# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Title:** | 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 |
| **Phase:** | 3 |
| **Protocol No.:** | MIN-101C07 |
| ClinicalTrials.gov ID: | NCT03397134 |
| **Protocol Version/ Date** | MIN-101C07.v2.0, Amendment 2 –26 September 2018 |
| **Analysis Plan Version and Date** | Final Version 1.0, 08 May 2020 |
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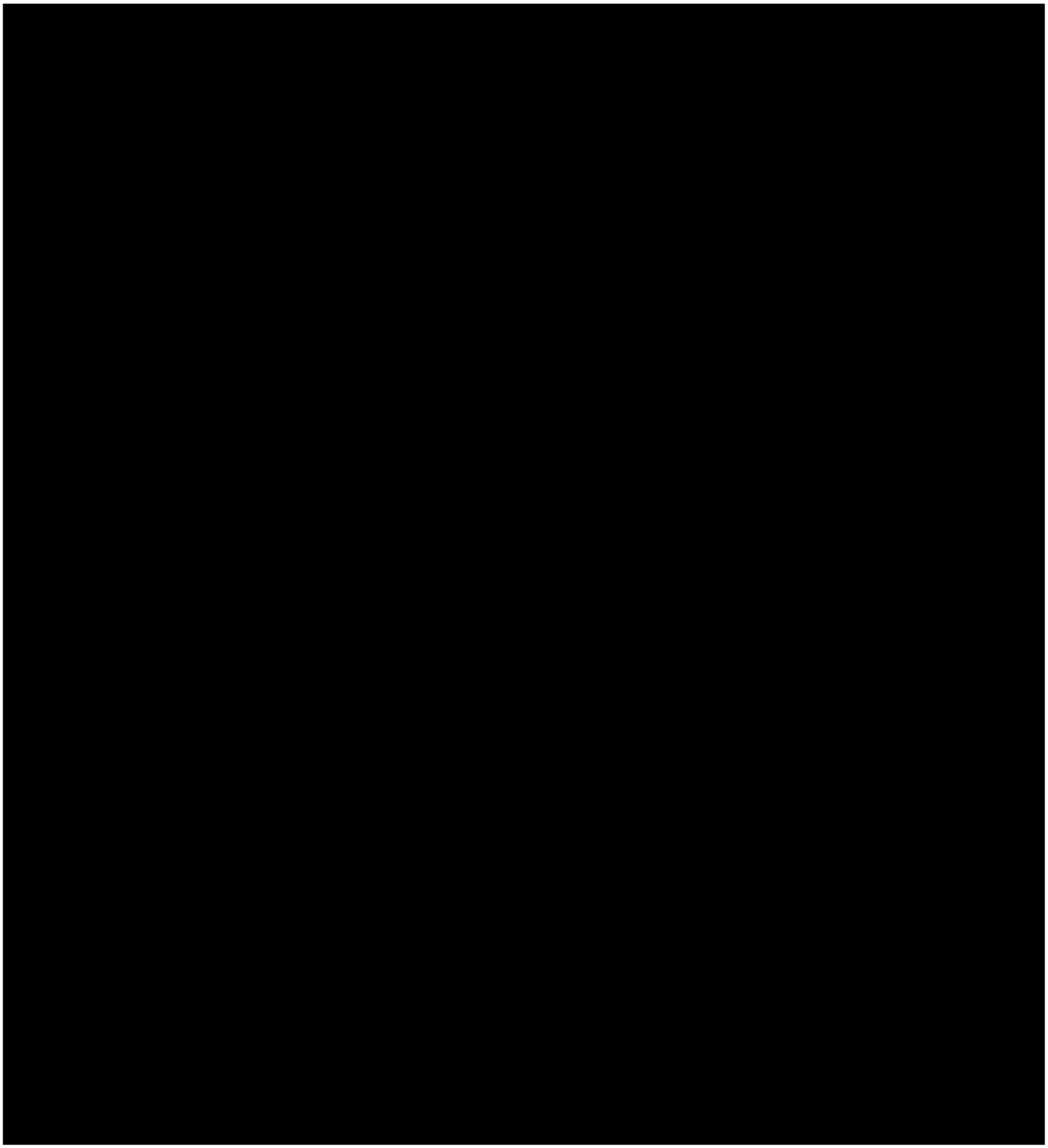
| **Prepared For:** | Minerva Neurosciences, Inc. [redacted] |

## STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL



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# 1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol MIN-101C07. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

## 1.1. STUDY OVERVIEW

Protocol MIN-101C07 is a 12-week, 3-arm, randomized, double-blind, placebo-controlled, parallel-group study to investigate the safety and efficacy of MIN-101 in male and female patients between the ages 18 to 55 with schizophrenia who present with negative symptoms but without severe symptoms of suspiciousness, agitation, hostility, or impulsivity, to yield a symptomatic but relatively stable study population. Approximately 501 patients will be randomly assigned to 1 of 3 treatment arms in equal proportion: MIN-101 64 mg, MIN-101 32 mg, or placebo, once daily and orally (PO), for 12 weeks.

Afterwards, all patients will continue treatment with active drug for an additional 40 weeks. The extension phase dose will be determined as follows: Patients 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 cross over to MIN-101 64 mg or MIN-101 32 mg in a 1:1 ratio.

The study design has 3 phases: a pre-treatment phase of up to 28 days (including washout), a 12-week double-blind treatment phase, and a 40-week open label extension phase. An end of study visit will occur within 2 weeks after completion of the open label treatment extension phase.

Pre-Treatment Phase:

- *Screening Period*: The Screening visit should take place no more than 28 days before the first administration of study drug. Patients must meet Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) diagnostic criteria for schizophrenia, have documented diagnosis for at least 1 year prior to screening, and be stable in terms of positive and negative symptoms of schizophrenia over the last 6 months. The Positive and Negative Syndrome Scale (PANSS) negative subscore must be > 20 at screening. Screening will include informed consent and detailed evaluation for eligibility in the study.
- *Washout Period: A*n 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 in order to standardize study procedures in all patients.
- *Baseline Visit:* All inclusion and exclusion criteria will be verified, including confirming that the PANSS negative subscore remains > 20 and is within 4 points absolute difference from the score at the screening visit. All assessments will be completed prior to initiation of the double-blind treatment phase.

12-Week Double-Blind Treatment Phase: On Day 1, 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 of 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, if discharged, the patient will come back for clinic visits at Weeks 1, 2, 3, 4, 8, and 12 for efficacy and/or safety assessments. Hospitalization on Visits 6 (Week 1) and 7 (Week 2) will be at the discretion of the investigator to ensure per-protocol ECG assessment and pharmacokinetic (PK) sampling are done. The patient or 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) assessments must be completed as soon as possible.

40-Week Open-Label Extension Phase: At the end of the 12-week double-blind treatment period 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. Patients and investigators will be aware that all participants are receiving MIN-101 in this phase but will not know the dose being given nor the dose used in the prior double-blind treatment phase. Patients will then be allowed to leave the hospital on Week 12 + 2 days at the discretion of the investigator and after drug intake and safety have been ascertained clinically, including having undergone ECG assessments at pre-dose and at the approximate time of $C_{max}$ of MIN-101 and of its metabolite BFB-520. RDQ will be completed prior to any authorization to leave the hospital. Hospitalization on Visits 14 (Week 13) and 15 (Week 14) 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. Visits will occur weekly through Week 16 and every 4 weeks thereafter.

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

## 1.2. TIME AND EVENTS SCHEDULES

**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 | | | | | | |
| AIMS | X | | X | | | | | | X | X | X |
| S-AS and BARS | X | | X | | | X | X | X | X | X | 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** |
| **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** | | | | | | | | | | | |
| PANSS | X | | X | | | | X | | X | X | X |
| PSP | | | X | | | | | | X | X | X |
| CGI-S | X | | X | | | | X | | X | X | X |
| [redacted] | | | | | | | | | | | |
| **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] 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; S-AS = 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 |
| 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 |
| S-AS 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** |
| **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] | | | | | | | | | | | | | | | | | |
| Verbal fluency test | X | | | | | | X | | X | | | X | | | | X | |
| [redacted] | | | | | | | | | | | | | | | | | |
| **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; S-AS = 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

## 1.3. GLOSSARY OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| AIMS | Abnormal Involuntary Movement Scale |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BARS | Barnes Akathisia Rating Scale |
| BMI | body mass index |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| CGI-S | Clinical Global Impression - Severity Scale |
| $C_{max}$ | maximum drug concentration (in plasma or serum) |
| CYP | cytochrome |
| DSB | diastolic blood pressure |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EMA | European Medicines Agency |
| EOS | end-of-study |
| F | female |
| FDA | Food and Drug Administration |
| HbA1C | hemoglobin A1c |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| ITT | intent-to-treat |
| IWRS | Interactive Web Response System |
| LNL | lower normal limit of laboratory reference range |
| LOCF | last observation carried forward |
| M | male |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation | Term |
|---|---|
| MINI | Mini International Neuropsychiatric Interview |
| MMRM | Mixed Model Repeated Measures |
| NSFS | Negative Symptoms Factor Score |
| PANSS | Positive and Negative Syndrome Scale |
| PCS | potentially clinically significant |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PO | oral, by mouth (orally) |
| PP | per-protocol |
| PSP | Personal and Social Performance |
| QTc | QT interval value corrected for heart rate |
| QTcF | QT interval value corrected for heart rate using Fridericia's formula |
| RDQ | Readiness for Discharge Questionnaire |
| SAE | serious adverse event |
| SAF | Safety population |
| SAP | Statistical Analysis Plan |
| S-AS | Simpson-Angus Scale |
| SAS | Statistical Analysis System, former initials of analytics software produced by SAS Institute Inc. |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SE | standard error |
| SI | Système International d'Unités, the International System of Units |
| SOC | System Organ Classification (part of MedDRA coding) |
| STS | Sheehan-Suicidality Tracking Scale |
| TD | tardive dyskinesia |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| US | United States (of America) |
| WHO | World Health Organization |

# 2. OBJECTIVES

## Primary Objective

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 from Baseline in the PANSS Marder negative symptoms factor score (NSFS) over 12 weeks of double-blind treatment.

## Key Secondary Objective

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

## Secondary and Exploratory Objectives

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.

# 3. GENERAL STATISTICAL CONSIDERATIONS

## 3.1. SAMPLE SIZE AND POWER

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 NSFS 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.

## 3.2. RANDOMIZATION AND BLINDING

Randomization to the initial double-blind phase (MIN-101 64 mg, MIN-101 32 mg, or placebo in a 1:1:1 ratio) and randomization of patients initially assigned to the placebo arm in a 1:1 ratio to the two active arms, MIN-101 64 mg and MIN-101 32 mg, in the open-label extension phase will be performed as part of a single randomization step at Baseline. Randomization of patients initially assigned to placebo to treatment in the open-label extension phase will be nested within the initial randomization, by assigning the eventual open-label treatment at the outset.

Central randomization will be implemented in this study. Patients will be randomized at Baseline to 1 of 4 treatment arms, 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.

Approximation 501 eligible patients will be randomized in a 2:2:1:1 ratio to the following treatment arms:

- 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.

At the outset of open-label extension phase, patients and investigators will be aware they are receiving active MIN-101 but will not have knowledge of the dose being given or the treatment received during the double-blind phase of the study. The study is "open-label" only to the extent of informing that all patients are receiving MIN-101.

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.

## 3.3. HANDLING OF DATA

### 3.3.1. Strata and Covariates

The primary efficacy analysis and corresponding sensitivity analyses will have Baseline NSFS as a covariate and region (United States [US], all other countries) as a fixed effect. Similarly, secondary endpoints and select additional efficacy analyses will contain covariates of their respective Baseline values and region as a fixed effect.

### 3.3.2. Examination of Patient Subsets

At present no analyses are planned to examine study results within patient subsets.

### 3.3.3. Multiple Testing and Comparisons

The study-wise type I error probability for testing the 2 MIN-101 doses versus placebo across both the primary and the key secondary endpoint comparisons will be controlled at the 2-sided 0.05 level using a truncated Hochberg procedure with a truncation parameter of $\gamma = 1$.

The primary family of hypotheses and key secondary family hypotheses will be tested using a sequential "gatekeeping" approach with suitable adjustment for multiplicity within the family of primary hypotheses and the family of key secondary hypotheses. A MIN-101 dose versus placebo null hypothesis contrast within the secondary family can only be evaluated when both of the null hypothesis contrasts in the primary family have been rejected.

#### 3.3.3.1. Primary Family of Hypotheses

The adjustment for multiplicity within the family of primary hypotheses (corresponding to the primary endpoint, change from Baseline in NSFS over 12 weeks of treatment) will be evaluated first. The truncated Hochberg procedure with a truncation parameter of $\gamma = 1$ will be used to assess the results. The 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 the largest p-value comparing either of these 2 doses versus placebo is $\leq 0.05$. Otherwise, the lowest of these 2 p-values must be $\leq 0.025$ to allow for rejecting the null hypothesis for the representative dose.

#### 3.3.3.2. Key Secondary Family of Hypotheses

Only when a significant treatment effect is demonstrated in both of the primary comparisons of MIN-101 versus placebo, the key secondary family of hypotheses (corresponding to the key secondary endpoint, change from Baseline in PSP total score over 12 weeks of treatment) will be evaluated and interpreted.

Under the Hochberg procedure, if both primary tests are successful, alpha of 0.05 will be carried over for use in the key secondary comparisons. This alpha would be applied to the two key

secondary comparisons in the same manner as within the primary family of hypotheses, where the null hypothesis of no treatment difference for both the 64 mg and 32 mg doses versus placebo will be rejected if the largest p-value comparing either of these 2 doses versus placebo is ≤0.05. Otherwise, the lowest of these 2 p-values must be ≤0.025 to allow for rejecting the null hypothesis for the representative dose.

### 3.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all patients who have been treated. Partial dates will be displayed as captured (without imputation) in subject data listings.

No imputation of data elements will be performed for the primary or key secondary analyses to be submitted to the US Food and Drug Administration (FDA). Pattern-mixture modelling imputation of missing primary and key secondary endpoint data will be performed as part of the primary and key secondary analyses to submit within the European Medicines Agency (EMA) dossier. This approach is detailed in Section 5.2.2.

Sensitivity analyses will be performed to examine the impact of assumptions made for the primary and key secondary analyses as outlined in Section 3.3.4.2.

#### 3.3.4.1. Multiple Imputation Using Pattern-Mixture Modelling

For the analyses to be submitted within the EMA dossier, multiple imputation using a pattern-mixture modelling approach will be used to impute values for missing primary (12-week NSFS) and key secondary (12-week PSP total score) endpoints data. For the US FDA analysis and dossier, however, the pattern-mixture modelling will serve as a sensitivity analysis.

In pattern-mixture modelling, missing values of each 12-week endpoint measure will be imputed using pattern imputation by treatment group. This method factors in that patients with missing outcome data can have different outcome distributions than those without missing outcome data. This method can accommodate when values of the 12-week endpoint measure are not missing at random (non-ignorable or informative missing data) such that missing values might be systematically different from observed values. Predictors will include changes in the 12-week measure from Baseline using existing data measured at prior post-Baseline visits, and additional factors of region, age grouping using median, gender, race, body mass index (BMI) grouping (≤30 $kg/m^2$, >30 $kg/m^2$), and treatment group. A total of 30 imputed datasets will be generated, analysis will be performed on multiple imputed datasets, and the results will be combined.

#### 3.3.4.2. Sensitivity Analysis of the Primary Endpoint

For the FDA analysis and dossier, three approaches will be used as sensitivity analyses to explore the potential impact of missing data on the primary and key secondary endpoint comparisons: Multiple imputation using pattern-mixture modelling (Section 3.3.4.1), last-observation-carried-forward (LOCF), and placebo mean imputation.

For the EMA analysis and dossier, a slightly different approach will be used for sensitivity analyses. The first will explore the difference between the use of only observed primary and key

secondary endpoint data, as well as the approaches of last-observation-carried-forward (LOCF) and placebo mean imputation.

#### 3.3.4.2.1. Last-Observation-Carried-Forward (LOCF)

The LOCF approach to impute values for missing primary (12-week NSFS) and key secondary (12-week PSP total score) endpoint data will be implemented as follows:

Missing values of the 12-week endpoint measure will be imputed to the last post-Baseline endpoint measure (of those measured at the prior post-Baseline visits), thus treating the evaluations of the endpoint measures as generally stable over time. Note that this assumption may give overly optimistic results if withdrawal in active arm(s) occurs earlier than in the control arm, such as due to improvement of the patient's condition or adverse events.

#### 3.3.4.2.2. Placebo Mean Imputation

The Placebo Mean Imputation approach to impute values for missing primary (12-week NSFS) and key secondary (12-week PSP total score) endpoint data will be implemented as follows:

Missing values of the 12-week endpoint measure will be imputed with the mean of available 12-week endpoint measures within placebo-treated patients. Note that this method can be influenced by the data from patients completing 12 weeks of the study, yet the outcomes of patients completing the study may not represent the outcomes of patients not completing the study, such as if patients with deterioration of their condition or adverse events were to drop out prematurely.

### 3.3.4.3. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of double-blind investigational product, then a severity of *mild* will be assigned. If the severity is missing for an AE that started on or after the date of the first dose of double-blind investigational product, then a severity of *severe* will be assigned. The imputed values for severity assessment will be used for the incidence summary, while the actual values will be presented in the data listings.

### 3.3.4.4. Missing Relationship to Investigational Product for Adverse Events

A relationship of *unrelated* to investigational product will be assigned if the AE started before the administration of the first dose of double-blind investigational product. If the relationship to investigational product is missing for an AE that started after the administration of the first dose of double-blind investigational product, a causality of *definitely related* will be assigned. The imputed values for relationship to double-blind investigational product will be used for the incidence summary, while the actual values will be presented in the data listings.

## 3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month, or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a patient. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

To minimize bias, the project statistician will impute dates in a systematic but reasonable manner. The following rules for missing or partial event dates for events will be implemented. For incomplete event start dates, if the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. If this method of imputation produces and invalid date, the last date of the month will be used. For incomplete end dates, the same process will be used, but using event start date to impute instead of Day 1. In the case where there is a known, complete event end date prior to Day 1, partial event start dates will be imputed using the event end date instead of Day 1.

### 3.3.6. Imputation of Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed for the purpose of quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries, the following imputation rules will be employed:

The limit of quantitation will be increased by one level of precision in the direction of the symbol that precedes the value. For example, "<0.1" will be imputed to "0.09", while ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1". Values reported as "≤" or "≥" will be imputed similarly. For example, "≤0.1" will be imputed to "0.09".

### 3.3.7. Presentations by Time Point

Visit designations used in statistical analyses will be derived by aligning actual visit dates within visit date windows as shown in Table 1. If assessments are collected multiple times within a given visit window, the result closest to the target day will be used for summary presentations. If two measurements have the same distance to the target day, the earlier value will be used. All planned, Unscheduled, and Early Termination assessments will be categorized similarly. All assessments will be presented in the listings.

**Table 1 Visit Designations**

| Derived Visit | Scheduled Visit (Day[a]) | Target Day | Window [lower bound, upper bound][b] |
|---|---|---|---|
| Baseline | Day -1 | | Days [-28, 1] and prior to first dose of study drug |
| Day 1 | Day 1 | 1 | Day [1] |
| Day 2 | Day 2 | 2 | Day [2] |
| Week 1 | Week 1 | 8 | Days [3,11] |
| Week 2 | Week 2 | 15 | Days [12, 18] |
| Week 3 | Week 3 | 22 | Days [19, 25] |
| Week 4 | Week 4 | 29 | Days [26, 43] |

| Derived Visit | Scheduled Visit (Day[a]) | Target Day | Window [lower bound, upper bound][b] |
|---|---|---|---|
| Week 8 | Week 8 | 57 | Days [44, 71] |
| Week 12 End of double-blind treatment period[c] | Week 12 | 85 | Days 72 through last day of double-blind treatment period. Final or termination visit during the double-blind treatment phase |
| Week 12.1 | Week 12 + 1 | 87 | First day of open-label treatment |
| Week 12.2 | Week 12 + 2 | 88 | First day of open-label treatment + 1 |
| Week 13 | Week 13 | 92 | First day of open-label treatment + 2 through Day 95 |
| Week 14 | Week 14 | 99 | Days [96, 102] |
| Week 15 | Week 15 | 106 | Days [103, 109] |
| Week 16 | Week 16 | 113 | Days [110, 127] |
| Week 20 | Week 20 | 141 | Days [128, 155] |
| Week 24 | Week 24 | 169 | Days [156, 183] |
| Week 28 | Week 28 | 197 | Days [184, 211] |
| Week 32 | Week 32 | 225 | Days [212, 239] |
| Week 36 | Week 36 | 253 | Days [240, 267] |
| Week 40 | Week 40 | 281 | Days [268, 295] |
| Week 44 | Week 44 | 309 | Days [296, 323] |
| Week 48 | Week 48 | 337 | Days [323, 351] |
| Week 52 | Week 52 | 365 | Days [352, 372] |
| Week 54 EOS period[c] | | | Final or termination visit during the open-label treatment period; date will be earlier if early study termination occurred. |

a Relative to the date of the first dose of double-blind investigational product. For example, Day 1 = the date of the first dose of double-blind investigational product. The lower and upper bounds reach approximately halfway between the windows. For example, weekly visit series use windows that are [-3 days,+3 days] surrounding each target day. However, visit windows leave no gaps in time for assessments to be uncategorized.

b Visit day is calculated as (visit date − date of the first dose of double-blind investigational product + 1) if the visit date is on or after the date of the first dose of double-blind investigational product. Otherwise, it's calculated as (visit date – date of the first dose of double-blind investigational product).

c Presented in analysis tables for safety parameters, including but not limited to electrocardiographic parameters, clinical laboratories, and vital signs.

### 3.3.8. Definitions and Terminology

Baseline Value

Baseline will be defined as the last valid evaluation done before the study drug administration on Day 1. For ECG, the mean of the 3 triplicate ECG assessments (9 assessments) performed on Day -1 will serve as the Baseline value.

Day 1

Day 1 is the earliest day that study drug is first initiated.

Study Day

Study Day is defined relative to Day 1. Thus, the study day of an event is calculated as:

For events occurring on or after Day 1, Study Day = event date – date of Day 1 + 1.

For events occurring prior to Day 1, Study Day = event date – date of Day 1

Scheduled Study Visit

Scheduled Study Visit is the nominal visit as recorded on the CRF.

Derived Study Visit

Derived Study Visit is the visit designation reflective of when an actual study assessment was measured, as defined in Section 3.3.7. When compliance with the planned schedule of visits is good, the derived study visit will be the same as the scheduled study visit. The derived study visits re-classifies visits that occur off schedule.

Last Dose of Study Drug (Double-Blind Phase)

Last Dose of Study Drug (Double-Blind Phase) is defined as the last date a patient received study drug during the double-blind phase (up to Week 12).

Last Dose of Study Drug (Open-Label Extension Phase)

Last Dose of Study Drug (Open-Label Extension Phase) is defined as the last date a patient received study drug through the end of the open label extension phase (up to Week 52). If a patient discontinued drug during the 12-week double-blind phase, the last dose of study drug for the open label extension would be the last dose of study drug in the double-blind phase.

Days on Treatment

Days on treatment will be calculated as the number of days from the date of first dose to the date of last dose, inclusive. This will be calculated separately for the 12-week double blind phase as well as for the full study to include the open-label extension phase.

Treatment Compliance

Treatment compliance (%) during a specified period is defined as the total number of tablets taken by a patient during that time divided by the number of tablets prescribed during that time, multiplied by 100. The number of tablets prescribed during a specified period will be calculated by multiplying the number of days in that period by the number of tablets prescribed per day.

Change from Baseline

Change from Baseline for a given endpoint is defined as the Derived Study Visit X value minus the Baseline Value.

PANSS and NSFS Response

PANSS and NSFS response are defined as experiencing a ≥ 30% decrease from Baseline in PANSS total score and NSFS score, respectively.

Additionally, the same analysis will be repeated using ≥ 20% decrease from Baseline in PANSS total score and NSFS score.

Relapse

Relapse is defined as a patient early terminating from the study due to a treatment-emergent adverse event (TEAE) or early termination decision based on the adverse events and preferred terms in Table 2.

**Table 2 Terms Defining Relapse**

| Adverse Event | Preferred Term |
|---|---|
| Worsening of paranoid schizophrenia with symptom of agitation | Agitation |
| Completed suicide by laying on the train tracks | Completed suicide |
| Hallucination increase | Hallucination |
| Worsening of mental status | Mental impairment |
| Worsening of psychosis | Psychotic disorder |
| Increase psychotic symptoms | Psychotic symptom |
| Agitation and aggressivity inside schizophrenia | Schizophrenia |
| Schizophrenia worsening | Schizophrenia |
| Exacerbation of schizophrenia | Schizophrenia |
| Schizophrenia relapse | Schizophrenia |

Additionally, disposition data will be examined for the identification of relapse in patients where an adverse event is not recorded as the cause of early termination from the study. Examples of such disposition data are comments such as: "Criterion #5 of study stopping rule", "worsening of psychotic symptoms", "Occurrence of dangerous behavior against self or others" or "Recurrence of positive symptoms".

Relapse will be defined in two ways: relapse in the Double-Blind phase, and relapse overall. Patients who are identified as possible cases of relapse will have their information recorded in a log which will undergo adjudication to confirm cases of relapse. For relapse in the Double-Blind phase, this adjudication will occur prior to unblinding of the Double-Blind phase. For all subsequent cases of relapse, this adjudication will occur prior to lock of the Open-Label extension phase.

Time to Relapse in Double-Blind Phase

Time to relapse in Double-Blind phase is defined as the number of days from Day 1 to the date of early termination in the Double-Blind phase due to relapse as defined above. If a patient is not

observed to have relapsed during the Double-Blind phase, he or she will be censored at the date of termination from or completion of the Double-Blind phase.

Time to Relapse in Study

Time to relapse in study is defined as the number of days from Day 1 to the date of early termination due to relapse as defined above. If a patient is not observed to have relapsed during the study, he or she will be censored at the date of termination from or completion of the study.

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 related to that medicinal (investigational or non-investigational) product or not.

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.

All adverse events will be recorded on the Adverse Event CRF.

Treatment-emergent Adverse Event

Any recorded adverse event that occurs on or after the initiation of study treatment and less than or equal to 14 days after the last dose of treatment is considered treatment-emergent. Additionally, it is assumed that an adverse event which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation study treatment. Hence, adverse events occurring on Day 1 without an onset time are assumed to be treatment emergent.

Adverse Event of Special Interest

Adverse events of special interest are any episode of palpitations or abnormal heart rhythms, dizziness or syncope, or an episode of seizure.

Serious Adverse Event (SAE)

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.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study treatment. This definition includes medications started prior to the initiation of study treatment but continuing concomitantly with study treatment.

Prior Medications

Prior medications are those medications taken and completed prior to the initiation of study treatment.

### 3.4. TIMING OF ANALYSIS

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 (the Week 12 visit), the database through the double-blind phase has been cleaned and locked, and the treatments are unblinded.

A final analysis of the cumulative data through the open-label extension phase will be conducted once the last patient completes or discontinues the study, the resulting clinical database has been cleaned, quality checked, the final database lock has occurred, and the MIN-101 dosing arms are unblinded.

## 4. ANALYSIS POPULATIONS

The populations for analysis will include the enrolled population, intent-to-treat population (ITT), the safety population (SAF), and the per-protocol population (PP).

### 4.1. ENROLLED POPULATION

The enrolled population represents all patients that signed the informed consent form. This population is being used for presentation of subject disposition, as well as for all listings.

### 4.2. INTENT-TO-TREAT POPULATION (ITT)

The intent-to-treat population for this study is defined as all patients that were randomly assigned to study drug and received at least one dose of study drug. Patients in this population will be analyzed according to the treatment to which they were randomized, regardless of what treatment they received. All efficacy analyses will be based on this population and treatment assignment. In addition, Baseline patient characteristics and anthropomorphic measures will be based on this population.

### 4.3. SAFETY POPULATION (SAF)

The safety population is the population of all patients who were randomly assigned to study drug and received at least one dose of study treatment. Patients in this population will be analyzed according to the treatment they received, regardless of which treatment they were randomly assigned. All safety and tolerability analyses will be based on this population and treatment assignment.

### 4.4. PER-PROTOCOL POPULATION (PP)

The per-protocol 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 (< 75%), 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.

All efficacy analyses will be performed on both the ITT and PP sets.

## 5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for selected endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of patients (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by treatment group, patient number, and by date within each patient number.

The term 'treatment group' refers to the three treatment arms of this study: Placebo, 32 mg MIN-101, and 64 mg MIN-101.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.050 unless stated otherwise.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be performed using formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

### 5.1. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient disposition will be presented for all patients. The number of patients who meet all eligibility criteria will be presented, as well as the number of patients included in the Enrolled, ITT, SAF, and PP populations. The number of patients who completed all study treatment or discontinued from the study will be provided.

The reasons for early study discontinuation will be presented by treatment group, for the study overall as well as separately within the double-blind and open label extension phases, by visit of discontinuation, and overall. Additionally, the number of days on study and within each study

phase will be summarized for all treated patients, as well as the frequency of patients in which the study blind was broken.

Demographic data, Baseline characteristics including age, weight, height, body mass index (BMI), gender, race, psychiatric and medical history, as well as efficacy parameters baseline scores will be summarized using descriptive statistics within the ITT and SAF populations, as appropriate, and will be presented by treatment group and overall. The number and percent of patients with a current or historical presence of abnormal finding in medical history excluding psychiatric disorders will be summarized by treatment group and overall. This information will be reviewed for Baseline differences, but no statistical testing will be performed.

Additionally, study treatment exposure and treatment compliance will be summarized by treatment group. The number of days on study treatment will be summarized for all treated patients. Treatment compliance over the double-blind and open label extension treatment periods will be similarly summarized by treatment group.

## 5.2. EFFICACY ANALYSIS

The efficacy analyses will be based on the ITT Population, although they will also be performed for the PP population for comparison.

All efficacy parameters will be summarized descriptively by treatment arm and visit, as appropriate. 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 carried out for all efficacy parameters as deemed applicable using the mixed-effects model for repeated measures (MMRM).

Sensitivity analyses will be performed to better understand the impact of missing data and/or imputation of the primary efficacy endpoint, as described in Section 3.3.4.2.

Impact of Coronavirus Disease 2019 (COVID-19) Pandemic

The impact of the COVID-19 pandemic on the conduct and integrity of the study data will be evaluated by examining the efficacy (primary and key secondary endpoints) and safety data (treatment-emergent adverse event [TEAE], and select ECG parameters) for changes based on the date cutoff of 01 February 2020, and using descriptive summaries as appropriate.

[redacted]

The integrity of the double-blind data from site [redacted] has come into question based on the blinded data review. Of concern are the use of the same scores for multiple patients over the course of all double-blind visits. One example is using a CGI-S score of 4 throughout the study for all patients despite changes on PANSS and PSP total scores, while [redacted] changes of 1 or 2 points were used. Additionally, all vital sign data (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP]) show no variability throughout the double-blind with similar patterns of repeat values for several patients and across several visits. The site will undergo a focused audit once the COVID-19 pandemic restrictions are lifted or relaxed.

Consequently, the analysis of the primary and key secondary endpoints for both the ITT and PP populations will be performed as planned above and will be repeated after excluding the site's data in full.

### 5.2.1. Primary Estimand

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

**Population**: Stable patients with schizophrenia with a predefined minimum PANSS negative symptom score before randomization.

**Endpoint**: Change in the PANSS Marder NSFS from Baseline to the end of Week 12.

The NSFS consists of the sum of the ratings (on a scale of 1-7, from least to highest severity of psychopathology) across the PANSS items N1, N2, N3, N4, N6, G7, and G16. Thus, each assessment is a number between 7 and 49.

N1. Blunted affect
N2. Emotional withdrawal
N3. Poor rapport
N4. Passive/apathetic social withdrawal
N6. Lack of spontaneity
G7. Motor retardation
G16. Active social avoidance

**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.

**Intercurrent events**: Early study discontinuation for any reason.

**Summary measure**: Difference in treatment means.

### 5.2.2. Primary Efficacy Analysis

As noted in Section 3.3.4, no imputation of data elements will be performed for the primary analysis to be submitted to the US FDA. Pattern-mixture modelling imputation of missing primary endpoint data will be performed before conducting the primary analysis to submit within the EMA dossier. In both approaches, the estimand and analytic approach of using MMRM to evaluate the potential treatment effects is the same, but the data used to analyze the estimand is different between the US FDA and EMA dossiers.

The PANSS Marder NSFS scores and change from Baseline will be summarized by treatment group and study visit. In addition, the trend in change from Baseline in Marder NSFS scores over the series of visit assessments will be presented graphically.

Change from Baseline to Week 12 in the PANSS Marder NSFS score will be analyzed using a MMRM with fixed effects for treatment group (MIN-101 64 mg, MIN-101 32 mg, and placebo), region, visit, and treatment-by-visit interaction, a random effect for patient within treatment group, 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. Comparison against placebo will be performed with the MIN-101 64 mg and 32 mg doses.

The hypotheses can be expressed as follows:

*Null Hypothesis ($H_o$): $\mu$MIN-101 64 mg - $\mu$Control = 0 and $\mu$MIN-101 32 mg - $\mu$Control = 0*

*Alternative Hypothesis (Ha): $\mu$MIN-101 64 mg - $\mu$Control ≠ 0 or $\mu$MIN-101 32 mg - $\mu$Control ≠ 0*

where ***$\mu$MIN-101 64 mg*** and ***$\mu$MIN-101 32 mg*** refer to the mean change from Baseline to week 12 in the PANSS Marder NSFS score at each of the 2 experimental doses, and $\mu_{Control}$ refers to the mean change from Baseline to week 12 in the PANSS Marder NSFS score in the placebo arm.

As described in Section 3.3.3.1, the adjustment for multiplicity within the family of primary hypotheses will utilize the truncated Hochberg procedure for the purpose of reporting 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 0.05. Otherwise, the lowest of these 2 p-values must be at or below 0.025 reject the null hypothesis for the representative dose.

Three approaches will be used to assess the sensitivity of the primary endpoint to patterns of early withdrawals or missing data as described in Section 3.3.4.2. The sensitivity analyses will implement the same analytic approach using MMRM to evaluate potential treatment effects.

Finally, a cumulative distribution function for the change from Baseline to Week 12 in the PANSS Marder NSFS score will be presented.

### 5.2.3. Additional Analyses of the Primary Endpoint

The primary analysis will be repeated under several subgroups. Subgroup analyses include age groups (cutoff based on tripartite), BMI (≤ median vs. > median), and history of use of specific antipsychotic medication (no treatment since screening vs. long-acting injectable treatment vs. oral treatment only).

Additionally, the MMRM analysis of the primary endpoint will be repeated, adding CDSS Baseline score as a covariate. The analysis will be repeated separately with Simpson-Angus Scale (S-AS) Baseline score as a covariate.

### 5.2.4. Key Secondary Estimand

The key secondary estimand is defined by the following components:

**Population**: Stable patients with schizophrenia with a predefined minimum PANSS negative symptom score before randomization.

**Endpoint**: Change in the PSP total score from Baseline to the end of Week 12.

> The PSP involves four subscale domains: (a) socially useful activities, (b) personal and social relationships, (c) self-care, and (d) disturbing and aggressive behaviors. After each of these four areas is scored on an anchored Likert-type scale (0-5), raters are instructed to select a 10-point range within a 100-point scale, guided by the area scores assigned during assessment. Within the 10-point range, clinicians are instructed to select a numeric score based on their clinical judgment. The resulting final value is a single measurement from 1 to 100% of functioning.

**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.

**Intercurrent events**: Early study discontinuation for any reason.

**Summary measure**: Difference in treatment means.

### 5.2.5. Key Secondary Efficacy Analysis

As noted in Section 3.3.4, no imputation of data elements will be performed for the key secondary analysis to be submitted to the US FDA. Pattern-mixture modelling imputation of missing key secondary endpoint data will be performed before conducting the key secondary endpoint analysis to submit within the EMA dossier. In both approaches, the estimand and analytic approach of using MMRM to evaluate the potential treatment effects is the same, but the data used to analyze the estimand is different between the US FDA and EMA dossiers.

The Personal and Social Performance (PSP) total score and change from Baseline will be summarized by treatment group and study visit. In addition, the trend in change from Baseline in PSP total score over the series of visit assessments will be presented graphically.

Change from Baseline to Week 12 in the PSP total score will be analyzed using a MMRM with fixed effects for treatment group (MIN-101 64 mg, MIN-101 32 mg, and placebo), region, visit, and treatment-by-visit interaction, a random effect for patient within treatment group, and Baseline PSP total score 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. Comparison against placebo will be performed with the MIN-101 64 mg and 32 mg doses.

As described in Section 3.3.3.2, the change from Baseline to Week 12 in the PSP total score will only be evaluated if both of the primary efficacy comparisons were significant. In this case the adjustment for multiplicity within the family of key secondary hypotheses will utilize the truncated Hochberg procedure for the purpose of reporting 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 0.05.

Otherwise, the lowest of these 2 p-values must be at or below 0.025 reject the null hypothesis for the representative dose.

Three approaches will be used to assess the sensitivity of the primary endpoint to patterns of early withdrawals or missing data as described in Section 3.3.4.2. The sensitivity analyses will implement the same analytic approach using MMRM to evaluate potential treatment effects.

Finally, a cumulative distribution function for the change from Baseline to Week 12 in the PSP total score will be presented.

### 5.2.6. Additional Analyses of the Key Secondary Endpoint

The key secondary analysis will be repeated under several subgroups. Subgroup analyses include age groups (cutoff based on tripartite), BMI (≤ median vs. > median), and history of use of specific antipsychotic medication (no treatment since screening vs. long-acting treatment vs. oral treatment only).

### 5.2.7. Additional Secondary and Exploratory Endpoints

Other secondary and exploratory endpoints include:

- Change from Baseline in the CGI-S score
    - The CGI-S is a single Likert-type scale assessing the severity of mental illness. The scale includes 0 (not assessed), then 1 (normal, not ill at all) to 7 (among the most extremely ill patients).

[redacted]

[redacted]

### 5.2.8. Secondary and Exploratory Analyses

- Change from Baseline in the CGI-S score: CGI-S scores and change from Baseline will be summarized by treatment group and study visit. Differences between treatment groups in change from Baseline at Week 12 will be analyzed using MMRM in the same manner as the analysis of the primary endpoint.

[redacted]

## 5.3. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

### 5.3.1. Pharmacokinetic Analyses

A separate population PK analysis plan will provide details of these analyses and results of the population pharmacokinetic analysis will be presented in a separate report.

For reference, plasma concentrations will be summarized by treatment. Nominal time points will be used. The summary will include mean, standard deviation and coefficient of variation, minimum and maximum.

### 5.3.2. Pharmacokinetic / Pharmacodynamic Analyses

Exposure-response relationship by visit will be graphically explored by plotting the mean ± SE of the plasma concentration that are sampled at the approximate time of $C_{max}$ using the concentration exposure bins described in Table 3 (x-axis) versus change from Baseline in PANSS and PSP scores, by visit. This analysis will be performed for Marder NSFS, PSP total score, PANSS total score and subscale scores (positive symptoms, negative symptoms, general psychopathology), and the 4 remaining Marder factor scores (positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression).

Additionally, exposure-response will be assessed by comparing differences in change from Baseline in the scales and subscales listed above between concentration exposure bins by means of a repeated measures analysis of covariance (ANCOVA) model with PK concentration bin group, gender, and visit as fixed effects, Baseline assessment value as a covariate, and subject as a random effect. Summary tables using descriptive statistics by concentration exposure bins will also be generated.

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

**Table 3 Concentration Exposure Bins**

| PK Concentration (ng/ml) | Concentration (exposure) Bin |
|---|---|
| > 0 and ≤ 1st Quartile (Q1) | A (0, Q1] |
| > Q1 and ≤ Q2 | B (Q1, Q2] |
| > Q2 and ≤ Q3 | C (Q2, Q3] |
| > Q3 and ≤ Q4 | D (Q3, Q4] |
| Placebo | E (Placebo) |

## 5.4. SAFETY ANALYSES

Safety and tolerability will be analyzed for the double-blind treatment phase using the Safety Population and will be repeated for the whole study. Safety assessments include adverse events (AEs), clinical laboratory parameters, vital signs including body weight and waist circumference, ECG parameters, physical examination, Abnormal Involuntary Movement Scale (AIMS), Barnes

Akathisia Rating Scale (BARS), S-AS, and the Sheehan Suicidality Tracking Scale (Sheehan-STS), and the Readiness for Discharge Questionnaire (RDQ).

### 5.4.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 preferred term and system organ classification. If a patient experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. As noted in Section 3.3.4.3 and Section 3.3.4.4, should an event have a missing severity or relationship, it will be classified as having the highest severity ("severe") and/or strongest relationship to study medication ("definitely related") if it is deemed treatment-emergent.

A summary of adverse events will provide an overview of the number of patients that experienced a TEAE and the total number of TEAEs observed within those patients. Similar summary measures will be included to display the number of patients and corresponding events within events that were related to study drug, were serious, led to discontinuation of study drug, or led to death.

The occurrence of TEAEs will be summarized by treatment group using preferred term, System Organ Classification (SOC), and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study treatment, treatment-emergent adverse events leading to discontinuation of study treatment, and treatment-emergent fatal adverse events will be generated. All adverse events reported will be listed for individual patients showing both verbatim and preferred terms, as well as SOC. All adverse events that occurred prior to the initiation of study treatment will be excluded from the tables but will be included in the listings.

TEAEs of special interest will be tabulated if any are observed. Adverse events of special interest (AESI) are:

- Palpitations or abnormal heart rhythms
- Dizziness or syncope
- Seizure

Missing onset dates will be imputed as previously outlined in Section 3.3.5 as required to determine treatment-emergent events. Adverse events occurring on Day 1 with missing onset times will be assumed to be treatment emergent.

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

Any patients that died, discontinued treatment due to a TEAE, or experienced an SAE will be listed separately.

Additionally, any SAEs occurring prior to randomization will be listed separately.

### 5.4.2. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results and change from Baseline will be presented by treatment group and visit. Laboratory results will be presented using the International System of Units (SI). Laboratory abnormalities will be determined using pre-defined normal ranges. Clinical laboratory values will be considered potentially clinically significant (PCS) for select parameters per Table 4. The number and percentage of patients

experiencing PCS laboratory abnormalities post-baseline will be summarized by treatment group. Additionally, shifts in Laboratory values with reference to the normal range from Study Baseline to Week 12 or early termination will be summarized by treatment group.

Listings will be provided for patients with any laboratory results outside the reference ranges, as well as for patients with any PCS (select parameters) laboratory results.

**Table 4 Criteria for Potentially Clinically Significant Laboratory Tests**

| Laboratory Parameter | | SI Units | Conversion Factor[a] | Traditional Units | PCS Criteria[b] Low Values | PCS Criteria[b] High Values |
|---|---|---|---|---|---|---|
| **Hematology** | | | | | | |
| Hemoglobin | F | g/L | 0.1 | g/dL | < 100 | — |
| | M | | | | < 120 | |
| Hematocrit | F | ratio | 100 | % | ≤ 32% and ≥3% decrease from baseline | — |
| | M | | | | ≤ 37% and ≥3% decrease from baseline | |
| White cell count | | $10^9$/L | 1 | $10^3$/µL | ≤ 2.5 | ≥ 15 |
| Eosinophils absolute cell count | | $10^9$/L | 1 | $10^3$/µL | — | ≥ 1.50 |
| Neutrophils absolute cell count | | $10^9$/L | 1 | $10^3$/µL | ≤ 1.50 | ≥ 12.0 |
| Lymphocyte absolute cell count | | $10^9$/L | 1 | $10^3$/µL | ≤ 0.8 | ≥ 4.0 |
| Platelet count | | $10^9$/L | 1 | $10^3$/µL | ≤ 75 | ≥ 700 |
| **Chemistry** | | | | | | |
| Albumin | | g/L | 0.1 | g/dL | < 28 | — |
| Alkaline phosphatase | | U/L | 1 | U/L | — | ≥ 2 × UNL |
| ALT | | U/L | 1 | U/L | — | ≥ 3 × UNL |
| AST | | U/L | 1 | U/L | — | ≥ 3 × UNL |
| Blood urea nitrogen | | mmol/L | 2.8011 | mg/dL | — | > 1.4 × UNL |
| Calcium | | mmol/L | 4.008 | mg/dL | < 1.97 | > 2.77 |
| Cholesterol | | mmol/L | 38.6698 | mg/dL | — | > 7.75 |
| Creatinine | | µmol/L | 0.0113 | mg/dL | — | > 1.4 × UNL |
| Glucose, fasting | | mmol/L | 18.015 | mg/dL | < 3.0 | > 7.6 × UNL |
| Potassium | | mmol/L | 1 | mEq/L | < 3.3 | > 5.5 |
| Sodium | | mmol/L | 1 | mEq/L | < 130 | > 150 |
| Total bilirubin | | µmol/L | 0.0585 | mg/dL | — | > 1.5 × UNL |
| **Urinalysis** | | | | | | |
| Protein | | — | — | — | — | ≥ 2 + |
| Glucose | | — | — | — | — | ≥ 1 + |

ALT = alanine aminotransferase; AST = asparate aminotransferase; LNL = lower normal limit of laboratory reference range; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); UNL = upper normal limit of laboratory reference range.

[a] Conversion factor is the multiplication factor to convert from SI units to traditional units.

[b] Criteria refer to SI units.

### 5.4.3. Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary version September 2017. Prior and concomitant medications will be presented in a data listing, and concomitant medications will be summarized by treatment group.

### 5.4.4. Assessment of Vital Signs

Descriptive summaries of vital signs data including oral or aural temperature, respiratory rate, pulse, and blood pressure (systolic and diastolic) and respective changes from Baseline, will be presented by time point and treatment group. Three consecutive blood pressure and pulse readings are recorded at each assessment time point and all blood pressure and pulse analyses will be based on the average of triplicate measurements.

The number and percentage of patients with any PCS vital sign occurring post-Baseline will also be summarized by time point and treatment group (Table 5). All vital signs will be listed with PCS vital signs flagged.

**Table 5 Criteria for Potentially Clinically Significant Vital Signs**

| Parameter | Flag | Criteria |
|---|---|---|
| | | Observed Value |
| Systolic blood pressure (mmHg) | High | ≥ 150 |
| | Low | ≤ 90 |
| Diastolic blood pressure (mmHg) | High | ≥ 100 |
| | Low | ≤ 50 |
| Heart rate/Pulse rate (bpm) | High | ≥ 110 |
| | Low | ≤ 50 |
| Temperature (°C) | High | ≥ 38 |
| | Low | < 35 |

### 5.4.5. ECG Assessments

ECG measurements will be provided by a central reader.

ECGs are recorded in triplicate one minute apart, and all ECG analyses will be based on the average of triplicate measurements. 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.

ECG variables and their change from Baseline will be summarized with descriptive statistics by time point and treatment group. ECG variables will include heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using Fridericia's correction, QTcF.

QTcF values will also be tabulated for their absolute values and tabulated relative to Baseline measurements in order to detect individual QTcF changes. Additionally, the number and percentage of patients who meet the PCS values defined in Table 6 will be summarized.

**Table 6 Criteria for Potentially Clinically Significant ECG Parameters**

| Parameter | Flag | Criteria | |
|---|---|---|---|
| | | Observed Value | Change from Baseline or Observed Value |
| Heart Rate (bpm) | High | > 110 | |
| | Low | ≤ 50 | |
| QTcF[a] Interval (msec) | High Male | > 450 | >30-60, > 60, > 450-480, > 480-500, > 500 |
| | High Female | > 470 | |
| QRS Interval (msec) | High | > 120 | |
| PR Interval (msec) | High | > 220 | |

[a] QTc interval is derived as: QTcF=QT Interval (msec) / (RR (msec)/1000)$^{(1/3)}$

To understand the effect of treatment arm on the change in QTcF, an ANCOVA will be performed 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.

Important abnormalities in ECG waveform that are changes from Baseline readings will also be reported in a listing, as well as PCS ECG parameters.

### 5.4.6. Physical Exams

Physical examinations will be listed by treatment group. Anthropomorphic measurements (height, weight, BMI, and waist circumference) will be summarized by treatment group and listed within the Vital Signs presentations.

### 5.4.7. Assessment Tools

- Abnormal Involuntary Movement Scale (AIMS): AIMS is rating scale that was designed to measure tardive dyskinesia (TD).
    - Scoring: The AIMS scale has 14 items that are rated from 0 (none) to 4 (severe). The analysis will be limited to items 1-10. A composite movement score will be derived as the sum of scores across items 1-7 of the AIMS categories I (orofacial movements), II (extremity and truncal dyskinesia), and III (global severity and distress).
    - Analysis: The observed composite movement score and Overall severity index [item 8, severity of abnormal movements overall), incapacitation (item 9) and patient awareness (item 10)] and changes from Baseline will be summarized by treatment group and study visit. Complete data will be presented in patient data listings by treatment group and visit.

- Barnes Akathisia Rating Scale (BARS) is a multiple-choice questionnaire to provide an assessment of akathisia, a state of motor restlessness.
    - Scoring: The BARS scale has 3 items that are rated from 0 (absence/no distress) to 3 (most severe) and one global assessment rated from 1 to 5. The BARS rating scale is scored by summing the scales for Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness yielding a total score ranging from 0 to 9. An additional Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.
    - Analysis: The BARS score and Global Clinical Assessment of Akathisia and change from Baseline will be summarized by treatment group and study visit. Complete data will be presented in patient data listings by treatment group and visit.
- Simpson-Angus Scale (S-AS): The S-AS measures drug-induced extrapyramidal syndromes.
    - Scoring: The S-AS is the sum of 10 items rated from 0 (normal/not present) to 4 (severe stiffness/rigidity). As such, the range of scores is 0 to 40, with increased scores indicate increased severity.
    - Analysis: The S-AS score and change from Baseline will be summarized by treatment group and study visit. Complete data will be presented in patient data listings by treatment group and visit.
- Sheehan Suicidality Tracking Scale (STS): This is a prospective rating scale that tracks treatment-emergent suicidal ideation and behaviors.

  - Scoring: Each item is scored on a 5-point Likert scale from 0 (not at all) to 4 (extremely). Data from the STS can be analyzed as individual item scores, a subscore for suicidal ideation (sum of scores from items 2, 3, and 4, plus score from item 5 if ≤ 1), a subscore for suicidal behavior (sum of scores from items 6, 7, and 8, plus score from item 5 if > 1) and the total scale 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.
  - Analysis: The two subscores and total scale score and change from Baseline will be summarized by treatment group and study visit. Complete data will be presented in patient data listings by treatment group and visit.

- The Readiness for Discharge Questionnaire (RDQ), assessed at hospital discharge after the initial dosing phase of the double-blind and open-label extension phases, will be presented in a listing by treatment and visit.

### 5.4.8. Pharmacokinetic and Concomitant Medication Samples Associated with Safety Signals

If needed, a summary listing will be created to align additional PK and concomitant medication samples temporally surrounding an untoward safety signal, such as and AESI, SAE, QTc prolongation, or withdrawal for safety reasons.

## 5.5. EXTENSION PHASE

Patients enrolled in the 40-week open-label extension phase will receive either MIN-101 32 mg or 64 mg. As described in section 3.2, patients who received placebo in the double-blind 12-week treatment phase will be randomized (at Baseline) to receive one of the two MIN-101 doses at the conclusion of the double-blind phase. To evaluate longer-term efficacy and safety effects, cumulative data from all patients enrolled in the 40-week extension phase (through the entire 52-week study period) will be summarized descriptively and/or graphically, as appropriate, by visit and treatment arm sequence using the following groups:

- Placebo to MIN-101 32 mg
- Placebo to MIN-101 64 mg
- Placebo to MIN-101 Total
- MIN-101 with 3 sub-headers
  - 32 mg
  - 64 mg
  - Total (all MIN-101 from the outset)
- Overall

The "overall" column will be used for demographic and patient characteristics data summaries, as appropriate.

Changes from Baseline for the patients treated with placebo that 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.

Efficacy trends in the extension phase, including relapses, will be presented in the ITT population only.

## 6. MAJOR PROTOCOL VIOLATIONS

Possible major protocol deviations will be identified and displayed in a summary table as well as a data listing and sorted by patient and study day (where applicable). The following deviations may be identified as major protocol deviations from the database:

- Violations of inclusion/exclusion criteria that could interfere with efficacy results, such as erroneous diagnosis
- Poor compliance with study drug (<75%)
- Intake of prohibited concomitant medication

## 7. CHANGES IN THE PLANNED ANALYSES

Relative to the protocol for MIN-101C07.v1.0, Amendment 2, dated 26 September 2018, there is a change in the conduct of the analysis. For the analyses planned for the EMA dossier, a multiple imputation approach will be used to impute values for missing primary (12-week NSFS) and key secondary (12-week PSP total score) endpoint data. Additionally, the PK/PD analysis discussed in the protocol will be part of the population PK analysis and reporting of the integrated data across multiple protocol, and a new PK/PD analyses were introduced in the Statistical Analysis Plan (SAP) to address exposure-response relationships, as outlined in Section 5.3.2.

Otherwise, the efficacy analyses were expanded from the protocol statistical plan but without additional deviations in the conduct of the study or the planned analysis being anticipated. Should any deviations from the analyses specified in the authorized SAP arise, such deviations will be documented in the final clinical study report.

# 8. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all patients.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of patients actually summarized within any given summary module; some patients in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of patients actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of patients in the analysis population due to missing data.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, patient number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
    - ♦ Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
    - ♦ Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.

- Means will be reported to the same number of significant digits as the parameter.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

# 9. PROPOSED TABLES, LISTINGS, AND FIGURES

## 9.1. ANALYSIS OF DOUBLE-BLIND PHASE

| Item | Number | Description | Population |
|---|---|---|---|
| **Accountability and Baseline Characteristics** | | | |
| Table | 14.1.1 | Patient Disposition | Enrolled |
| Table | 14.1.2 | Protocol Deviations | ITT |
| Table | 14.1.3 | Analysis Sets | Enrolled |
| Table | 14.1.4.1 | Demographics and Disease Characteristics at Baseline | ITT |
| Table | 14.1.4.2 | Demographics and Disease Characteristics at Baseline | PP |
| Table | 14.1.5 | Medical History | ITT |
| Table | 14.1.6 | Study Drug Exposure and Compliance | Safety |
| Table | 14.1.7 | Concomitant Medications by ATC Classification and Preferred Term | Safety |
| **Efficacy** | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

| Item | Number | Description | Population |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] Personal and Social Performance (PSP) Score, by Visit | ITT |
| Table | 14.2.2.1.3 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit | PP |
| Table | 14.2.2.2.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, Age Subgroup Analysis | ITT |
| Table | 14.2.2.3.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, BMI Subgroup Analysis | ITT |
| Table | 14.2.2.4.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, Antipsychotic Medication History Subgroup Analysis | ITT |
| Table | 14.2.2.5.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, 01 February 2020 Cutoff Analysis | ITT |
| Table | 14.2.2.6.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, [redacted] | ITT |
| Table | 14.2.2.6.2 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit, [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.2.4.1 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] and Social Performance (PSP) Subscale Scores, by Visit | ITT |
| Table | 14.2.6.2 | Summary and Change from Baseline in Personal and Social Performance (PSP) Subscale Scores, by Visit | PP |
| Table | 14.2.7.1 | Summary and Change from Baseline in Clinical Global Impression of Severity (CGI-S) Score, by Visit | ITT |
| Table | 14.2.7.2 | Summary and Change from Baseline in Clinical Global Impression of Severity (CGI-S) Score, by Visit | PP |
| Table | 14.2.8.1 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
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| [redacted] | [redacted] | [redacted] | [redacted] |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.2.12.2 | [redacted] | PP |
| **Pharmacokinetics and Pharmacodynamics** | | | |
| Table | 14.2.13.1 | Plasma Concentrations of MIN-101, by Visit | ITT (with PK) |
| Table | 14.2.13.2 | Plasma Concentrations of MIN-101 Metabolite BFB-520, by Visit | ITT (with PK) |
| Table | 14.2.14.1.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Total Score | ITT (with PK) |
| Table | 14.2.14.1.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Total Score | PP (with PK) |
| Table | 14.2.14.1.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Total Score | ITT (with PK) |
| Table | 14.2.14.1.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Total Score | PP (with PK) |
| Table | 14.2.14.2.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | ITT (with PK) |
| Table | 14.2.14.2.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | PP (with PK) |
| Table | 14.2.14.2.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | ITT (with PK) |
| Table | 14.2.14.2.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | PP (with PK) |
| Table | 14.2.14.3.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Subscale Scores | ITT (with PK) |
| Table | 14.2.14.3.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Subscale Scores | PP (with PK) |
| Table | 14.2.14.3.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Subscale Scores | ITT (with PK) |
| Table | 14.2.14.3.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Subscale Scores | PP (with PK) |
| Table | 14.2.14.4.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Factor Scores | ITT (with PK) |
| Table | 14.2.14.4.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Factor Scores | PP (with PK) |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.2.14.4.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Factor Scores | ITT (with PK) |
| Table | 14.2.14.4.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Factor Scores | PP (with PK) |
| **Safety** | | | |
| Table | 14.3.1.1.1 | Summary of Adverse Events | Safety |
| Table | 14.3.1.1.2 | Summary of Adverse Events, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.2.1 | Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Maximum Severity | Safety |
| Table | 14.3.1.2.2 | Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Maximum Severity, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.3.1 | Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Classification, Preferred Term and Maximum Severity | Safety |
| Table | 14.3.1.3.2 | Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Classification, Preferred Term and Maximum Severity, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.4.1 | Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Classification, Preferred Term and Maximum Severity | Safety |
| Table | 14.3.1.4.2 | Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Classification, Preferred Term and Maximum Severity, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.5.1 | Treatment-Emergent Fatal Adverse Events by System Organ Classification and Preferred Term | Safety |
| Table | 14.3.1.5.2 | Treatment-Emergent Fatal Adverse Events by System Organ Classification and Preferred Term, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.6.1 | Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term | Safety |
| Table | 14.3.1.6.2 | Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, 01 February 2020 Cutoff | Safety |
| Table | 14.3.1.7.1 | Treatment-Emergent Adverse Events of Special Interest: Palpitations or Abnormal Heart Rhythms, Dizziness or Syncope, and Seizure | Safety |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.3.1.7.2 | Treatment-Emergent Adverse Events of Special Interest: Palpitations or Abnormal Heart Rhythms, Dizziness or Syncope, and Seizure, 01 February 2020 Cutoff | Safety |
| Table | 14.3.4.1 | Clinical Laboratory Hematology Parameters by Time Point | Safety |
| Table | 14.3.4.2 | Clinical Laboratory Chemistry Parameters by Time Point | Safety |
| Table | 14.3.4.3 | Clinical Laboratory Urinalysis Parameters (Continuous) by Time Point | Safety |
| Table | 14.3.4.4 | Clinical Laboratory Parameter Shifts from Baseline | Safety |
| Table | 14.3.4.5 | Potentially Clinically Significant Laboratory Values | Safety |
| Table | 14.3.5.1 | Vital Sign and Anthropomorphic Parameters and Changes from Baseline, by Time Point | Safety |
| Table | 14.3.5.2.1 | Potentially Clinically Significant Vital Signs Occurring Post-Baseline | Safety |
| Table | 14.3.5.2.2 | Vital Signs Parameter Shifts from Baseline | Safety |
| Table | 14.3.5.3.1.1 | ECG Parameters and Change from Baseline by Time Point | Safety |
| Table | 14.3.5.3.1.2 | ECG Parameters and Change from Baseline by Time Point, 01 February 2020 Cutoff | Safety |
| Table | 14.3.5.3.2.1 | QTcF (msec) Values and Change from Baseline Relative to Predefined Thresholds of Clinical Significance | Safety |
| Table | 14.3.5.3.2.2 | QTcF (msec) Values and Change from Baseline Relative to Predefined Thresholds of Clinical Significance, 01 February 2020 Cutoff | Safety |
| Table | 14.3.5.3.3.1 | Effect of Treatment Arm on Changes in QTcF using ANCOVA | Safety |
| Table | 14.3.5.3.3.2 | Effect of Treatment Arm on Changes in QTcF using ANCOVA, 01 February 2020 Cutoff | Safety |
| Table | 14.3.5.3.4.1 | Patients with Clinically Significant ECG Abnormalities Occurring Post-Baseline | Safety |
| Table | 14.3.5.3.4.2 | Patients with Clinically Significant ECG Abnormalities Occurring Post-Baseline, 01 February 2020 Cutoff | Safety |
| Table | 14.3.5.3.5.1 | Patients with Potentially Clinically Significant ECG Abnormalities Occurring Post-Baseline | Safety |
| Table | 14.3.5.3.5.2 | Patients with Potentially Clinically Significant ECG Abnormalities Occurring Post-Baseline, 01 February 2020 Cutoff | Safety |
| Table | 14.3.5.3.5.3 | ECG Parameter Shifts from Baseline | Safety |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.3.6.1 | Summary and Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) Composite Movement Score and Severity Index, by Visit | Safety |
| Table | 14.3.6.2 | Summary and Change from Baseline in Barnes Akathisia Rations Scale (BARS) and Global Clinical Assessment of Akathisia, by Visit | Safety |
| Table | 14.3.6.3 | Summary and Change from Baseline in Simpson-Angus Scale (S-AS) Score, by Visit | Safety |
| Table | 14.3.6.4 | Summary and Change from Baseline in Sheehan Suicidality Tracking Scale (STS) Subscores and Total Scale Score, by Visit | Safety |
| **Listings** | | | |
| Listing | 16.2.1 | Patient Disposition | Enrolled |
| Listing | 16.2.2.1 | Protocol Deviations | ITT |
| Listing | 16.2.2.2 | Inclusion/Exclusion Criteria | Enrolled |
| Listing | 16.2.3 | Inclusion in Analysis Populations | Enrolled |
| Listing | 16.2.4.1 | Demographic and Baseline Characteristics | ITT |
| Listing | 16.2.4.2 | Psychiatric and Medical History | ITT |
| Listing | 16.2.4.3 | Schizophrenia Characteristics at Baseline | ITT |
| Listing | 16.2.4.4 | CYP2D6 Genotyping | Enrolled |
| Listing | 16.2.4.5 | Concomitant Medication Blood Sampling | Enrolled |
| Listing | 16.2.4.6 | Urine Drug and Alcohol Screening | Enrolled |
| Listing | 16.2.4.7 | Hospital Admissions and Discharge/Continuation | ITT |
| Listing | 16.2.5.1 | Study Drug Administration and Compliance | Safety |
| Listing | 16.2.5.2 | Prior and Concomitant Medications | Enrolled |
| Listing | 16.2.5.3 | Plasma Concentrations of MIN-101 and BFB-520 | ITT (with PK) |
| Listing | 16.2.6.1 | [redacted] | ITT |
| Listing | 16.2.6.2 | Personal and Social Performance (PSP) Assessments | ITT |
| Listing | 16.2.6.3 | Clinical Global Impression of Severity (CGI-S) Assessments | ITT |
| Listing | 16.2.6.4 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | ITT |

| Item | Number | Description | Population |
|---|---|---|---|
| | | [redacted] | |
| Listing | 16.2.7.1 | Adverse Events | Enrolled |
| Listing | 16.2.7.2 | Treatment-Emergent Adverse Events | Enrolled |
| Listing | 16.2.7.3 | Adverse Events Leading to Discontinuation of Study Treatment | Enrolled |
| Listing | 16.2.7.4 | Fatal Adverse Events | Enrolled |
| Listing | 16.2.7.5 | Serious Adverse Events | Enrolled |
| Listing | 16.2.7.6 | Serious Adverse Events Occurring Prior to Randomization | Enrolled |
| Listing | 16.2.7.7 | Adverse Events for Subjects with Potentially Clinically Significant QTcF Values | Enrolled |
| Listing | 16.2.7.8 | Adverse Events for Subjects with Potentially Clinically Significant HR, QRS, or PR Values | Enrolled |
| Listing | 16.2.7.9 | Adverse Events of Special Interest | Enrolled |
| Listing | 16.2.8.1.1 | Laboratory Data – Chemistry | Enrolled |
| Listing | 16.2.8.1.2 | Laboratory Data – Hematology | Enrolled |
| Listing | 16.2.8.1.3 | Laboratory Data – Urinalysis | Enrolled |
| Listing | 16.2.8.1.4 | Laboratory Data - Serology | Enrolled |
| Listing | 16.2.8.1.5 | Laboratory Data – Serum Pregnancy Testing | Enrolled |
| Listing | 16.2.8.1.6 | Laboratory Results Outside Reference Range | Enrolled |
| Listing | 16.2.8.1.7 | Potentially Clinically Significant Laboratory Results | Enrolled |
| Listing | 16.2.8.2.1 | Vital Signs and Anthropomorphic Measures | Enrolled |
| Listing | 16.2.8.2.2 | Potentially Clinically Significant Vital Signs | Enrolled |
| Listing | 16.2.8.3 | Physical Examinations | Enrolled |
| Listing | 16.2.8.4 | 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.5 | Clinically Significant 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.6 | Potentially Clinically Significant 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.6 | Abnormal 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.9.1 | Abnormal Involuntary Movement Scale (AIMS) Assessments | Enrolled |
| Listing | 16.2.9.2 | Barnes Akathisia Rating Scale (BARS) Assessments | Enrolled |
| Listing | 16.2.9.3 | Simpson-Angus Scale (S-AS) Assessments | Enrolled |
| Listing | 16.2.9.4 | Sheehan Suicidality Tracking Scale (STS) Assessments | Enrolled |
| | | | |

| Item | Number | Description | Population |
|---|---|---|---|
| **Figures** | | | |
| Figure | 14.2.1.1.2 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | PP |
| Figure | 14.2.2.1.2 | Change from Baseline in Personal and Social Performance (PSP) Score using the Least Squares Means (±SE) from MMRM, by Visit | ITT |
| Figure | 14.2.2.1.4 | Change from Baseline in Personal and Social Performance (PSP) Score using the Least Squares Means (±SE) from MMRM, by Visit | PP |
| Figure | 14.2.11.2 | Time to Relapse in the Double-Blind Phase | ITT |
| Figure | 14.2.11.4 | Time to Relapse in the Double-Blind Phase | PP |
| Figure | 14.2.14.1.1.2 | Change from Baseline in PANSS Total Score by MIN-101 Plasma Concentration Quartiles | ITT (with PK) |
| Figure | 14.2.14.1.2.2 | [redacted] | ITT (with PK) |
| Figure | 14.2.14.2.1.2 | Change from Baseline in Marder Negative Symptoms [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | ITT (with PK) |

## 9.2. ANALYSIS OF OPEN-LABEL EXTENSION PHASE

Note that some output will be re-run to include the later visit time points, and others are customized for the extended treatment period. For those that are re-run, the same numbering is preserved but titles/headers within the output will clearly distinguish which output represents the open label extension.

| Item | Number | Description | Population |
|---|---|---|---|
| **Accountability and Baseline Characteristics** | | | |
| Table | 14.1.1 | Patient Disposition | Enrolled |
| Table | 14.1.2 | Protocol Deviations | ITT |
| Table | 14.1.3 | Analysis Sets | Enrolled |
| Table | 14.1.6 | Study Drug Exposure and Compliance | Safety |
| Table | 14.1.7 | Concomitant Medications by ATC Classification and Preferred Term | Safety |
| **Efficacy** | | | |
| Table | 14.2.1.1.1 | Summary and Change from Baseline in Positive and [redacted] | ITT |
| Table | 14.2.2.1.1 | Summary and Change from Baseline in Personal and Social Performance (PSP) Score, by Visit | ITT |
| Table | 14.2.2.2.1 | [redacted] | [redacted] |
| Table | 14.2.2.3.1 | Summary and Change from Baseline in Clinical Global Impression of Severity (CGI-S) Score, by Visit | ITT |
| Table | 14.2.2.4.1 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| **Pharmacokinetics and Pharmacodynamics** | | | |
| Table | 14.2.3.1 | Plasma Concentrations of MIN-101, by Visit | ITT (with PK) |
| Table | 14.2.3.2 | Plasma Concentrations of MIN-101 Metabolite BFB-520, by Visit | ITT (with PK) |
| Table | 14.2.14.1.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Total Score | ITT (with PK) |
| Table | 14.2.14.1.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Total Score | PP (with PK) |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.2.14.1.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Total Score | ITT (with PK) |
| Table | 14.2.14.1.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Total Score | PP (with PK) |
| Table | 14.2.14.2.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | ITT (with PK) |
| Table | 14.2.14.2.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | PP (with PK) |
| Table | 14.2.14.2.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | ITT (with PK) |
| Table | 14.2.14.2.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Negative Symptoms Factor Score (NSFS) | PP (with PK) |
| Table | 14.2.14.3.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Subscale Scores | ITT (with PK) |
| Table | 14.2.14.3.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in PANSS Subscale Scores | PP (with PK) |
| Table | 14.2.14.3.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Subscale Scores | ITT (with PK) |
| Table | 14.2.14.3.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in PANSS Subscale Scores | PP (with PK) |
| Table | 14.2.14.4.1.1 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Factor Scores | ITT (with PK) |
| Table | 14.2.14.4.1.3 | Effect of Plasma concentration exposure of MIN-101 on Change from Baseline in Marder Factor Scores | PP (with PK) |
| Table | 14.2.14.4.2.1 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Factor Scores | ITT (with PK) |
| Table | 14.2.14.4.2.3 | Effect of Plasma concentration exposure of BFB-520 on Change from Baseline in Marder Factor Scores | PP (with PK) |
| **Safety** | | | |
| Table | 14.3.1.1 | Summary of Adverse Events | Safety |
| Table | 14.3.1.2 | Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term and Maximum Severity | Safety |
| Table | 14.3.1.3 | Treatment-Emergent Adverse Events Related to Study Treatment by System Organ Classification, Preferred Term and Maximum Severity | Safety |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.3.1.4 | Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Classification, Preferred Term and Maximum Severity | Safety |
| Table | 14.3.1.5 | Treatment-Emergent Fatal Adverse Events by System Organ Classification and Preferred Term | Safety |
| Table | 14.3.1.6 | Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term | Safety |
| Table | 14.3.1.7 | Treatment-Emergent Adverse Events of Special Interest: Palpitations or Abnormal Heart Rhythms, Dizziness or Syncope, and Seizure | Safety |
| Table | 14.3.4.1 | Clinical Laboratory Hematology Parameters by Time Point | Safety |
| Table | 14.3.4.2 | Clinical Laboratory Chemistry Parameters by Time Point | Safety |
| Table | 14.3.4.3 | Local Laboratory Urinalysis Parameters (Continuous) by Time Point | Safety |
| Table | 14.3.4.4 | Clinical Laboratory Parameter Shifts from Baseline | Safety |
| Table | 14.3.4.5 | Potentially Clinically Significant Laboratory Values | Safety |
| Table | 14.3.5.1 | Vital Sign and Anthropomorphic Parameters and Changes from Baseline, by Time Point | Safety |
| Table | 14.3.5.2.1 | Potentially Clinically Significant Vital Signs Occurring Post-Baseline | Safety |
| Table | 14.3.5.2.2 | Vital Signs Parameter Shifts from Baseline | Safety |
| Table | 14.3.5.3.1 | ECG Parameters and Change from Baseline by Time Point | Safety |
| Table | 14.3.5.3.2 | QTcF (msec) Values and Change from Baseline Relative to Predefined Thresholds of Clinical Significance | Safety |
| Table | 14.3.5.3.3 | Effect of Treatment on Changes in QTcF from Baseline | Safety |
| Table | 14.3.5.3.4 | Clinically Significant ECG Abnormalities Occurring Post-Baseline | Safety |
| Table | 14.3.5.3.5 | Potentially Clinically Significant ECG Abnormalities Occurring Post-Baseline | Safety |
| Table | 14.3.5.3.6 | ECG Parameter Shifts from Baseline | Safety |
| Table | 14.3.6.1 | Summary and Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) Composite Movement Score and Severity Index, by Visit | Safety |
| Table | 14.3.6.2 | Summary and Change from Baseline in Barnes Akathisia Rations Scale (BARS) and Global Clinical Assessment of Akathisia, by Visit | Safety |

| Item | Number | Description | Population |
|---|---|---|---|
| Table | 14.3.6.3 | Summary and Change from Baseline in Simpson-Angus Scale (S-AS) Score, by Visit | Safety |
| Table | 14.3.6.4 | Summary and Change from Baseline in Sheehan Suicidality Tracking Scale (STS) Subscores and Total Scale Score, by Visit | Safety |
| **Listings** | | | |
| Listing | 16.2.1 | Patient Disposition | Enrolled |
| Listing | 16.2.2.1 | Protocol Deviations | ITT |
| Listing | 16.2.4.7 | Hospital Admissions and Discharge/Continuation | ITT |
| Listing | 16.2.5.1 | Study Drug Administration and Compliance | Safety |
| Listing | 16.2.5.2 | Prior and Concomitant Medications | Enrolled |
| Listing | 16.2.5.3 | Plasma Concentrations of MIN-101 and BFB-520 | ITT (with PK) |
| Listing | 16.2.6.1 | Positive and Negative Syndrome (PANSS) Assessments: Marder Negative Symptoms Factor Score (NSFS), PANSS Total Score, Subscale, and Marder Factor Scores | ITT |
| Listing | 16.2.6.2 | Personal and Social Performance (PSP) Assessments | ITT |
| Listing | 16.2.6.3 | Clinical Global Impression of Severity (CGI-S) Assessments | ITT |
| Listing | 16.2.6.4 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | ITT |
| Listing | 16.2.7.1 | Adverse Events | Enrolled |
| Listing | 16.2.7.2 | Treatment-Emergent Adverse Events | Enrolled |
| Listing | 16.2.7.3 | Adverse Events Leading to Discontinuation of Study Treatment | Enrolled |
| Listing | 16.2.7.4 | Fatal Adverse Events | Enrolled |
| Listing | 16.2.7.5 | Serious Adverse Events | Enrolled |
| Listing | 16.2.7.6 | Serious Adverse Events Occurring Prior to Randomization | Enrolled |
| Listing | 16.2.7.7 | Adverse Events for Subjects with Potentially Clinically Significant QTcF Values | Enrolled |
| Listing | 16.2.7.8 | Adverse Events for Subjects with Potentially Clinically Significant HR, QRS, or PR Values | Enrolled |
| Listing | 16.2.7.9 | Adverse Events of Special Interest | Enrolled |
| Listing | 16.2.8.1.1 | Laboratory Data – Chemistry | Enrolled |
| Listing | 16.2.8.1.2 | Laboratory Data – Hematology | Enrolled |
| Listing | 16.2.8.1.3 | Laboratory Data – Urinalysis | Enrolled |
| Listing | 16.2.8.1.5 | Laboratory Data – Serum Pregnancy Testing | Enrolled |

| Item | Number | Description | Population |
|---|---|---|---|
| Listing | 16.2.8.1.6 | Laboratory Results Outside Reference Range | Enrolled |
| Listing | 16.2.8.1.7 | Clinically Significant Laboratory Results | Enrolled |
| Listing | 16.2.8.2.1 | Vital Signs and Anthropomorphic Measures | Enrolled |
| Listing | 16.2.8.2.2 | Potentially Clinically Significant Vital Signs | Enrolled |
| Listing | 16.2.8.3 | Physical Examinations | Enrolled |
| Listing | 16.2.8.4 | 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.5 | Clinically Significant 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.6 | Potentially Clinically Significant 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.8.6 | Abnormal 12-Lead ECG Findings | Enrolled |
| Listing | 16.2.9.1 | Abnormal Involuntary Movement Scale (AIMS) Assessments | Enrolled |
| Listing | 16.2.9.2 | Barnes Akathisia Rating Scale (BARS) Assessments | Enrolled |
| Listing | 16.2.9.3 | Simpson-Angus Scale (S-AS) Assessments | Enrolled |
| Listing | 16.2.9.4 | Sheehan Suicidality Tracking Scale (STS) Assessments | Enrolled |
| **Figures** | | | |
| Figure | 14.2.1.1.2 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | PP |
| Figure | 14.2.2.1.2 | Change from Baseline in Personal and Social Performance (PSP) Score using the Least Squares Means (±SE) from MMRM, by Visit | ITT |
| Figure | 14.2.2.1.4 | Change from Baseline in Personal and Social Performance (PSP) Score using the Least Squares Means (±SE) from MMRM, by Visit | PP |
| Figure | 14.2.11.2 | Time to Relapse in Study | ITT |
| Figure | 14.2.11.4 | Time to Relapse in Study | PP |
| Figure | 14.2.14.1.1.2 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | ITT (with PK) |

| Item | Number | Description | Population |
|---|---|---|---|
| Figure | 14.2.14.2.2.2 | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | ITT (with PK) |