basis for rating – Verbal report during the course of the interview and corresponding physical manifestations.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Expresses some worry, overconcern or subjective restlessness, but no somatic and behavioural consequences are reported or evidenced.
4 **Moderate** – Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.
5 **Moderate Severe** – Patient reports serious problems of anxiety which have significant physical and behavioural consequences, such as marked tension, poor concentration, palpitations or impaired sleep.
6 **Severe** – Subjective state of almost constant fear associated with phobias, marked restlessness or numerous somatic manifestations.
7 **Extreme** – Patient's life is seriously disrupted by anxiety, which is present almost constantly and at times reaches panic proportion or is manifested in actual panic attacks.

G3. **GUILT FEELINGS** – Sense of remorse or self-blame for real or imagined misdeeds in the past.

Basis for rating – Verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.
4 **Moderate** – Patient expresses distinct concern over his responsibility for a real incident in his life but is not pre-occupied with it and attitude and behaviour are essentially unaffected.
5 **Moderate Severe** – Patient expresses a strong sense of guilt associated with self-depreciation or the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.
6 **Severe** – Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he should receive harsh sanctions such as punishment.
7 **Extreme** – Patient's life is dominated by unshakable delusions or guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts of attribution of others' problems to one's own past misdeeds.

G4. **TENSION** – Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating and restlessness.

Basis for rating – Thought content expressed in the interview.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of positions, or fine rapid hand tremor.
4 **Moderate** – A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.
5 **Moderate Severe** – Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating and restlessness, but conduct in the interview is not significantly affected.
6 **Severe** – Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.
7 **Extreme** – Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

G5. **MANNERISMS AND POSTURING** – Unnatural movements or posture as characterized by an awkward, stilted, disorganised, or bizarre appearance.

Basis for rating – Verbal report during the course of the interview and corresponding physical manifestations.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Slight awkwardness in movements or minor rigidity of posture.
4 **Moderate** – Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.
5 **Moderate Severe** – Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.
6 **Severe** – Frequent repletion of bizarre rituals, mannerisms or stereotyped movements, or a controlled posture is sustained for extended periods.
7 **Extreme** – Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.

G6. **DEPRESSION** – Feelings of sadness, discouragement, helplessness and pessimism.

Basis for rating – Verbal report of depressed mood during the course of interview and its observed influence on attitudes and behaviour.

1 **Absent** – Definition does not apply
2 **Minimal** – Questionable pathology; may be a the upper extreme of normal limits
3 **Mild** – Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanor.
4 **Moderate** – Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behaviour or social functioning and the patient usually can be cheered up.
5 **Moderate Severe** – Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and some interference in appetite and sleep. The patient cannot be easily cheered up.
6 **Severe** – Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.
7 **Extreme** – Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self neglect, possible depressive or nihilistic delusions and/or possible suicidal thoughts or action.

G7. **MOTOR RETARDATION** – Reduction in motor activity as reflected in slowing or lessening or movements and speech, diminished responsiveness of stimuli, and reduced body tone.

Basis for rating – Manifestations during the course of interview as well as reports by primary care workers as well as family.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.

4 **Moderate** – Patient is clearly slow in movements, and speech may be characterized by poor productivity including long response latency, extended pauses or slow pace.

5 **Moderate Severe** – A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.

6 **Severe** – Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.

7 **Extreme** – Patient is almost completely immobile and virtually unresponsive to external stimuli.

G8. **UNCOOPERATIVENESS** – Activity refusal to comply with the will of significant others, including the interviewer, hospital staff or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility or belligerence.

Basis for rating – Verbal report during the course of the interview and corresponding physical manifestations.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Complies with an attitude of resentment, impatience, or sarcasm. May offensively object to sensitive probing during the interview.

4 **Moderate** – Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive or negative attitude but usually can be worked with.

5 **Moderate Severe** – Patient frequently is incompliant with the demands of his milieu and may be characterized by others as an “outcast” or having “a serious attitude problem”. Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.

6 **Severe** – Patient is highly uncooperative, negativistic and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.

7 **Extreme** – Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff and participate even briefly in an interview.

G9. **UNUSUAL THOUGHT CONTENT** – Thinking characterized by strange, fantastic or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical and patently absurd.

Basis for rating – Thought content expressed during the course of interview.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Thought content is somewhat peculiar, or idiosyncratic, or familiar ideas are framed in an odd context.

4 **Moderate** – Ideas are frequently distorted and occasionally seem quite bizarre.

5 **Moderate Severe** – Patient expresses many strange and fantastic thoughts, (e.g., Being the adopted son of a king, being an escapee from death row), or some which are patently absurd (e.g., Having hundreds of children, receiving no radio message from outer space from a tooth filling).

6 **Severe** – Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet.

7 **Extreme** – Thinking is replete with absurd, bizarre and grotesque ideas.

G10. **DISORIENTATION** – Lack of awareness of one's relationship to the milieu, including persons, place and time, which may be due to confusion or withdrawal.

Basis for rating – Responses to interview questions on orientation.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address, knows hospital staff names but not their functions, knows the month but confuses the day of the week with an adjacent day, or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the mayor, governor, or president.

4 **Moderate** – Only partial success in recognizing persons, places, and time. For example, patient knows he is in a hospital but not its name, knows the name of the city but not the borough or distinct, knows the name of his primary therapist but not many other direct care workers, knows the year or season but not sure of the month.

5 **Moderate Severe** – Considerable failure in recognizing persons, place and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly but not know the current month, day of week or even the season.

6 **Severe** – Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his whereabouts, confuses the date by more than one year, can name only one or two individuals in this current life.

7 **Extreme** – Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year and even the most familiar people, such as parents, spouse, friends, and primary therapist.

G11. **POOR ATTENTION** – Failure in focused alertness manifested by poor concentration, distractibility for internal and external stimuli, and difficulty in harnessing, sustaining or shifting focus to new stimuli.

Basis for rating – Manifestations during the course of interview.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Limited concentration evidenced by occasional vulnerability to distraction and faltering attention toward the end of the interview.

4 **Moderate** – Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.

5 **Moderate Severe** – Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.

6 **Severe** – Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.

7 **Extreme** – Attention is so disrupted that even brief conversation is not possible.

G12. **LACK OF JUDGMENT AND INSIGHT**– Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation or consequences, and unrealistic short-term and long-range planning.

Basis for rating – Thought content expressed during the interview.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Recognises having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.

4 **Moderate** – Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganised thinking, suspiciousness and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension and sleep difficulty.

5 **Moderate Severe** – Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.

6 **Severe** – Patient denies ever having had a psychiatric disorder. He disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.

7 **Extreme** – Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient thus refuses to cooperate with therapists, medication or other aspects of treatment.

G13. **DISTURBANCE OF VOLITION** – Disturbance in the willful initiation, sustenance and control of one's thoughts, behaviour, movements, and speech

Basis for rating – Thought content and behaviour manifested in the course of interview.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.

4 **Moderate** – Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alteration in thinking, and in consequence, verbal and cognitive functioning is clearly impaired.

5 **Moderate Severe** – Disturbance of volition interferes in thinking as well as behaviour. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.

6 **Severe** – Disturbance of volition interferes in the execution of simple automatic motor functions, such as dressing or grooming, and markedly affects speech.

7 **Extreme** – Almost complete failure of volition is manifested by gross inh bition of movement and speech resulting in immobility and/or mutism.

G14. **POOR IMPULSE CONTROL** – Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary or misdirected discharge of tension and emotions without concern about consequences.

Basis for rating – Behaviour during the course of interview and reported by primary care workers or family.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.

4 **Moderate** – Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.

5 **Moderate Severe** – Patient exh bits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or PRN sedation.

6 **Severe** – Patient frequently impulsive aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behaviour and may also be sexually offensive and possibly respond behaviourally to hallucinatory commands.

7 **Extreme** – Patient exhibits homicidal, sexual assaults, repeated brutality, or self-destructive behaviour. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

G15. **PREOCCUPATION** – Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour.

Basis for rating – Interpersonal behaviour observed during the course of interview.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.

4 **Moderate** – Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.

5 **Moderate Severe** – Patient often appears to be engaged in autistic experiences, as evidence by behaviours that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.

6 **Severe** – Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.

7 **Extreme** – Gross absorption with autistic experiences, which profoundly affects all major realms of behaviour. The patient constantly may be responding verbally or behaviourally to hallucinations and show little awareness of other people or the external milieu.

G16. **ACTIVE SOCIAL AVOIDANCE** – Diminished social involvement associated with unwarranted fear, hostility, or distrust.

Basis for rating – Reports of social functioning from primary care workers or family.

1 **Absent** – Definition does not apply

2 **Minima**l – Questionable pathology; may be a the upper extreme of normal limits

3 **Mild** – Patient seems ill at ease in the presence of others and prefers to spend time alone, although he participates in social functions when required.

4 **Moderate** – Patient begrudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.

5 **Moderate Severe** – Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.

6 **Severe** – Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he tends to isolate himself from others.

7 **Extreme** – Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others.

ATTACHMENT 6: PERSONAL AND SOCIAL PERFORMANCE SCALE

Please rate the patient on his/her level of functioning during the reference period (e.g., past month or last 7 days). Consider what the person is doing, taking into account if she needs help or prompting by others.

The four main domains of functioning considered in this scale are (a) personal and social relationships; (b) socially useful activities, including work and study; (c) self-care; and (d) disturbing and aggressive behaviors.

In each area, consider the worst behavior observed in the reference period. One difficulty is that areas a, b, and c include more subareas. In this case, give the score corresponding to the subarea where the worst functioning would be rated with the lowest degree of severity score 0–6 (see below). For area a, subareas are work or study and other socially useful activities (e.g., housework, voluntary work, "useful" hobbies as gardening); for area b, subareas are relationship with partner (only if the patient has a partner and usually lives with him/her, otherwise ignore), family relationships, and social relationships; for area c, subareas are personal hygiene, care of one's appearance, and attire.

Other areas (different from the main four areas) (e.g., self-management of the disorder; having interests and being informed about social, political, or even sport issues; instrumental activities as managing money, using the phone, travelling) may be taken into account to define the score inside each ten-point interval.

If there was a recent crisis, you may want to give two scores, one for the crisis period (e.g., last 7 days) and one for the month before the beginning of the crisis.

There are two different sets of operational criteria to judge the degree of difficulties:			
One for areas a–c and one for area d			
Degrees of severity areas a – c		**Degrees of severity area d**	
0.	Absent	0.	Absent
1.	Mild: difficulties that are known only by someone who is very familiar with the person	1.	Mild: corresponding to mild rudeness, unsociability, or whining
2.	Manifest, but not marked (equivalent to moderate): difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's sociocultural context, age, gender, and educational levels; rate area a as "manifest" if the person has a sheltered work and the performance is good	2.	Manifest or moderate: such as speaking too loudly or speaking to others in a too familiar manner or eating in a socially unacceptable manner
3.	Marked: difficulties interfering severely with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able to reach the previous level of functioning	3.	Marked: insulting others in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (e.g., stripping or urinating in public) not occasionally
4	Severe: the person is unable to perform any role in that area without help or has a harmful influence; the person's health, bur not his/her life, may be at risk	4	Severe: frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries not occasionally

There are two different sets of operational criteria to judge the degree of difficulties:			
One for areas a–c and one for area d			
Degrees of severity areas a – c		**Degrees of severity area d**	
5.	Very severe: impairments and difficulties of such intensity to endanger the person's survival. Suicide risk should be taken into account only as much as suicide ideation and rumination interferes with social functioning	5.	Very severe: defined as aggressive acts, aimed at or likely to cause severe injuries not occasionally

For a disturbing behavior to be considered as "occasional," it must have taken place only once in the preceding week or 1–2 times in the preceding month, and in the judgment of mental health professionals and caregivers, it is unlikely to happen again in the next 6 months. If a behavior meets this definition of "occasional," the rating should be decreased by one point (e.g., severe to marked, moderate to mild). An injury has to be considered "severe" if it would need to be treated in an emergency department, if available.

The following table may be used to score the severity of problems in each main area							
		Absent	**Mild**	**Manifest**	**Marke**	**Seve e**	**Very severe**
1)	Soc lly useful activities, including ork and study	€			f	”	…
2)	Personal and social relationships	€		’	f	”	…
3)	Self-care	€		’	f	”	…
4)	Disturbing and aggressive behaviors	€		’	f	”	…

Overall score instructions on the basis of the four main areas' scores

100–91	Excellent functioning in all four main areas. He/she is held in high consideration for his/her good qualities, copes adequately with life problems and is involved in a wide range of interests and activities
90–81	Good functioning in all four areas, presence of only common problems and difficulties
80–71	Mild difficulties in one or more of the areas a–c
70–61	Manifest, but not marked, difficulties in one or more areas a–c or mild difficulties in d. For area a, include here sheltered work, if the performance is good
60–51	Marked difficulties in only one area a–c or manifest difficulties in d
50–41	Marked difficulties in two or three of the areas a–c or severe difficulties in only one area a–c without marked difficulties in the other two; no marked difficulties in d
40–31	Severe difficulties only in one area a–c and marked difficulties in at least one of the other two; or marked difficulties in d
30–21	Severe difficulties in two areas a–c or severe difficulties in d, even if severe and marked difficulties in the areas a–c are absent
20–11	Severe difficulties in all areas a–c or very severe difficulties in d, even if severe difficulties in area –-c are absent. If the person reacts to external prompts, the suggested scores are 20–16; if not, they are 15–11

10–1	Lack of autonomy in basic functioning with extreme behaviors but without survival risk (scores 10–6) or with survival risk, e.g., death risk due to malnutrition, dehydration, infections, and inability to recognize situations of marked danger (scores 5–1)
	5) Overall score |___|___|___|
Summary meaning of PSP total score	
71–00	These ratings reflect absence of disability or only mild difficulties
31–70	These ratings reflect varying degrees of disability
–30	These ratings reflect functioning so poor that the patient requires intensive support or supervision

ATTACHMENT 7: CLINICAL GLOBAL IMPRESSION – SEVERITY RATING

Severity of illness

Considering your total clinical experience with this particular patient, how mentally ill is the patient at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

ATTACHMENT 8: [redacted]

[redacted]

ATTACHMENT 9: COGNITIVE TESTING

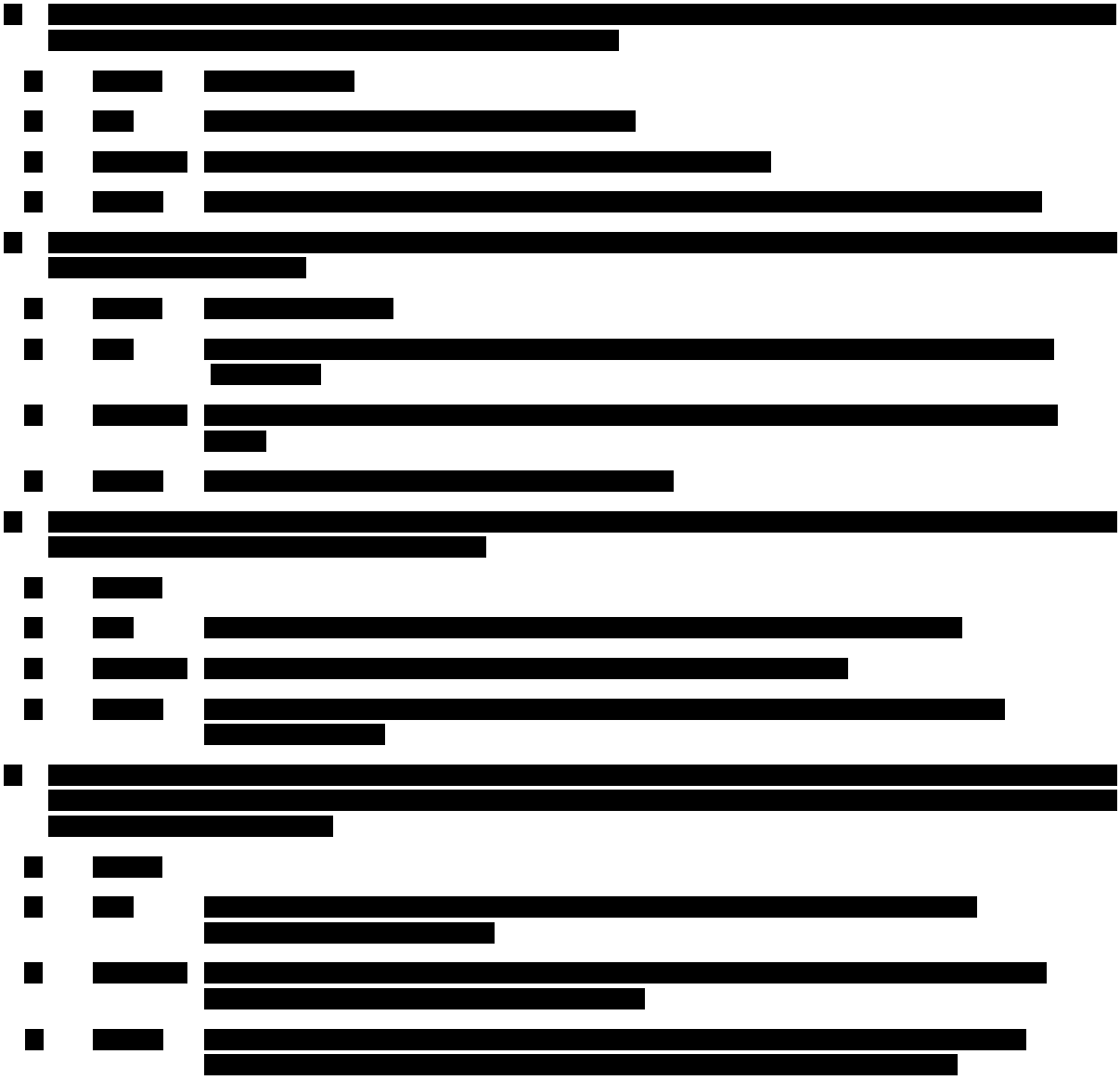
It is imperative that personnel who will be testing patients practice administering and scoring the entire test battery at their institutions in order to become familiar with the materials. Some tests require simultaneous administration and scoring; in others, additional attention must be paid to scoring details. All the tests require specific and rigorous adherence to instructions to preserve standardization.

There are alternate forms for the tests that may be sensitive to practice effect or learning due to previous test administration. Patients should not receive the same forms or versions two times consecutively.

Verbal Fluency

Letter Fluency. In two separate trials, patients will be given 60 seconds to generate as many words as possible.

Measures: number of words generated



ATTACHMENT 11: SHEEHAN SUICIDALITY TRACKING SCALE

SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS)

1.	did you have any accident? (this includes taking too much of your medication accidentally) IF NO, SKIP TO QUESTION 2. IF YES, GO TO QUESTION 1a:	NO ☐			YES ☐	
		Not at all	**A little**	**Moderately**	**Very**	**Extremely**
1a.	how seriously did you plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose? IF THE ANSWER TO QUESTION 1a IS 0 (= Not at all), SKIP TO QUESTION 2. IF THE SCORE IS 1 OR HIGHER, GO TO QUESTION 1b:	0	1	2	3	4
1b.	did you intend to die as a result of any accident?	NO ☐			YES ☐	
	Since your last visit, how seriously did you:	**Not at all**	**A little**	**Moderately**	**Very**	**Extremely**
2.	think (even momentarily) that you would be better off dead, need to be dead or wish you were dead? How many times? ____	0	1	2	3	4
3.	think (even momentarily) about harming or hurting or injuring yourself – with at least some intent or awareness that you might die as a result – or think about suicide (killing yourself)? How many times? ____	0	1	2	3	4
4.	have a voice or voices telling you to kill yourself or have dreams with any suicidal content? mark either or both: ☐ a voice or voices ☐ a dream	0	1	2	3	4
5.	have any suicide method in mind (i.e. how)? #	0	1	2	3	4
6.	have any suicide means in mind (i.e. with what)? #	0	1	2	3	4
7.	have any place in mind to attempt suicide (i.e. where)? * #	0	1	2	3	4
8.	have any date / timeframe in mind to attempt suicide (i.e. when)?*#	0	1	2	3	4
9.	intend to act on thoughts of killing yourself? mark either or both: did you intend to act: ☐ at the time ☐ at some time in the future	0	1	2	3	4
10.	intend to die as a result of a suicidal act? mark either or both: did you intend to die: ☐ at the time ☐ at some time in the future	0	1	2	3	4
11.	feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? mark either or both: was this: ☐ to kill yourself ☐ to plan to kill yourself mark either or both: was this: ☐ largely unprovoked ☐ provoked	0	1	2	3	4
12.	take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)?	0	1	2	3	4
13.	injure yourself on purpose without intending to kill yourself? How many times? ____	0	1	2	3	4
14.	attempt suicide (try to kill yourself)?	0	1	2	3	4

**A suicide attempt is a potentially self-injurious behavior, associated with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury." (FDA 2012 definition[1-2]).* * Note: Items 7 & 8 on S-STS ("a plan for suicide") means not going beyond ideas or talking about a plan for suicide. If actual behaviors occurred, the event should not be coded on item 7 or 8, but as "preparatory behavior" (item 12). Both events can occur separately over the same timeframe. # Note: clinician should ask for details.

Page 1 of 3

SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS) - EVENTS REPORT

15. IF ANSWER 14 IS POSITIVE ASK:

Since your last visit, how many times did you attempt suicide? ____

	When? dd/MMM/yyyy	How?	How serious was each attempt? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Attempt (halted by self, by another person or event, or not at all)
Level **1**: You started the suicide attempt, but then **you decided to stop** and did not finish the attempt.
Level **2**: You started the suicide attempt, but then **you were interrupted** and did not finish the attempt.
Level **3**: You went through the suicide attempt **completely** as you meant to.

16. IF ANSWER 12 IS POSITIVE ASK:

Since your last visit, how many times did you take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? ____
(Include only the times when you stopped short of making an actual suicide attempt.)

	When? dd/MMM/yyyy	How?	How serious was each preparation? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Preparation
Level **1**: You took active steps to prepare to kill yourself, but you did not start the suicide attempt.
Level **2**: You were about to try to kill yourself, but then **you stopped yourself** just before harming yourself.
Level **3**: You were about to try to kill yourself, but then **someone or something stopped you** just before harming yourself.

TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS OVER THE PAST 6 MONTHS:
Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent per day: ____ hours ____ minutes.
Most amount of time spent per day: ____ hours ____ minutes.

SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS) - CLINICIAN USE ONLY

Complete this section *if the patient does not return for the scheduled follow up visit* and is not available to permit completion of pages 1 and 2.

FOR CLINICIAN USE ONLY

	NO	YES
17. Missed appointment - reason: subject died from a completed suicide?	0	100
18. Missed appointment - reason: subject died, but not enough information to code as a suicide?	0	0
19. Missed appointment - reason: subject died from cause(s) other than suicide?	0	0
20. Missed appointment - reason: subject alive, but not available because of a suicide attempt?	0	4
21. Missed appointment - reason: subject alive, but not available for known reasons other than suicide?	0	0
22. Missed appointment - reason: subject alive, but not available, for uncertain reasons, or "lost to follow up"?	0	0

Total Scale Score Add scores from Questions 1a (only if 1b is coded YES), + 2 through 11 + [the highest of 12 or any row of 16] + [the highest of 14 or any row of 15] + 17 + 20 [on page 3]. **TOTAL** ☐

☐ I have reviewed the answers on Pages 1 and 2 with the patient.

_____ _____
Clinician Signature dd/MMM/yyyy

☐ I have reviewed the answers on Pages 1 and 2 with my doctor or clinician.

_____ _____
Patient Signature dd/MMM/yyyy

References

1. Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. August 2012. Revision 1. U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Silver Spring, MD 20992-0002. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/ Direct download from www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf
2. Posner K, Oquendo MA et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. C-CASA Definitions in Table 2, page 1037. Am J Psychiatry 2007; 164:1035-1043

The author is grateful to JM Giddens for very valuable advice in the development of the S-STS and of the S-STS CMCM versions.

ATTACHMENT 12: SIMPSON-ANGUS SCALE

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and Is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. GAIT: The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:	
0 = Normal	☐
1 = Diminution in swing while the patient is walking	☐
2 = Marked diminution in swing with obvious rigidity in the arm	☐
3 = Stiff gait with arms held rigidly before the abdomen	☐
4 = Stopped shuffling gait with propulsion and retropulsion	☐
2. ARM DROPPING: The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:	
0 = Normal, free fall with loud slap and rebound	☐
1 = Fall slowed slightly with less audible contact and little rebound	☐
2 = Fall slowed, no rebound	☐
3 = Marked slowing, no slap at all	☐
4 = Arms fall as though against resistance; as though through glue	☐
3. SHOULDER SHAKING: The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows.	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐

4. ELBOW RIGIDITY: The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐
5. WRIST RIGIDITY or Fixation of position: The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulner and radial deviation:	
0 = Normal	☐
1 = Slight stiffness and resistance	☐
2 = Moderate stiffness and resistance	☐
3 = Marked rigidity with difficulty in passive movement	☐
4 = Extreme stiffness and rigidity with almost a frozen shoulder	☐
6. LEG PENDULOUSNESS: The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the Jack of swinging form the basis for the score on this item:	
0 = The legs swing freely	☐
1 = Slight diminution in the swing of the legs	☐
2 = Moderate resistance to swing	☐
3 = Marked resistance and damping of swing	☐
4 = Complete absence of swing	☐

7. HEAD DROPPING: The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder and in extreme parkinsonism it is absent. The neck muscles are rigid and the head docs not reach the examining table. Scoring is as follows:	
0 = The head falls completely with a good thump as it hits the table	☐
1 = Slight slowing in fall, mainly noted by lack of slap as head meets the table	☐
2 = Moderate slowing in the fall quite noticeable to the eye	☐
3 = Head falls stiffly and slowly	☐
4 = Head does not reach the examining table	☐
8. GLABELLA TAP: Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:	
0 = 0 - 5 blinks	☐
1 = 6 – 10 blinks	☐
2 = 11 – 15 blinks	☐
3 = 16 - 20 blinks	☐
4 = 21 and more blinks	☐
9. TREMOR: Patient is observed walking into examining room and is then reexamined for this item:	
0 = Normal	☐
1 = Mild finger tremor, obvious to sight and touch	☐
2 = Tremor of hand or arm occurring spasmodically	☐
3 = Persistent tremor of one or more limbs	☐
4 = Whole body tremor	☐
10. SALIVATION: Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:	
0 = Normal	☐
1 = Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised	☐
2 = When excess salivation is present and might occasionally result in difficulty in speaking	☐
3 = Speaking with difficulty because of excess salivation	☐
4 = Frank drooling	☐

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____

[redacted]Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted]

Institution: Minerva Neurosciences, Inc.

Signature: Date: [redacted]

(Day Month Year)

Note If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.