STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b, In-Patient Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of the Co-Administration of Roluperidone and Olanzapine in Adult Subjects with Moderate to Severe Negative Symptoms of Schizophrenia
Phase:	1
Protocol No.:	MIN-101C18
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

[redacted]

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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-101C18. 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

This is a prospective, open-label, one-sequence, inpatient, clinical study of CYP2D6 normal metabolizer (NM) subjects with moderate to severe negative symptoms of schizophrenia. be coadministered to subjects already being administered roluperidone to determine its effect on the PD and PK of roluperidone. Eligible subjects will undergo 3 study phases as follows:

- Screening Phase: Between 2 and up to 28 days during which study eligibility will be established and subjects receiving psychotropics will be washed out. Discontinuation of psychotropics must occur at least 2 days prior to the start of Treatment Phase 1 (Day 1). Subjects will be admitted to the site on Day -2 and complete a Baseline Visit on Day -1.
- Treatment Phase 1: After the Baseline Visit (Day -1), roluperidone 64 mg/day will be administered as a monotherapy for 7 days (Days 1-7).
- Treatment Phase 2: Concomitant administration of olanzapine 10 mg/day and roluperidone 64 mg/day for 10 days, starting on Day 8 (Days 8-17). Subjects may be discharged from the clinic at least 48 hours after the last administration of the study drugs and after the collection of the last plasma sample; however, the inpatient period may be extended at the discretion of the investigator.

An End of Study (EOS) visit will take place at least 14 days after the last dose of study treatment. After the EOS visit, the medications and clinical care of the subject will be managed as per the judgement of the investigator/clinician.

1.2. STUDY MEASUREMENTS AND VISIT SCHEDULE

Phase	**SCR**	**Admis-sion**	**BL**	**Treatment Phase 1**							**Treatment Phase 2**												**EOS/ ET**
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**31 (+2)**
Informed consent	X																						
Inclusion & exclusion criteria	X		X[a]																				
Demographics	X																						
Medical history/update	X		X																				
Physical examination	X		X																	X			X
Institutionalization			←•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	→		
Roluperidone administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Olanzapine administration											X	X	X	X	X	X	X	X	X	X			
Vital signs[b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X							X										X			X
Height	X																						
Triplicate ECG[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 genotype	X[d]																						
Chemistry & hematology	X		X							X										X			X
Urinalysis[e]	X		X							X										X			X
Drug screen, alcohol test, and COVID-19	X		X																				
PK samplesf				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serology	X																						
Serum pregnancy test	X		X																	X			X
FSH test	X																						
Tuberculosis test	X																						
MINI	X																						
C-SSRS	X		X	X						X	X									X			X
[redacted]	X		X							X										X			X
CGI-S	X		X							X										X			X
BARS	X		X							X	X									X			X
AIMS	X		X							X	X									X			X
[redacted]	X		X							X										X			X

Phase	**SCR**	**Admis-sion**	**BL**	**Treatment Phase 1**							**Treatment Phase 2**												**EOS/ ET**
Study Day	**-28 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**31 (+2)**
Prior & Concomitant medications	X		←••••••→																				
Adverse events	X		←••••••→																				

NOTE: There is no washout period between Treatment Phases.

Abbreviations: AIMS = abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; [redacted]; CGI-S = Clinical Global Impression – Severity C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end-of-study; ET = early termination; PK = pharmacokinetics; SCR = screening; [redacted] SCR = screening.

[a] Verify eligibility.

[b] Vital signs include blood pressure (standing and supine), pulse, oral/tympanic temperature, and respiratory rate. During Treatment Phase 1, vital signs are assessed prior to PK sampling at pre-dose and 6 hours post-dose on Days 1-7. During Treatment Phase 2, vital signs are assessed prior to PK sampling at pre-dose and 6 hours post-dose on Days 8-17 and 24 hours and 48 hours after last dose of study drug is administered (eg, Days 18 and 19).

[c] Three sets of triplicate ECGs (1 minute apart within 5 minutes; total of 9 ECGs are recorded at Baseline (Day -1). Other ECG assessments are recorded in triplicate prior to PK sampling. During Treatment Phase 1, ECGs are recorded at pre-dose and 6 hours post-dose on Days 1-7. During Treatment Phase 2, ECGs are recorded pre-dose and 6 hours post-dose on Days 8-17 and 24 hours and 48 hours after last dose of study drug is administered (eg, Days 18 and 19).

[d] CYP2D6 genotyping to be performed.

[e] Urinalysis will be performed by dipstick. Urine will be sent to the laboratory for microscopic analysis only in the event that the dipstick results are abnormal.

[f] After vital signs and triplicate ECG. During Treatment Phase 1, PK samples for roluperidone will be obtained at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 24 hours post-dose on Days 1 and 7, at 6 hours post dose on Day 2, and at pre-dose and 6 hours post-dose on Days 3-6. During Treatment Phase 2, PK samples for roluperidone and olanzapine will be obtained at 6 hours post-dose on Day 8, time 0 (pre-dose) and 6 hours post-dose on Days 9-16, and starting on Day 17 at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 28, 32, 36, and 48 hours post-dose. If a significant prolongation in QT is observed, a PK sample should be obtained.

1.3. GLOSSARY OF ABBREVIATION

AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal involuntary movement scale
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
AUC	Area under the plasma concentration-time curve (ng.h/mL)
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to concentration C24 at the 24-hour time point (ng.h/mL)
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity (ng.h/mL)
BARS	Barnes akathisia rating scale
BFB-520	Metabolite of roluperidone
BLQ	Below limit of quantitation
BMI	Body mass index
BUN	Blood urea nitrogen
[redacted]	[redacted]
CGI-S	Clinical global impression - severity rating
CI	Confidence interval
C_{last}	Last measurable concentration (ng/mL)
C_{max}	Maximum drug concentration (ng/mL)
CSR	Clinical study report
C-SSRS	Columbia suicide severity rating scale
CV	Coefficient of variation
CYP2D6	Cytochrome P450 2D6 enzyme
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-study
LLN	Lower limit of normal laboratory reference range
MedDRA	Medical dictionary for regulatory activities

NA	Not applicable
NM	Normal metabolizer
[redacted]	[redacted]
PCS	Potentially clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
QTc	QT interval value corrected for heart rate
QTcB	QT interval value corrected for heart rate using Bazett's formula
QTcF	QT interval value corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAF	Safety set
SARS-CoV	Severe acute respiratory syndrome coronavirus 2
SCR	Screening
SD	Standard Deviation
SEM	Standard Error of Mean
SI	Le Système International d'Unités (International System of Units)
SOC	System Organ Classification
TEAE	Treatment-emergent adverse event
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to maximum drug concentration (h)
UNL	Upper normal limit of laboratory reference range
WHO	World Health Organization

2. OBJECTIVES

Primary Objective:
To evaluate the pharmacodynamics (PD), including safety and tolerability of the coadministration of roluperidone 64 mg and olanzapine.

- Adverse events (AEs)
- Laboratory evaluations
- Physical examination (including weight, baseline height and BMI)
- Vital signs (including blood pressure, heart rate, respiratory rate, pulse, temperature)
- 12-Lead electrocardiograms (ECGs)
- Extrapyramidal symptoms (assessed by Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Rating Scale (BARS))
- Suicidal ideation (assessed by the Columbia Suicide Severity Rating Scale (C-SSRS))

Secondary Objective:
To evaluate the effect of the coadministration of roluperidone and olanzapine on the pharmacokinetics (PK) of roluperidone in subjects with moderate to severe negative symptoms of schizophrenia. The secondary endpoint, PK, will include the following parameters:

- PK parameters of roluperidone and its metabolite, BFB-520, following single dose and at steady state.
- PK parameters of roluperidone and BFB-520 when administered concomitantly with olanzapine.
- PK parameters of olanzapine administered concomitantly with roluperidone compared to its pharmacokinetic profile based on monotherapy administration from published literature.

PK parameters are included but are not limited to the variables given below:

- C_{max}: observed maximum plasma concentration (ng/mL).
- t_{max}: time to reach the observed maximum plasma concentration (h).
- AUC_{0-24}: area under the plasma concentration-time curve from time 0 to concentration C_{24} (ng.h/mL) at the 24-hour time point.
- AUC_{∞}: area under the plasma concentration-time curve from time 0 to infinite time, calculated according to the following equation $AUC_{\infty} = AUC_{last} + C_{last} / \lambda z$ (ng.h/mL), where C_{last} is the last measurable plasma concentration and λz is the terminal elimination rate constant.

[redacted] Clinical Global Impression- Severity Rating (CGI-S).

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

The planned sample size is approximately 18 subjects dosed with 64 mg roluperidone in Treatment Phase 1 such that at least 12 subjects can complete dosing with 64 mg roluperidone and 10 mg olanzapine during Treatment Phase 2. The selected sample size is sufficient to calculate the 90% confidence interval of the estimated ratio of C_{max} and AUC of roluperidone with and without coadministration of olanzapine for a true within subject standard deviation of 0.25 or 0.40 with maximum imprecision of 20.5% or 30.8%, respectively.

3.2. RANDOMIZATION AND BLINDING

This is an open-label, one-sequence study; therefore, randomization and blinding will not be performed. Eighteen (18) subjects will be enrolled in the study to ensure 12 subjects complete the study. Eligible subjects will be assigned a subject identification number in sequential order.

3.2.1. Examination of Subject Subsets

Select PK summaries will be presented by sex, as detailed in Section 5.2.4.

3.2.2. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple comparisons.

3.2.3. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been treated. For analysis purposes, imputation of dates may be necessary and is described below in Section 3.2.3.1. Additionally, some results may be reported as alphanumeric. For the purposes of calculating summary statistics, these values may be imputed as described in Section 3.2.3.2. No other imputation of values for missing data will be performed for this study.

3.2.3.1. Missing 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 subject.

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.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

- Missing start day, but month and year present:

If the event occurs in the same month and year as the dosing of the study drug, then the start day of the study drug will be assigned to the day of first dose of the study drug.

Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If event occurs in the same year as the study drug dosing, then the start date of the event will be assigned to Day 1 of Treatment Phase 1.

  Otherwise, the start day and month will be set to 01 January.

- Missing all components of a start date:

  Assign the date of Day 1 of Treatment Phase 1.

- Missing end day, but month and year present:

  The day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the date of study completion (EOS Visit Date).

  However, if the study completion year is greater than the year of the event, then the day and month will be set to 31 December.

- In the event of a completely missing end date (year not present and ongoing not checked), the end date will be imputed as the date of study completion or discontinuation. If the imputed date is later than the date of study withdrawal, then the date of study withdrawal will be imputed for the date.

If any imputed date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If any imputed date causes the start date of the event to occur after the end date of the event, the end date of the event will be used for the imputation of the start date. In subject data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

3.2.3.2. 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". For PK values, values reported as "BLQ" will be imputed to 0. BLQ values will not be presented on graphs for plots of semi-log values.

3.2.4. Presentations by Time Point

Subjects are institutionalized from washout phase to Day 19 (+2 days after the last dose on Day 17). See Section 1.2 for specifics regarding when assessments are measured within a phase. The timeline of assessment measurements is repeated for each treatment phase. Assessments after screening and occurring on Day -1 after a washout period will be attributed to the following treatment phase.

Nominal Time Points as obtained from the eCRF or laboratory will be utilized for summary displays. Unscheduled visits will not be windowed and be excluded from summary tables and figures but will be listed.

If assessments are collected multiple times within a given nominal time point, the result closest to the scheduled time will be used for summary presentations. If two measurements have the same distance to the expected time, the earlier value will be used. If a scheduled assessment and an early termination assessment are collected within a given time point window, the value from the scheduled assessment will be chosen over the value from the early termination assessment.

3.2.5. Definitions and Terminology

Baseline Value

For quantitative safety measures, Baseline will be defined as the last valid evaluation completed before the study drug administration on Day 1. For ECG measures, including QTcF, Baseline will be defined as the mean of the triplicate set (total of 3 ECGs) performed pre-dose on Day 1 in Treatment Phase 1. This will also be referred to as Study Baseline.

A second Baseline will be used and will be referred to as the Treatment Phase 2 Baseline. For ECG, Treatment Phase 2 Baseline will be the mean of the triplicate ECGs (total of 3 ECGs) performed pre-dose on Day 8.

Study Day

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

Study Day = event date – date of Day 1 + 1.

The study day of an event occurring prior to Day 1 is calculated as:

Study Day = event date – date of Day 1.

Days on Study

Days on Study is calculated as Final Day on Study based on the EOS eCRF page – First Day on Study Drug + 1.

Treatment Phase Day

The study day within a treatment phase. Treatment Phase Day will be defined within each Treatment Phase 1 or 2.

Treatment Phase Day = event date – date of Day 1 of Treatment Phase X + 1.

Study Time Point

Study Time Point is the nominal time point as recorded on the CRF.

Change from Baseline

Change from Baseline for a given endpoint is defined as the Study Time Point X value minus the Baseline Value. Change from Baseline may be study-specific (i.e., across all study phases), or Treatment Phase-specific (within any specific Treatment Phase). In the latter case, Baseline will be Treatment Phase specific.

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject 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 or not related to that medicinal (investigational or non-investigational) product.

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 page of the CRF.

Serious Adverse Event (SAE)

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

- **Death**: The subject died as the result of the event.
- **Life-threatening event**: Any AE that places the subject, 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 subject exposed to the Investigational Product.
- **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 subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Treatment-emergent Adverse Event (TEAE)

Any recorded Adverse Event that occurs on or after the initiation of study drug is considered treatment-emergent. TEAEs will be attributed to the most recent treatment group that was received prior to the start of the AE. For AEs with partial dates, the event will be attributed to the earliest period the event could have occurred in based on the date. AEs that occur on a Day 1 of any Treatment Phase with no time will be attributed to the treatment received on that day.

Adverse Event of Special Interest (AESI)

AESIs are defined as the any of the following events:

- Syncope
- Sudden death, cardiac death
- TdP, QT/QTc prolongation, long QT syndrome
- ECG T wave and U wave abnormalities
- Ventricular arrhythmia, tachycardia, fibrillation / flutter

Treatment-emergent Clinically Significant Laboratory Abnormality

A Treatment-emergent Clinically Significant Laboratory Abnormality is defined as any post-Baseline laboratory assessment occurring from Day 1 to the EOS determined to be clinically significant by the investigator, and for which the Baseline is not considered clinically significant. If the Baseline value is missing, normal, or not clinically significant, any clinically significant abnormality that occurs following initiation of study drug is considered treatment-emergent.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of roluperidone on Day 1 of Treatment Phase 1. This definition includes medications that started prior to the initiation of roluperidone and continued concomitantly with roluperidone.

Prior Medications

Prior medications are those medications taken and stopped prior to the initiation of roluperidone.

3.3. TIMING OF ANALYSIS

A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, the pre-analysis meeting has occurred, and the final database lock has occurred.

4. ANALYSIS POPULATIONS

The populations for analysis will include the full set, safety (SAF) set, the PK set, and the PK Completer set.

4.1. FULL SET

The full set is the population of all subjects who sign an informed consent form.

4.2. SAFETY SET (SAF)

The SAF set is the population of all subjects who receive at least one dose of roluperidone. Subjects in this population will be analyzed according to the treatment(s) they receive. All safety analyses will be based on this population and treatment assignment.

4.3. PK SET

The PK set will consist of all subjects who completed all the PK assessments of at least 1 study phase, up to and including the 48-hour PK blood sample collection, provided they have no major protocol violations that could affect the pharmacokinetics of roluperidone. The PK evaluations will be based on the PK set.

4.4. PK COMPLETER SET

The PK Completer set will consist of all subjects who completed all the PK assessments, up to and including the 48-hour PK blood sample collection, provided they have no major protocol violations that could affect the pharmacokinetics of roluperidone. Select PK evaluations ($C_{max,}$ AUC_{24}, AUC_{last}, and AUC_{∞}) will be performed for the PK Completer set.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study.. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data, and coefficient of variation (%CV) for PK analysis. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment, subject number, and then by date within each subject number. For all other tables presenting data collected on-treatment, summaries will be presented by treatment group.

The term ‘treatment group’ refers to the administration of roluperidone alone or concomitantly with olanzapine to yield 2 groups.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to 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. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition will be presented for all subjects and the following will be presented: the number of subjects who meet all eligibility criteria, the number of subjects included in the Full, SAF and PK sets (PK set, and PK Completer set), the number of subjects who completed the study and discontinued from the study, and the reasons for early discontinuation at any point.

Demographic data and Baseline characteristics will be summarized using descriptive statistics for the SAF set. The following variables will be included in the tables:

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic or Latino/not Hispanic or Latino/ Not Reported)
- Race (American Indian or Alaska Native/Asian/Black or African American/ Native Hawaiian or Other Pacific Islander/White/Not Reported/Other)
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m2)
- Childbearing potential

This information will be reviewed for Baseline differences, but no statistical testing will be performed.

5.2. PHARMACOKINETIC ANALYSES

The secondary objective of the statistical analysis will be to evaluate the effect of the coadministration of roluperidone and olanzapine on the pharmacokinetics (PK) of roluperidone in subjects with moderate to severe negative symptoms of schizophrenia. The PK parameters of interest will be the natural log-transformed estimated AUCs and C_{max}. Only the data from subjects who completed all the PK assessments, up to and including the 48-hour PK blood sample collections (PK Completer set), will be included in the statistical analysis, but all available data will be analyzed as well (PK set).

5.2.1. Pharmacokinetic Sampling

During Treatment Phase 1, all subjects will have plasma PK samples will be drawn for roluperidone and its metabolite BFB-520 at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 24 hours post-dose on Days 1 and 7, at 6 hours post dose on Day 2, and at pre-dose and 6 hours post-dose on Days 3-6. During Treatment Phase 2, PK samples for roluperidone and olanzapine will be obtained at 6 hours post-dose on Day 8, time 0 (pre-dose) and 6 hours post-dose on Days 9-16, and starting on Day 17 at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 28, 32, 36, and 48 hours post-dose.

5.2.2. Assay Results Below the Lower Limit of Quantification

For purposes of calculation, plasma concentration values below the limit of quantification (BLQ) will be treated as zero for the determination of summary and order statistics. For purposes of data presentation, individual values that are BLQ will be presented as “BLQ” in the concentration data

listing. If the minimum, median, or maximum concentration is BLQ, it will be presented as BLQ in the table. If the mean concentration is BLQ, it will be presented as BLQ and SD and % coefficient of variation (CV) will be presented as "NA" (not applicable). If 1/3 or more of subjects have values of BLQ at any time point, descriptive statistics will not be calculated at that time point. The Geometric mean will not be calculated at the pre-dose time point. For post-dose values, concentration values equal to one-half the lower level of quantification (i.e., 0.125 ng/mL) will be used for BLQ values for calculation of the geometric mean.

5.2.3. Pharmacokinetic Methods

Pharmacokinetic parameters to be estimated from plasma concentration-time data are listed in Table 1.

Table 1. Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Observed maximum plasma concentration (ng/mL)
T_{max}	Time to reach the observed maximum plasma concentration (h)
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to Concentration C_{24}(h.ng/mL) at the 24-hour time point
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinite time, calculated according to the following equation $AUC = AUC_{last} + C_{last} / \lambda_z$ (h.ng/mL)), where Clast is the last measurable plasma concentration and λ_z is the terminal elimination rate constant AUC_{∞} will be reported if $t_{1/2, \lambda}$ is calculable and if C_{last} / λ_z represented 30% or less of the AUC value. AUC values where C_{last} / λ_z is less than 30% but greater than or equal to 20% of the AUC value will be flagged in the report.
$t_{1/2}$	Elimination half-life

5.2.4. Statistical Analyses of Pharmacokinetic Data

Plasma concentration data for roluperidone, BFB-520 and olanzapine will be summarized by treatment group. Nominal time point will be used for presentation of tables and figures. Summaries will include mean, SD, %CV, minimum and maximum.

All estimated PK parameters for roluperidone, BFB-520 and olanzapine will be summarized by treatment group, with summaries including arithmetic mean, median, geometric mean, minimum, maximum, SD, and %CV (arithmetic and geometric) for each treatment. For the calculation of geometric mean, observed values of 0 (BLQ) will be included as 0.0001 before the natural log transformation.

Descriptive summaries of T_{max}, $C_{max,}$ AUC_{0-24}, and AUC_{∞} will also be summarized within each treatment group.

Treatment ratios (roluperidone + olanzapine versus roluperidone alone) for C_{max}, AUC_{0-24}, and AUC_{∞} at steady state will be summarized using the same descriptive statistics as above. LS means (±90% confidence interval [CI]) for log transformed C_{max}, $AUC_{0\ 24}$, and AUC_{∞} will be evaluated by a linear mixed effects model with a fixed term for treatment and a random term for subject, fit by estimated generalized least squares with restricted maximum likelihood estimates of random effects. If deemed relevant to test for a treatment difference in T_{max}, a Wilcoxon signed rank test will be used.

Results for roluperidone, BFB-520, olanzapine will also be presented graphically. Figures will include plasma concentration-time profiles for the mean ± standard error of mean (SEM), which will be presented by treatment group. Additionally, plasma concentration-time profiles for each subject by treatment group will be presented. All figures will be produced on both the natural log-linear and linear-linear scales.

The plasma pharmacokinetic parameters of olanzapine from Day 17 will be compared with its pharmacokinetic profiles available in published literature.

5.2.5. Other Analyses

Other pharmacokinetic analyses may be performed as deemed appropriate.

5.3. SAFETY ANALYSES

5.3.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 preferred term and system organ classification. If a subject experiences multiple events that map to a single preferred term during the same treatment phase, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication.

The occurrence of TEAEs will be summarized by treatment group using preferred terms (PT), system organ classifications (SOC), severity, and/or relationship. A similar summary of (Serious) TEAEs related to study drug will be generated. Separate summaries of treatment-emergent SAE, events of special interest, events leading to the discontinuation of roluperidone, and events leading to death will be generated by SOC and PT. Additionally, an overall summary of the number of subjects experiencing each of these types of TEAEs, along with the overall number of events of each type will be presented. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. 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. Any treatment-emergent adverse events occurring after the EOS visit will not be summarized.

The overall summary table will include following types:

- Any TEAE
- Any serious TEAE

- Any drug related TEAE
- Any drug related serious TEAE
- Any AESI TEAE
- TEAEs by maximum severity
- TEAEs by maximum relationship
- Any TEAE leading to drug discontinuation
- Any TEAE leading to death

Missing onset dates will be imputed as previously outlined in Section 3.2.3.1 as required to determine treatment-emergent events.

5.3.2. Clinical Laboratory Assessments

All laboratory parameters collected at each center's local laboratory will be standardized by converting values in original units to values in standard units and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization.

Laboratory evaluations (including hematology, biochemistry, and urinalysis) will be listed by Treatment Phase and time point. Descriptive summaries of selected (quantitative) clinical laboratory results, and changes from Study Baseline (for Treatment Phase 1) and from Treatment Phase 2 Baseline (for Treatment Phase 2), will be presented by time point and treatment group.

The number and percentage of subjects experiencing treatment-emergent clinically significant laboratory abnormalities will be summarized by treatment group. See Table 2 for parameter specific criteria. All abnormalities that occur post-baseline, regardless of Baseline status will be included. Additionally, shifts in laboratory values with reference to the normal range from Baseline to 48 hours post-dose and from Baseline to EOS will be summarized by treatment.

Listings will be provided for subjects with any laboratory results outside the reference ranges, as well as for subjects with any potentially clinically significant (PCS) laboratory results as defined in Table 2.

Table 2. 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	g/L	0.1	g/dL	< 0.9 × LLN	—
Hematocrit	ratio	100	%	< 0.9 × LLN	—
White cell count	10^9/L	1	10^3/µL	≤ 2.5	≥ 15
Eosinophils absolute cell count	10^9/L	1	10^3/µL	—	≥ 1.5
Neutrophils absolute cell count (not Black)	10^9/L	1	10^3/µL	< 1.5	> 15.0
Neutrophils absolute cell count (Black)	10^9/L	1	10^3/µL	< 1.1	> 15.0
Lymphocyte absolute cell count	10^9/L	1	10^3/µL	< 0.75	≥ 5.0
Platelet count	10^9/L	1	10^3/µL	< 125.000	≥ 700
Chemistry					
Albumin	g/L	0.1	g/dL	< 27	—
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	—	> 1.3 × 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	—	> 1.3 × UNL
Glucose, fasting	mmol/L	18.015	mg/dL	< 3.4	> 6.16
Potassium	mmol/L	1	mEq/L	< 3.4	> 5.3
Sodium	mmol/L	1	mEq/L	< 131	> 146
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 2 × UNL
Urinalysis					
Protein	—	—	—	—	≥ 2 +
Glucose	—	—	—	—	≥ 1 +

a Conversion factor is the multiplication factor to convert from SI units to traditional units.
b Criteria refer to SI units.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of normal 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.

All laboratory abnormalities that occurred before dosing for a given treatment phase will be excluded from the tables but will be included in the listings. This includes any unscheduled laboratory assessments.

5.3.3. Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary version WHODrug Global b3 September 2023 release. Concomitant medications will be summarized by ATC Classification, preferred name, and treatment group. Prior and concomitant medications will be presented in a data listing.

5.3.4. Other Safety Analyses

Descriptive summaries of vital signs and their respective change from Baseline values will be presented by time point and treatment group. The number and percentage of subjects with PCS vital signs occurring post-baseline will also be summarized by time point and treatment group. All abnormalities that occur post-baseline, regardless of Baseline status will be included. All vital signs will be listed with PCS vital signs flagged.

Table 3. Criteria For Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria
Systolic Blood Pressure (mmHg)	High	≥ 150 mmHg
	Low	≤ 80 mmHg
Diastolic Blood Pressure (mmHg)	High	≥100 mmHg
	Low	≤ 45 mmHg
Heart Rate (bpm)	High	> 115 bpm
	Low	< 45 bpm
Temperature (°C)	High	≥ 38 °C
	Low	< 35 °C

ECG parameters and their change from Baseline (using both Study Baseline and Treatment Phase 2 Baseline) will be summarized with descriptive statistics by time point and treatment group. ECG parameters will include heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using QTcB and 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 subjects with post-baseline QTcF interval > 450 - 480 milliseconds (msec), > 480 - 500 msec, or > 500 msec will be summarized, as will the number and percentage of subjects with QTcF interval increases from Baseline of >30 – 60 msec or > 60 msec. For these summaries, worst-case assignments will be made to ensure subjects with such values are not counted more than once. For example, a subject with QTc interval > 500 msec will count once in the > 500 msec category and will not appear in the > 450 - 480 or > 480 - 500 msec categories. Similar conventions will be used for the >30 - 60 and >60 msec categories.

All ECG assessments and abnormalities in ECG waveform that are changes from Baseline readings will also be reported in a listing.

Table 4. Potentially Clinically Significant Criteria for ECG

Variable	Units	PCS Criteria Low Values	PCS Criteria High Values	Change from Baseline or Observed Value
Heart Rate	beats/min	<45	>115	-
QTcF Interval	msec	-	>450 Males >470 Females	>30-60, > 60, > 450-480, > 480-500, > 500
QRS Interval	msec	-	>120	-
PR Interval	msec	-	>220	-

All physical examination results will be listed.

Extrapyramidal symptoms will be assessed by AIMS and BARS. Observed and change from baseline (both Study Baseline and Treatment Phase 2 Baseline) in AIMS and BARS will be summarized by treatment group and time point for Safety Set. Separate listings will be provided for AIMS and BARS for Safety Set.

Suicidal ideation will be assessed by C-SSRS. Observed and change from baseline (both Study Baseline and Treatment Phase 2 Baseline) in C-SSRS will be summarized by treatment group and time point for Safety Set. Separate listings will be provided for C-SSRS for Safety Set.

Tuberculosis, FSH, Pregnancy Test, Drug Screen and Alcohol Breath Test, SARS-CoV2 Test, and Serology Test will be listed for the Safety Set.

[redacted] CGI-S [redacted]

[redacted] CGI-S [redacted]

6. PROTOCOL VIOLATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by Treatment-Phase, subject, and study day (where applicable). The following deviations may be identified as protocol deviations from the database:

- Missing ECG or PK assessments
- Violations of inclusion/exclusion criteria
- Non-compliance with roluperidone and/or olanzapine

7. CHANGES IN THE PLANNED ANALYSES

No deviations in the conduct of the study or the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report (CSR).

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 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings but may vary for figures. The output should be printed in Courier New with point size of 8.
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- 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 subjects actually summarized within any given summary module; some subjects 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 percentage 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 subjects contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects 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, subject 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 and medians will be reported to the same number of significant digits as the parameter.
- ♦ Calculated percentages will be reported with no decimals.

- 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

Summary Tables

Accountability and Baseline Characteristics

14.1.1.1 Subject Disposition, Full Set
14.1.1.2 Analysis Sets, Full Set
14.1.2 Demographics and Baseline Characteristics, Safety Set
14.1.3 Medical and Psychiatric History, Safety Set
14.1.4 Concomitant Medications, Safety Set

[redacted]

14.2.1.3 Clinical Global Impression- Severity Rating (CGI-S) by Treatment Phase, Safety Set

Pharmacokinetics

14.2.3.1.1 Plasma Concentrations of Roluperidone, PK Set
14.2.3.1.2 Plasma Concentrations of Roluperidone Metabolite BFB-520, PK Set
14.2.3.1.3 Plasma Concentrations of Olanzapine, PK Set
14.2.3.2.1 Plasma PK Parameters for Roluperidone, PK Set
14.2.3.2.2 Plasma PK Parameters for Roluperidone Metabolite BFB-520, PK Set
14.2.3.2.3 Plasma PK Parameters for Olanzapine, PK Set
14.2.3.2.4 Plasma PK Parameters for Roluperidone, PK Completer Set
14.2.3.2.5 Plasma PK Parameters for Roluperidone Metabolite BFB-520, PK Completer Set
14.2.3.2.6 Plasma PK Parameters for Olanzapine, PK Completer Set

Safety

14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events, Safety Set
14.3.1.2 Treatment-Emergent Adverse Events by System Organ Classification and Preferred Term, Safety Set
14.3.1.3 Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, and Maximum Severity, Safety Set
14.3.1.4 Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, and Maximum Relationship, Safety Set
14.3.1.5 Treatment-Emergent Adverse Events Related to Study Drug by System Organ Classification, Preferred Term, and Maximum Severity, Safety Set
14.3.1.6 Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, Safety Set
14.3.1.7 Treatment-Emergent Serious Adverse Events Related to Study Drug by System Organ Classification, Preferred Term, and Maximum Severity, Safety Set
14.3.1.8 Treatment-Emergent Adverse Events of Special Interest by System Organ Classification and Preferred Term, Safety Set

Figures

Data Listings

[redacted]	[redacted]
[redacted]	[redacted]
16.2.6.3	Clinical Global Impression - Severity Rating (CGI-S)
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.8.1.1	Laboratory Data – Chemistry
16.2.8.1.2	Laboratory Data – Hematology
16.2.8.1.3	Laboratory Data – Urinalysis
16.2.8.1.4	Laboratory Data – Other
16.2.8.1.5	Laboratory Results Outside Reference Range
16.2.8.1.6	Laboratory Abnormalities
16.2.8.1.7	Drug Screen and Alcohol Breath Test
16.2.8.1.8	Serum Pregnancy Test
16.2.8.1.9	Tuberculosis Test
16.2.8.1.10	FSH Test
16.2.8.2	Vital Signs, Weight, Height and BMI
16.2.8.3	Potentially Clinically Significant Vital Signs
16.2.8.4	Physical Examinations
16.2.8.5	12-Lead ECG Findings
16.2.8.6	Potentially Clinically Significant 12-Lead ECG Findings
16.2.8.7	12-Lead ECG Waveform Findings
16.2.8.8	Extrapyramidal Symptoms
16.2.8.9	Suicidal Ideation