[redacted]

Statistical Analysis Plan

Title: *A Randomized, Double-blinded, Placebo-controlled, Multicenter Study to Evaluate the Antipsychotic Efficacy and Safety of LB-102 in the Treatment of Adult Patients with Acute Schizophrenia*

Protocol Number: [redacted]

Protocol Version: *3.0 / 8 February 2024*

SAP Version: *Version 4.0, 20 November2024*

SAP Author: [redacted]

Previous SAP Versions

Version 1.0, 24 November 2023

Version 2.0, 14 December 2023

Version 3.0, 17 May 2024

[redacted]

[redacted]

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale
1.0	24-Nov-2023	-	-	First final version issued
2.0	14-Dec-2023	2.3	Changed the relevant analysis set for the estimands	ITT will be used as primary analysis set, but a caveat has been added to move to the mITT if this substantially overlaps with the ITT.
		5.1	Exclusion of the Per-Protocol Analysis Set	The Per-Protocol Analysis Set is not useful from a regulatory standpoint and provides results that are difficult to interpret in the best of cases, so it has been agreed to remove it.
		5.2.4	Clarification of ET assessments remapping	The rules for remapping assessments performed during an ET visit have been clarified, and some alternative options have been proposed.
3.0	17-May-2024	5.2	Derivation of questionnaires scores	The definition and rules for scoring study questionnaires have been added.
		5.3	Added details for PK summary statistics.	Since PK is usually summarized with geometric summaries details for these have been added.
		5.11.3	The structure and content of the sensitivity analysis section was revised	All sensitivity analyses are now described in this section, and the rules to identify the tipping-point have been clarified to account for the use of the Hochberg multiplicity adjustment across doses.
		5.12	Analyses of PK endpoints have been detailed more clearly.	The scope of reporting for PK parameters has been clarified and an analysis for dose-proportionality

[redacted]

[redacted]

				has also been added in line with protocol requirements.
4.0	20-November-2024	5.11.2	Adjusted the MNAR imputation description to remove any mention of post-ICE data imputation and the SAS sample codes have been adjusted for clarity	As part of the primary estimand, data collected after ICE is retained in the statistical analysis.
		5.11.3.3	Clarified that no imputation is done with regard to data collected after ICEs.	As part of the primary estimand, data collected after ICE is retained in the statistical analysis.
		5.11.5.1	The analysis method for the CGI-S response endpoint has been adjusted to reflect computational issues occurred during the dry-run.	Exact calculations are computationally intensive with this size and give rise to log issues, so an alternative has been pursued.
		5.11.5.5	SITE was removed as a covariate to avoid quasi-separation and convergence issues.	Sites enrolling few subjects will likely have all responders or all non-responders, thus leading to model convergence issues.
		5.13.1	The model to estimate event rates was simplified to handle data sparsity.	The originally planned model led to many estimation errors and issues, and such a simpler (yet valid) model has been considered instead.

[redacted]

[redacted]

REVIEW / APPROVAL SIGNATURES

[redacted]	[redacted]
[redacted]	

[redacted]

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
aPTT	Activated partial thromboplastin time
ATC	Anatomic Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BPD	Borderline Personality Disorder
CGI-S	Clinical Global Impressions-Severity of Illness
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
ECG	Electrocardiogram
EPS	Extrapyramidal side effects
ICE	Intercurrent event
INR	International normalized ratio
LLOQ	Lower Limit of Quantitation
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures

Abbreviation	Definition
NCS	Not Clinically Significant
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetics
PMM	Predictive Mean Matching
PT	Prothrombin time
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SD	Standard Deviation
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFL	Tables, Figures, and Listings
TSH	Thyroid-stimulating hormone

1 INTRODUCTION

This document details the planned statistical analyses for LB Pharmaceuticals Inc., [redacted] study titled "A Randomized, Double-blinded, Placebo-controlled, Multicenter Study to Evaluate the Antipsychotic Efficacy and Safety of LB-102 in the Treatment of Adult Patients with Acute Schizophrenia".

The proposed analyses are based on the contents of the amended version (Version 3.0) of the protocol (dated 8 February 2024).

This is a Phase 2 randomized, double-blinded, placebo-controlled, fixed dose, multicenter clinical study, designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of LB-102 50 mg QD, LB-102 75 mg QD, and LB-102 100 mg QD versus placebo in patients diagnosed with schizophrenia having an acute exacerbation of psychosis. The study includes a 7-day inpatient screening phase, an inpatient Study Treatment Period with 4 weeks of daily study treatment, an inpatient Stabilization Period of up to 5 days (during which patients will be stabilized on standard antipsychotic medication), and an outpatient Final Safety Follow-up of approximately 2 weeks after the end of the Treatment Period.

2 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is:

- To determine whether LB-102 [redacted] administered orally to patients with acutely exacerbated schizophrenia demonstrates antipsychotic efficacy, as determined by a change from Baseline on the Positive and Negative Syndrome Scale (PANSS) total score, compared to placebo.

2.1.2 Secondary Objectives

Secondary objectives of this study are:

- To evaluate the safety and tolerability of LB-102 in patients with acutely exacerbated schizophrenia.
- To assess the effect of LB-102 on the severity of illness in patients with acutely exacerbated schizophrenia, as determined by a change from Baseline in the Clinical Global Impressions-Severity of Illness scale (CGI-S) score.
- To assess the effect of LB-102 on PANSS subscale and Marder Factor scores in patients with acutely exacerbated schizophrenia.

[redacted]

2.1.3 Exploratory Objectives

- To explore the effect of LB-102 on Cogstate test score

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this study is:

- Change from Baseline to Week 4 in the PANSS total score, compared to placebo

2.2.2 Secondary Efficacy Endpoints

The secondary endpoints of this study are:

- Change from Baseline to Week 4 in the CGI-S score
- Change from Baseline to Week 4 in PANSS positive subscale score
- Change from Baseline to Week 4 in PANSS negative subscale score
- Change from Baseline to Week 4 in PANSS Marder Factor scores
- Response rate, defined as
  - Reduction of ≥20% from Baseline in PANSS total score at Week 4

2.2.3 Exploratory Endpoint

- Effect of LB-102 on Cogstate test score

2.2.4 Safety Endpoints

Safety will be assessed by the following:

- AE reporting
- Physical examination
- Vital signs
- Body weight, body mass index (BMI; derived programmatically from body weight and height measurements), and waist circumference
- Clinical laboratory tests (hematology, serum chemistry [including prolactin], urinalysis, and pregnancy tests); prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), glycosylated hemoglobin (HbA1c), cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH) and total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)
- 12-lead ECGs
- Assessments of EPS: the Simpson-Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS)

[redacted]

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

2.3 Estimands

The primary study estimand is described in Table 1 below.

Table 1. Primary Study Estimand: PANSS Total Score at Week 4

Objective: To determine whether LB-102 [redacted] administered to patients with acutely exacerbated schizophrenia demonstrates antipsychotic efficacy as determined by a change from Baseline on the PANSS total score, compared to placebo	
Estimand: Treatment effect of LB-102 vs Placebo regardless of intercurrent events (treatment-policy)	
Treatment: LB-102 (50 mg or 75 mg) and matching Placebo	
ESTIMAND	ANALYSIS
Target population	**Analysis set**
Adult patients with acute schizophrenia as identified by the study eligibility criteria	Intent-to-Treat (ITT) analysis set, defined as all randomized patients. Should the ITT and modified ITT (mITT) analysis sets overlap substantially (i.e. 95% of patients in the former are also in the latter), the mITT will be considered as the reference analysis set for all estimand-related analyses.
Variable	**Outcome measure**
PANSS Total Score at Week 4	Change from Baseline to Week 4 in the PANSS total score
Handling of intercurrent events	**Handling of missing data**
• Taking a prohibited medication prior to Week 4 • Starting an emergency treatment prior to Week 4 All of these intercurrent events (ICEs) will be handled via a treatment-policy strategy, i.e. data collected after their occurrence will be included in the statistical analysis of the endpoint.	All missing data due to study discontinuation for lack of efficacy or drug-related adverse events (AEs) will be imputed assuming a Missing Not at Random (MNAR) mechanism and assuming that after withdrawal the patients revert to the distribution of the worst PANSS score values observed up to time of discontinuation, whereas missing data due to discontinuation for any other reason, will be imputed under a Missing at Random (MAR) assumption using a Multiple Imputation (MI) approach. As a sensitivity analysis, missing data that was imputed under a MAR mechanism in the primary analysis will be imputed under a MNAR mechanism using a tipping-point approach to check robustness of the main analysis

[redacted]

	results. Another sensitivity analysis will adopt a reference-based imputation to further explore the impact of the MNAR assumption for missing data on the primary analysis results. Another sensitivity analysis will use assessments from re-mapped early termination visits (see Section 5.2.4 for details) in the analysis, adopting the same strategy for missing data as described for the primary analysis.
Population-level summary measure	**Analysis approach**
Mean difference between patients treated LB-102 (50 mg or 75 mg) and those treated with matching Placebo in the change from Baseline to 4 weeks post-baseline in the PANSS total score.	The difference between treatment arms of the Least Squares (LS) means of change from Baseline to 4 weeks post-baseline in the PANSS total score will be estimated from a Mixed Model for Repeated Measures (MMRM), including treatment, visit, treatment-by-visit interaction, study site and Baseline PANSS total score. The model will be fit across all imputed datasets and results pooled using Rubin's rules to obtain one single treatment effect estimate and its 95% confidence interval (CI). For the sensitivity analysis, the same model (MMRM) and analytical approach (pooling across imputations) will be adopted and one treatment effect estimate provided for each pre-planned delta/shift.

In addition to the above, a secondary estimand for the secondary endpoint related to response rate (i.e. a reduction of ≥20% from Baseline in PANSS total score at Week 4) is also defined and presented in Table 2.

Table 2. Secondary Study Estimand: Response Rate (PANSS-based) at Week 4

Objective: To determine whether [redacted] (LB-102) administered to patients with acutely exacerbated schizophrenia demonstrates antipsychotic efficacy, as determined by a change from Baseline on the PANSS total score, compared to placebo	
Estimand: Treatment effect of LB-102 vs Placebo assuming intercurrent events classify as non-responders	
Treatment: LB-102 (50 mg or 75 mg) and matching Placebo	
ESTIMAND	ANALYSIS
Target population	**Analysis set**
Adult patients with acute schizophrenia as identified by the study eligibility criteria	Intent-to-Treat (ITT) analysis set, defined as all randomized patients.

[redacted]

	Should the ITT and mITT analysis sets overlap substantially (i.e. 95% of patients in the former are also in the latter), the mITT will be considered as the reference analysis set for all estimand-related analyses.
Variable	**Outcome measure**
PANSS Total Score at Week 4	Response rate, defined as a ≥20% decrease from baseline to Week 4 in the PANSS total score
Handling of intercurrent events	**Handling of missing data**
• Taking a prohibited medication prior to Week 4 • Starting an emergency treatment prior to Week 4 All of these intercurrent events (ICEs) will be handled via a composite strategy, i.e. patients will be considered as non-responders	Missing data at Week 4 because of discontinuation due to 'Lack of Efficacy' or a drug-related AE will be imputed as non-responders. For all other missing data, the PANSS total score imputed for the primary analysis of the primary endpoint will be dichotomized as responders or not. As a sensitivity analysis, all missing data will be imputed as non-responders.
Population-level summary measure	**Analysis approach**
Difference between patients treated with LB-102 (50 or 75 mg QD) and those treated with matching placebo in the PANSS response rate at Week 4 post-baseline.	This endpoint will be analyzed using a logistic regression model including treatment and Baseline PANSS score as covariates to estimate the odds ratio (OR) of response of LB-102 (50 or 75 mg QD) vs placebo. The model will be fit separately to all imputed datasets and results pooled across imputations to obtain one single treatment effect estimate alongside 95% CI. The same model will also be fit for the sensitivity analysis and a single OR (alongside its 95% CI).

3 SAMPLE SIZE

[redacted] patients will be randomized in a 3:3:3:1 ratio to placebo, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD, respectively, with [redacted] patients randomized to each of the first 3 arms and [redacted] to the last one (LB-102 100 mg). This will ensure at least 85% power at a 2-sided 5% significance level to detect a treatment difference on the primary endpoint of 8 between either LB-102 50 mg or 75 mg and placebo QD, assuming a common SD of 18, an overall drop-out rate of 25% and a Hochberg procedure to adjust for multiplicity. The sample size was estimated via Monte Carlo simulations using 10,000 simulated trials.

4 RANDOMIZATION

Patients will be randomized in a 3:3:3:1 ratio to placebo, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD. An unblinded biostatistician, contracted with [redacted] will be responsible for generating and implementing the randomization scheme that will determine treatment assignment. Randomization will occur through an integrated response technology (IRT) system. The IRT system will generate the randomization number and the randomization number will be captured by and integrated into the electronic data capture (EDC) system. The patient identification will be a 6-digit number (i.e., the 1-digit country number, followed by a 2-digit site number followed by a 3-digit consecutive number). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

5 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) must be approved prior to database lock (DBL). If post DBL, additional statistical analyses or changes to the statistical analysis are required, then those will be documented in a Post DBL SAP Addendum.

5.1 Analysis Sets

5.1.1 Screened Set

The Screened Set includes all patients screened.

5.1.2 Intent-to-treat (ITT) Analysis Set

The ITT Analysis Set will include all randomized patients, irrespective of whether they received the drug or not. This will be the main analysis population for efficacy analysis purposes and patients will be analyzed based on the treatment they were randomized to.

5.1.3 Modified Intent-to-treat (mITT) Analysis Set

The mITT Analysis Set will include all randomized patients with at least 1 dose of study drug. This will be a secondary analysis set for the analysis of the primary endpoint, however should the ITT and the mITT substantially overlap (i.e. at least 95% of ITT patients are also in the mITT), the latter will be used as primary efficacy analysis set for all efficacy endpoints.

5.1.4 Safety Analysis Set

The Safety Analysis Set will include all patients who received any study drug. Analyses based on this population will use the actual treatment received rather than the randomized one.

5.1.5 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will include all patients who provide plasma concentration samples.

5.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

5.2.1 Race

Where more than one race category has been selected for a patient, these race categories will be combined into a single category labelled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

5.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the patient receives the first dose of study drug.

5.2.3 Change from Baseline

Change from Baseline for any variable at a given visit will be calculated by subtracting the Baseline value of that variable from the value of the variable at the given visit, e.g. for the Week 4 timepoint:

Change from Baseline to Week 4 = Week 4 value – Baseline value

Percent change from Baseline will be calculated as follows for all variables:

Percent change from Baseline to Week 4 = ((Week 4 value – Baseline value)/Baseline value) × 100

5.2.4 Early Terminations Assessments

Early termination assessments will be mapped to closest scheduled visit using the analysis windows described in Table 3. If the planned visit that an early termination assessment is mapped to has occurred and data was collected, then the early termination assessment will not be included in the statistical analyses or summaries of any endpoint but will only be included in the listing, otherwise if the planned visit hasn't occurred or it has occurred but not all applicable assessments were completed, then assessments from the early termination visit mapped to that visit will be used in the statistical analyses and summaries.

Table 3. Analysis Windows

Visit	Window Start Day	Window End Day
Day 8	Day 2	Day 11
Day 15	Day 12	Day 18
Day 21	Day 19	Day 24

Day 28	Day 25	Day 30

For sensitivity analyses of the primary endpoint purposes, should an early termination assessment occur that is mapped to a window where a planned visit was collected and where the PANSS score was correctly completed, the PANSS score collected at the early termination assessment will be used to replace the primary endpoint value at the planned visit.

5.2.5 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

5.2.6 Conventions for Missing and Partial Dates

Missing and partial start and stop date will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved, or the patient has stopped taking the concomitant medication, the stop date will be imputed as the date of the patient's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first application of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the patient's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as the date of application of study drug. "If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first application of study drug in which case the date of first application of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial start date.

All dates presented in the individual patient listings will be as recorded on the Electronic Case Report Form (eCRF).

5.2.7 Exposure to Study Drug

Exposure to study drug will be calculated as follows:

date of last dosing minus the first day of dosing + 1

The exposure calculation will not take into account breaks in therapy. In addition to the above, The number of doses received will also be derived, to account for any break in therapy.

5.2.8 Treatment Compliance

Treatment compliance will be derived as the ratio between the planned number of doses (i.e. 28 for patients completing the inpatient treatment period or the number of days from the first dose to the early termination date for patients not completing the inpatient treatment period, one for each planned day of the inpatient treatment period) and the actual number of doses received, as follows:

$$\%\ Compliance = 100 \times \frac{Actual\ Received\ Doses}{Total\ Planned\ Doses}$$

Compliance will also be categorised as follows:

- <70% (poorly compliant)
- 70% to 90% (moderately compliant)
- 90% to 100% (fully compliant)

5.2.9 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes. The inexact value, inclusive of the symbol, will be reported in the listings.

5.2.10 Electrocardiogram (ECG) Data

For ECG data recorded on continuous scales, triplicate values recorded at a time point will be averaged and rounded to the integer for summarization purposes. For the overall interpretation, the

most severe (worst case) of the replicate readings will be taken (separately for the central reader and the investigator assessment).

5.2.11 Vital Signs

For blood pressure (both systolic and diastolic) and pulse rate, the orthostatic changes will be calculated as standing minus sitting readings.

A patient will be defined to have orthostatic hypotension if either or both of the below criteria are met:

- a decrease of > 20 mm Hg in systolic blood pressure in measurements from supine to standing
- a decrease of > 10 mm Hg in diastolic pressure in measurements from supine to standing

Temperatures reported in Fahrenheit will be converted to Celsius for reporting using the following formula:

Celsius = (Fahrenheit – 32)/1.8

Weights reported in pounds will be converted to kilograms using the following formula:

Kilograms = pounds* 0.453592

Heights and waist circumferences reported in inches will be converted to centimeters using the following formula:

Centimeters = inches*2.54

5.2.12 Positive and Negative Symptoms Scale (PANSS)

The PANSS is a questionnaire consisting of 30 items, divided in 3 subscales (negative symptoms, positive symptoms, and general psychopathology), where each item (representing a symptom construct) can be rated with a value ranging from 1 to 7. The total score is obtained by summing the scores for each item/symptom, and similarly the sub-scale scores are obtained by summing the scores of the individual items included in each of them.

In addition to this, PANSS Marder factor scores are defined as a further combination of the items, using the mapping described in Table 4. The scores for each factor are obtained by summing up the scores of each individual item listed in the table below for the respective factor.

Table 4 PANSS Marder Factors Mapping

Factor Name	**Items**
Negative Symptoms	Blunted affect Emotional withdrawal

	Poor rapport Passive social withdrawal Lack of spontaneity Motor retardation Active social avoidance
Positive Symptoms	Delusions Hallucinatory behavior Grandiosity Suspiciousness Stereotyped thinking Somatic concern Unusual thought content Lack of judgement and insight
Disorganized Thought	Conceptual disorganization Difficulty in abstract thinking Mannerism and posturing Poor attention Disturbance of volition Preoccupation Disorientation
Uncontrolled Hostility/Excitement	Excitement Hostility Uncooperativeness Poor impulse control
Anxiety/Depression	Anxiety Guilt Tension Depression

5.2.13 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent

Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide

Suicidal Ideation since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behavior since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

5.2.14 Clinical Global Impression – Severity (CGI-S)

The CGI-S assesses the physician/investigator's assessment of the severity of the patient's illness, using a 7-point rating scale ranging from 1 (= normal, not at all ill) to 7 (= among the most extremely ill patients).

A patient will be classified as a responder on the CGI-S if they provide a score of either 1 (= normal, not at all ill), 2 (= borderline mentally ill) or 3 (=mildly ill).

5.2.15 Simpson-Angus Scale (SAS)

The SAS is a measure of extrapyramidal side effects (EPS) and consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms, and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

5.2.16 Abnormal Involuntary Movement Scale (AIMS)

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). The AIMS movement rating score is defined as the sum of items 1 through 7 (i.e., items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

5.2.17 Unscheduled Visits

Only values collected at scheduled assessments values will be tabulated, unless otherwise stated. All repeat/unscheduled assessments will be included in all listings in the relevant appendices to the Clinical Study Report (CSR).

5.2.18 Pooled Study Site

Sites enrolling fewer than 10 patients might be pooled such that the smallest pooled site becomes the size of the smallest standalone site but not larger than approximately three times the size of the smallest standalone site. The choice of which sites to pool will be done preliminarily once 75% of all patients have been randomized and will be confirmed at the end of the recruitment period and will be based on geographical considerations. The exact pooling strategy will be agreed upon prior to unblinding and database lock and detailed in the CSR.

5.3 Conventions

All data listings, summaries, figures, and statistical analyses will be generated using SAS© version 9.4 or higher[2].

Summaries will be presented by treatment group or overall. Treatment group labels will be displayed as follows:

LB-102 50 mg (N=XX)	LB-102 75 mg (N=XX)	LB-102 100 mg (N=XX)	Placebo (N=XX)

Listings will be sorted in the following order: treatment group, patient, visit, and parameter, unless otherwise stated. All data will be listed, and patients who were not randomized (i.e. screen failures) will be displayed after the randomized treatment groups in relevant listings.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation (SD), and minimum and maximum. Summaries of PK concentrations will also include geometric means and coefficient of variations (CV), the former being derived as $exp(\mu_{ln})$ and the latter as $\sqrt{exp(\sigma_{ln}^2) - 1}$ where μ_{ln} and σ_{ln}^2 are, respectively, the mean and variance calculated on the natural log-transformed concentrations.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based either on the number of patients in the column header or on the number of patients in the respective analysis set with available data, as specified in the table footnotes. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Means, medians, and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum

and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P-values will be quoted to 4 decimal places consistent with SAS PVALUE*w.d* format set to PVALUE6.4. P-values < 0.0001 will be presented as p<0.0001.

5.4 Patient Disposition

Patient disposition will be summarized as follows:

- The number of patients who were screened and who failed screening will be tabulated for the Screened Set alongside the reason for screen failure.
- The number of patients randomized, and who are in each analysis set will be summarized separately for each study site by treatment group and overall.
- The number of study and treatment discontinuations and the reasons for discontinuation will be tabulated by treatment group and overall for all randomized patients.
- The number of patients present at each scheduled visit will be summarized by treatment group for the Safety Analysis Set.

All patient disposition data will be listed.

5.5 Protocol Deviations

PDs will be summarized by classification (minor, major) and reason. A listing of PDs will be provided within Appendix 16.2 of the CSR.

5.6 Baseline Comparability

The comparability of treatment groups with respect to patient demographics and baseline characteristics will be assessed in a descriptive manner.

Standard continuous or categorical variable summaries will be presented for the Safety Analysis Set by actual treatment group for the following variables:

- Demographics
  - Age at Informed Consent (years),
  - Gender, n (%) ('Male', 'Female'),
  - Fertility status for women, n (%) (a) ('Childbearing Potential', 'Post-menopausal', 'Surgically Sterile'),
  - Ethnicity, n (%) ('Hispanic or Latino', 'Not Hispanic or Latino'),
  - Race, n (%) ('American Indian or Alaska Native', 'Asian', 'Black or African American', 'Native Hawaiian or Other Pacific Islander', 'White', 'Multiple Race', 'Unknown', 'Not Reported').
- Other baseline characteristics

- Weight (kg),
- Height (cm),
- Body Mass Index (kg/m^2),
- Waist Circumference (cm).

The MINI 7.0.2 questionnaire with the Borderline Personality Disorder (BPD) module will only be listed.

5.7 Medical History

Separate tabulations of previous and ongoing conditions at screening will be presented by actual treatment group and overall for the Safety Analysis Set. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) primary system organ class and preferred term, using version 26.1 or higher for coding.

All medical history information will also be listed.

5.8 Prior and Concomitant Medications

Prior medications are defined as all medications that were stopped in the 30 days before ICF sign-off, whereas concomitant medications are defined as medications taken on or after such date.

Separate tabulations will be produced for prior and concomitant medications presented by actual treatment group and overall for the Safety Analysis Set. Concomitant medications will be coded using the WHO dictionary (version B3 Global Mar-2023 or later) and summarized using Anatomic Therapeutic Chemical (ATC) Level 2.

Prior medication washout information will also be listed separately.

5.9 Exposure to Study Drug

Extent of exposure will be summarized descriptively by actual treatment group for the Safety Analysis Set, including the following parameters:

- Length of exposure (days)
- Number of doses received
- Number of doses missed

5.10 Treatment Compliance

Treatment compliance will be summarized descriptively by treatment groups for the Safety Analysis Set. In addition, the categories of compliance defined in Section 5.2.8 will also be summarized with counts and percentages.

5.11 Efficacy Analyses

[redacted]

Statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. For the primary analysis of the primary endpoint, a multiplicity strategy will be in place to ensure that the familywise error rate (FWER) is controlled at this level across the doses tested (see Section 5.11.7 for details).

All comparisons between treatments will be reported with 95% confidence intervals for the difference.

5.11.1 Primary Endpoint

The primary endpoint is the change from Baseline to Week 4 in the PANSS total score. The null hypothesis associated with this endpoint is that the decrease from Baseline to Week 4 in either the LB-102 50 mg or 75 mg arms are equal or smaller than what observed in the Placebo arm, and the alternative being that the decrease in the active arm is larger than in the Placebo arm. This set of hypotheses can be formalized as follows:

<u>LB-102 50 mg arm:</u>

$H_{01}: \mu_{\text{LB-102 50 mg}} \geq \mu_{\text{Placebo}}$

$H_{11}: \mu_{\text{LB-102 50 mg}} < \mu_{\text{Placebo}}$

<u>LB-102 75 mg arm:</u>

$H_{02}: \mu_{\text{LB-102 75 mg}} \geq \mu_{\text{Placebo}}$

$H_{12}: \mu_{\text{LB-102 75 mg}} < \mu_{\text{Placebo}}$

No formal hypothesis will be tested for the LB-102 100 mg arm, but data will be included in any analysis model for all the primary and secondary efficacy endpoints and CIs and p-values provided for descriptive purposes.

Methods to control type I error rate at the nominal 5% level are described in Section 5.11.7.

5.11.2 Primary Efficacy Analysis

In line with the primary study estimand, prior to performing the statistical modelling missing data due to a discontinuation related to either lack of efficacy or drug-related AEs will be imputed assuming a MNAR mechanism whereas missing data due to discontinuation for any other reason or non-monotone missing data will be imputed under a MAR mechanism.

The MAR imputation will use a fully conditional specification approach with a predictive mean matching (PMM) method, where a missing value is imputed using a value randomly selected from a set of k (= 5) observed values that are the closest to the predicted value for the missing data point. This imputation will be performed using the following SAS code:

[redacted]

```
proc mi data = <input-dataset> nimpute = 100 seed = 99 out = impute01 minimum
= 30 maximum = 210 round = 1;
  by trt01p;
  var baseline week_1 week_2 week_3 week_4;
  fcs nbiter = 1000 regpmm( baseline);
  fcs nbiter = 1000 regpmm(week_1 = baseline);
  fcs nbiter = 1000 regpmm(week_2 = baseline week_1);
  fcs nbiter = 1000 regpmm(week_3 = baseline week_1 week_2);
  fcs nbiter = 1000 regpmm(week_4 = baseline week_1 week_3);
run;
```

Missing values for patients dropping out from the study because of lack of efficacy or drug-related AEs will be imputed iteratively assuming that after withdrawal the patients will follow the distribution of the worst values observed up to the study visit at which they withdraw. A schematic illustration of the process would be as follows:

a) All patients with non-missing Week 1 PANSS score values (including both those with an actual observed Week 1 value and those who had this value imputed as part of the MAR imputation step described above) will have a variable (WORST1) calculated which is the maximum PANSS score values observed between baseline and Week 1, whereas those with a missing Week 1 value will have a missing value for WORST1 as well
b) The imputation step will use WORST1 as the variable to be imputed and baseline and Week 1 values as predictors using the PMM method described above for the MAR imputation step. Patients with a missing Week 1 value will thus have their Week 1 value imputed by the WORST1 value predicted by the imputation procedure.
c) A similar approach will thus be followed for Week 2, i.e. creating a WORST2 variable, imputing it using a PMM approach and using this imputed value as the Week 2 value for patients with a missing assessment at that visit.
d) This approach will then be repeated for Week 3 and 4, until at last all values missing because of lack of efficacy or drug-related AEs have been imputed/replaced.

The below sample SAS code implements the above steps, with the input dataset of the first DATA STEP being the output dataset of the PROC MI step above and including the patient ID and the MAR-imputed PANSS data in wide format, one column for timepoint, i.e. baseline, Week 1, 2, 3 and 4:

```
* Create WORST1 variable;

data step1;
  set analysis02;
  if not missing(week_1) then worst1 = max(baseline, week_1);
run;

* Impute WORST1 for patients with missing Week 1 data;
```

```
proc mi data = step1 nimpute = 1 seed = 99 out = step2a minimum = 30 maximum
= 210;
  by _imputation;
  var baseline worst1;
  fcs nbiter = 1000 regpmm(worst1 = baseline);
run;

* Set Week 1 = WORST1 for missing data and create WORST2 variable;

data step2b;
  set step2a;
  week_1 = ifn(missing(week_1), worst1, week_1);
  if not missing(week_2) then worst2 = max(baseline, week_1, week_2);
run;

* Impute WORST2 for patients with missing Week 2 data;

proc mi data = step2b nimpute = 1 seed = 99 out = step3a minimum = 30 maximum
= 210;
  by _imputation;
  var baseline week_1 worst2;
  fcs nbiter = 1000 regpmm(worst2 = baseline week_1);
run;

* Set Week 2 = WORST2 for missing data and create WORST3 variable;

data step3b;
  set step3a;
  week_2 = ifn(missing(week_2), worst2, week_2);
  if not missing(week_3) then worst3 = max(baseline, week_1, week_2, week_3);
run;

* Impute WORST3 for patients with missing Week 3 data;

proc mi data = step3b nimpute = 1 seed = 99 out = step4a minimum = 30 maximum
= 210;
  var baseline week_1 week_2 worst3;
  fcs nbiter = 1000 regpmm(worst3 = baseline week_1 week_2);
run;

* Set Week 3 = WORST3 for missing data and create WORST4 variable;

data step4b;
  set step4a;
  week_3 = ifn(missing(week_3), worst3, week_3);
  if not missing(week_4) then worst4 = max(baseline, week_1, week_2, week_3,
week_4);
run;

* Impute WORST4 for patients with missing Week 4 data;

proc mi data = step4b nimpute = 1 seed = 99 out = step5a minimum = 30 maximum
= 210;
```

```
  var baseline week_1 week_2 week_3 worst4;
  fcs nbiter = 1000 regpmm(worst4 = baseline week_1 week_2 week_3);
run;

* Set Week 4 = WORST4 for missing data;

data step5b;
  set step5a;
  week_4 = ifn(missing(week_4), worst4, week_4);
run;
```

Upon completion of the above imputation steps, the change from baseline in the PANSS score will be derived and used in the statistical modelling. To such aim, a MMRM will be fit for each imputed dataset, including pooled study site, visit, treatment and treatment by visit interaction as categorical effects and Baseline PANSS total score as continuous covariate and the change from Baseline in the PANSS total score at 1, 2, 3 and 4 weeks after baseline as response. Correlation between repeated observations within a patient will be accounted for via an unstructured correlation matrix, however, should this structure lead to convergence issues, the following decreasingly complex alternative structures will be fit in turn until the model converges: Toeplitz, first-order autoregressive, and compound symmetry. The assessment of model convergence will be done prior to unblinding. The LS means for change from Baseline to all post-Baseline timepoints in the PANSS total score and their differences between the active treatment arms (50 and 75 mg) and placebo will be estimated for each imputed dataset. Model assumptions will be examined graphically for a random selection of 10% imputations (i.e. 10) via inspection of conditional residuals scatterplots (residuals vs predicted values), quantile-quantile plots and histograms. Should any substantial violation be observed, non-parametric analyses (e.g. Wilcoxon rank-sum test) will be adopted, and this decision will be documented based on blinded data prior to database lock. This model will be fit using the example SAS code below:

```
ods output estimates = est LSMeans = lsm diffs = diff;
proc mixed data = <input-dataset> plots (only) = studentpanel(marginal);
  by _imputation_;
  class subjid trt01pn avisitn siteid;
  model chg = trt01pn siteid avisitn trt01pn*avisitn base / ddfm = kr;
  repeated avisitn / type = un subject = subjid;
  lsmeans trt01pn*avisitn / diff cl;
run;
```

The model estimates (LS means and their differences between treatment arms) will be pooled using Rubin's combination rules[3] to incorporate the between-imputation with the within-imputation variability and to obtain one single point and interval treatment effect estimate for each active arm using the PROC MIANALYZE procedure. The below sample SAS code implements the pooling across imputations:

```
proc mianalyze data = <input-dataset>;
  by trt01pn avisitn;
```

```
  modeleffects estim;
  stderr sem;
  ods output parameterestimates = parmest;
run;
```

where *estim* and *sem* are the point and variability estimates from the MMRM analysis for each imputed dataset for each relevant parameter. In the above code, the BY statement ensures that the pooling is done across imputations within each level of TRT01PN and AVISITN (these variable names might change depending on the actual variable used in the analysis). LS means and their differences between the active arms and Placebo alongside 95% CIs and p-values for the differences will thus be reported after the above pooling has been done, inclusive of the results of the multiplicity adjustment procedure described in Section 5.11.7. The estimated LS means over time will be graphically displayed alongside their 95% CI in a line plot. A descriptive summary of PANSS total scores and their changes from baseline will also be presented.

This analysis (inclusive of the graphical representation) will be performed for the ITT analysis set and repeated also for the mITT Analysis Set, however should the two analysis sets overlap substantially (i.e. if at least 95% of the patients in the ITT are also included in the mITT) the primary analysis will be performed for the mITT and the ITT only be regarded as supportive information.

All PANSS score data, inclusive of individual items responses as well as subscale scores, will also be listed.

5.11.3 Sensitivity Analysis

5.11.3.1 Sensitivity Analysis #1: Re-mapped Early Termination Assessments

The primary analysis will be repeated but including PANNS values obtained during early termination assessments in the analysis, i.e. by re-mapping them to the analysis windows described in Section 5.2.4 in place of PANSS collected at the planned visit mapped to the same analysis window. Similar displays and quantities to the primary analysis will be provided.

5.11.3.2 Sensitivity Analysis #2: Tipping-Point Analysis

As an additional sensitivity analysis, all missing PANSS total score values that have been imputed using a MAR approach as described in Section 5.11.2 will be imputed under a MNAR mechanism using a tipping-point approach, i.e. by adding a treatment-specific constant shift to the MAR-imputed values in order to assess how severe a MAR violation needs to be for the results to change, i.e. for the results of the primary analysis to no longer be deemed as statistically significant (that is, for neither of the 50 or 75 mg arms to meet the thresholds described in Section 5.11.7). The following set of shifts values will be initially considered: 2, 4, 6, 8 and 10, with the potential combinations across arms described in Table 5 below.

[redacted]

Table 5. Shift combinations for tipping point analysis

		LB-102 Arms Shift				
		2	4	6	8	10
Placebo Arm Shift	2	x	x	x	x	x
	4		x	x	x	x
	6			x	x	x
	8				x	x
	10					x

The lower triangle will not be investigated because it would be associated with scenarios where the penalties are larger for the Placebo arm, thus unlikely to reveal any negative change in study results.

The same MMRM as considered for the primary analysis will then be fit for each multiply imputed dataset by shift pair, and results pooled to obtain, for every set of shift values, one treatment effect for each active arm. This analysis will only be performed if at least one active arm's primary analysis result was deemed as statistically significant under the multiple testing strategy defined in Section 5.11.7. The first combination of shifts where significance can't be concluded for any active arm (using the same multiplicity approach as for the primary analysis) will be identified as the tipping-point, and its plausibility evaluated. For this purpose, the shifts combinations will be ordered column-wise, e.g. assuming that a combination of placebo/active shifts of 8-8 is more 'plausible' then a 2-10. If no tipping-point is identified using the above combinations, extra shifts will be evaluated by shifting the values for LB-102 arms by a value of 12 and then, within this, exploring shifts from 2 to 12 for Placebo, and so on until a shift is identified or all MAR imputed data have been imputed to maximum PANSS total score possible (= 210).

For each of the above pairs, the treatment effects and associated p-values for both arms will be presented, alongside results of the multiplicity adjustment procedure described in Section 5.11.7.

5.11.3.3 Sensitivity Analysis #3: Reference-based Imputation

For this sensitivity analysis, all missing data due to drop-out will be imputed using a pattern-mixture model, whereby data will be imputed only using data from patients with no missing data from the Placebo (reference) arm, i.e. assuming that all patients randomized to an active arm had had a profile on the primary endpoint similar to that of patients randomized to Placebo. To achieve this, first non-monotone missing data on the PANSS will be imputed under a MAR mechanism using a Markov-Chain Monte Carlo (MCMC) approach, using the below sample SAS code:

```
proc mi data = <input-dataset> nimpute = 100 seed = 99 out = <output-dataset>
minimum = 30 maximum = 210;
  by trt01pn;
  var base d8 d15 d21 d28;
```

[redacted]

```
  mcmc chain = multiple impute = monotone initial = em prior = jeffreys;
run;
```

Where the variables included in the VAR statement represent the PANSS total score at the relevant timepoints throughout the study, the IMPUTE = MONOTONE option means that missing data points will be imputed to achieve a monotone missing data pattern, and the PRIOR = JEFFREYS option specifies a non-informative prior for the imputation process, so that the posterior distribution used for the imputation is largely affected by the observed data themselves. These imputed datasets will then be imputed using the copy-reference method via the below SAS code:

```
proc mi data = <input-dataset> nimpute = 1 seed = 99 out = <output-dataset>
minimum = 30 maximum = 210;
  by _imputation_;
  class trt01p;
  var baseline d8 d15 d21 d28;
  fcs nbiter = 1000 regpmm(baseline d8 d15 d21 d28);
  mnar model(baseline d8 d15 d21 d28/ modelobs = (trt01p = 'Placebo'));
run;
```

The BY statement will ensure that the above MNAR imputation is performed separately for each MAR-imputed dataset as generated by the previous imputation step. The same MMRM will then be fit to all imputed datasets and results pooled across imputations, using the SAS code described in Section 5.11.2 for both the analysis and the pooling, and thus reporting similar quantities from the model.

5.11.4 Exploratory Analysis

5.11.4.1 Subgroup analysis

The primary analysis model (MMRM) described in Section 5.11.2 will be used for the purposes of subgroups analyses, with no prior imputation for missing data. For each subgroup variable stratum the model will be fit and estimates of LS means and their differences over time will be provided, alongside 95% CIs as well as, for differences, p-values (only for descriptive purposes). The following subgroups will be explored:

- BMI at Baseline: ≤ 25 kg/m^2, 25 to 30 kg/m^2, ≥ 30 kg/m^2
- Baseline PANSS (disease severity): ≤ 95, > 95

The results for these subgroups analysis will also be displayed in a forest plot (Week 4 only).

5.11.4.2 Site Effect

Descriptive summaries of observed and change from baseline values for the PANSS total score will be provided by study site (regardless of pooling), but no statistical analysis will be performed.

5.11.5 Secondary Endpoints

[redacted]

All secondary endpoints will be analyzed on the ITT analysis set. As described in Section 5.11.2, should the ITT and mITT analysis sets overlap substantially, secondary endpoints will only be analyzed on the mITT analysis set.

5.11.5.1 Change from Baseline to Week 4 in the CGI-S score

The change from Baseline in the CGI-S score will be analyzed using a similar MMRM as the one for the primary endpoint, replacing baseline CGI-S as covariate in the model. Similar quantities (LS means and their differences, with 95% CIs and p-values) will be presented. Descriptive summaries of observed and change from Baseline values will be presented for all treatment arms.

CGI-S response, defined as a CGI-S score ≤ 3, will also be analyzed separately for each time-point, categorizing any patient with missing data as a non-responder. The number of patients meeting this definition will be summarized descriptively on the mITT analysis set with counts and percentages, including approximate Wald-type 95% CI (with a continuity correction). The difference between treatment arms in the above defined responder rate will be analyzed by reporting the estimated difference in proportions alongside its 95% Wald-type 95% CI with a continuity correction as well as the *P*-value derived from Fisher's exact test (using a Monte Carlo approximation to deal with the large sample size). Example SAS code is provided below:

```
ods output RiskDiffCol2 = diff FishersExact = fisher;
proc freq data = <input-dataset>;
  by atptn;
  tables trt01pn*avalc / riskdiff (column = 2 cl = (wald(correct))) chisq;
  exact fisher / mc seed = 123;
run;
```

For the derivation of the exact p-value, it is assumed that the 2x2 table for each visit has the following form:

Treatment	Non-Response	Response
LB-102	a	b
Placebo	c	d

Under the above structure, Fisher's test as implemented in PROC FREQ is defined based on the value *a* in the first row/column and the associated one-sided p-values support different alternative hypotheses (the null being that of independence between row and columns):

- Left-sided p-value: supports the alternative that the probability of a patient treated with LB-102 of being a non-responder is smaller than what would be expected under the independence null;
- Right-sided p-value: supports the alternative that the probability of a patient treated with LB-102 of being a non-responder is larger than what would be expected under the independence null.

[redacted]

Since the hypothesis we're interested in is that patients treated with LB-102 are more likely to be responders than non-responder, a small left-sided p-value supports this hypothesis and as such this is the p-value that will be reported in the table. All CGI-S data will also be listed.

5.11.5.2 Change from Baseline to Week 4 in PANSS positive subscale score

This endpoint will be analyzed as described in Section 5.11.5.1, both with respect to the modelling strategy (inclusive of the imputation step and with appropriate changes to the baseline measurement to use as a covariate) and the descriptive summary approach.

All PANSS subscale scores will be listed alongside the total score.

5.11.5.3 Change from Baseline to Week 4 in PANSS negative subscale score

This endpoint will be analyzed as described in Section 5.11.5.1, both in terms of model to fit and quantities to report.

5.11.5.4 Change from Baseline to Week 4 in PANSS Marder Factor scores

This endpoint will be analyzed as described in Section 5.11.5.1, both in terms of model to fit and quantities to report (but with no imputation step), separately for each factor score described in Section 5.2.12.

5.11.5.5 Response rate, defined as a reduction of ≥20% from Baseline in PANSS total score at Week 4

As described in Table 2, prior to analysis the PANSS score data imputed under a MAR mechanism will be dichotomized as being a responder or non-responder, and then missing data due to discontinuation because of lack of efficacy or drug-related AE as well as any data collected after any relevant ICE (start of emergency of prohibited treatment prior to Week 4) will be imputed as non-responders. The resulting dataset will be analyzed using a logistic regression using the response status at Week 4 as a response and baseline PANSS score, and treatment as covariates, using the below sample SAS code:

```
ods output Diffs = <outut-dataset>;
proc logistic data = <input-dataset> descending;
  by _imputation_;
  class trt01p (ref = 'Placebo');
  model response = trt01p baseline / link = logit;
  lsmeans trt01p / diff ilink om oddsratio;
run;
```

From the above, the log odds ratio alongside its standard error will be estimated and then pooled across imputed datasets to return one single estimate, which will be exponentiated (alongside its 95% CI) to obtain an OR for each treatment arm. The proportion of responders at day 28 will also

be descriptively summarized (based purely on observed data), with an approximate 95% CI reported, derived using the following sample SAS code:

```
ods output RiskDiffCol2 = <output-dataset>;
proc freq data = <input-dataset>;
  table trt01p*response / riskdiff (column = 2);
run;
```

This endpoint will also be analyzed by imputing all missing data as non-responders and fitting the same logistic regression as above, from which the OR for each arm will be estimated.

Response status will be listed in the general PANSS listing.

5.11.6 Exploratory Endpoints

All exploratory endpoints will be analyzed on the ITT analysis set. As described in Section 5.11.2, should the ITT and mITT analysis sets overlap substantially, secondary endpoints will only be analyzed on the mITT analysis set.

5.11.6.1 Effect of LB-102 on Cogstate test scores

Summaries for the actual and change from Baseline values for each of the Cogstate test scores (International Shopping List Test, Detection Test, Identification Test, One Back Test and Modified Groton Maze Learning Test) will be provided by treatment group. In addition, an analysis of covariance (ANCOVA) model will also be fit including pooled study site and treatment as categorical covariates and baseline Cogstate test score as continuous covariate and change from baseline to day 28 in the Cogstate test score as the response. LS means and their differences alongside 95% CIs and p-values for the comparison of active arms vs placebo will be reported. The following sample SAS code will be used:

```
ods output estimates = est LSMeans = lsm diffs = diff;
proc mixed data = <input-dataset> plots (only) = studentpanel(marginal);
  by test;
  class trt01pn siteid;
  model chg = trt01pn siteid base / ddfm = kr;
  lsmeans trt01pn / diff cl;
run;
```

All Cogstate test score results will also be listed.

5.11.7 Multiplicity

Results from the analysis of the primary endpoint across the 50 and 75 mg doses will be adjusted for multiplicity using a standard Hochberg procedure. This approach involves ranking the P values from the smallest ($P_{(1)}$) to the largest ($P_{(2)}$) and then comparing $P_{(2)}$ against 0.05 and if this hypothesis is rejected then reject also the one associated with $P_{(1)}$, otherwise $P_{(1)}$ is further tested

at a local 0.025 two-sided level, and if the test is significant at this level than the null hypothesis associated with it is rejected, whereas the one associated with $P_{(2)}$ is retained.

5.12 Pharmacokinetic Analyses

Blood samples for determination of plasma concentrations of drug will be collected on Day 1, 8 and 21 at the following time-points: pre-dose (only at Day 1), 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours post dose. Concentration-time data will be tabulated by nominal (planned) time, analyte, and treatment using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to half the lower limit of quantitation (LLOQ).

Individual patient and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.

The following PK parameters will also be summarized by analyte and treatment using descriptive statistics: area under the concentration-time curve from time zero to time (AUC_{0-t}), area under the concentration-time curve from time of dosing up to 24 hours (AUC_{0-24}), area under the concentration-time curve from time zero to infinity (AUC_{0-inf}), area under the concentration-time curve from time 0 to the last available sampling time (AUC_{last}), area under the concentration-time curve extrapolated from time t to infinity as a percentage of the total AUC ($AUC_{\%extrap}$), oral clearance (CL/F), maximum concentration (C_{max}), time to reach C_{max} (T_{max}), terminal elimination rate constant (λ_z), and apparent terminal half-life ($t_{½}$).

Dose proportionality will be assessed by using a power model separately for the C_{max} and AUC_{last} separately for each applicable visit. In this model the log-transformed PK parameter of interest will be considered as the response variable and the log-transformed dose (i.e. 50, 75 and 100 mg) will be the only model covariate. The model will be fit using the following sample SAS code:

```
ods output parameterestimates = parms;
proc mixed data = <input-dataset> plots = none;
  by visit;
  model logaval = logdose / ddfm = kr;
run;
```

From the above model the slope estimate β will be derived alongside its 90% confidence interval, and dose proportionality will be met if the confidence intervals lie entirely within this range:

$$1 + \frac{ln(\Theta_L)}{\ln(r)} \; to \; 1 + \frac{ln(\Theta_H)}{\ln(r)}$$

Where r is the ratio between the largest and the smallest dose (= 100/50 = 2) and Θ_L and Θ_H are defined as 0.8 and 1.25 (similar to standard bioequivalence margins). As such the dose-proportionality range for the slope parameter is 0.678 to 1.322.

5.13 Safety Analyses

The safety analyses will be presented by treatment received for the Safety Analysis Set.

5.13.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are reported according to protocol as any AE that has an onset on or after the dose of study drug or any pre-existing condition that has worsened on or after the first dose of study drug through 14 days following last dose of study drug. The following TEAE flag will be applied to distinguish AEs from TEAEs:

- Any AE that has a start date and time on or after the first dose of study drug and before last dose of study drug + 14 days

A treatment-related AE is defined as an AE as being possibly related or related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs incidence and/or number of events will be reported as appropriate:

- Overall summary of AEs:
    - TEAEs
    - Treatment-related TEAEs
    - Treatment-emergent serious adverse events (TESAEs)
    - Treatment-related TESAEs
    - TEAEs by severity
    - TEAEs leading to study discontinuation
    - Deaths
- TEAEs by system organ class and preferred term
- Treatment related TEAEs by system organ class and preferred term
- TESAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term and maximum severity
- TEAEs by system organ class, preferred term and strongest relationship
- TEAEs leading to study discontinuation by system organ class and preferred term
- Listing of Serious AEs.
- Listing of Deaths.

Adverse event incidence is counted only once per system organ class and once per preferred term. The number and percent of patients experiencing events are reported. Outputs reported at maximum severity or strongest relationship show the highest severity/relationship reported by a patient per system organ class and preferred term.

In addition to the above summary tables, relative risks for the occurrence of any AE (i.e., at least 1 AE) during the course of the study as well as for each system organ class/preferred term will be estimated for each LB-102 dose vs placebo via a log-binomial regression model. For such analysis, the binary indicator for the presence of a given system organ class/preferred term (or any AE) will be used as response and the treatment group will be the only covariate, whose estimated regression coefficient will be exponentiated to return the associated relative risk, alongside their 95% CI and p-values. To such aim, the following sample SAS code will be used:

```
ods output estimates = rr;
proc genmod data = <input-dataset> descending;
  by aedecod aeterm;
  class subjid trt01an;
  model ae_binary = trt01an / dist = binomial link = log;
  estimate 'RR LB-102 50 mg vs. Placebo' trt01pn 1 0 0 -1 / exp alpha = 0.05;
  estimate 'RR LB-102 75 mg vs. Placebo' trt01pn 0 1 0 -1 / exp alpha = 0.05;
  estimate 'RR LB-102 100 mg vs. Placebo' trt01pn 0 0 1 -1 / exp alpha = 0.05;
run;
```

The above code assumes that the TRT01PN variable is ordered such that placebo is the last arm (i.e.TRT01PN = 4) and the others are sorted in ascending order, lowest to highest, and that AEDECOD and AETERM are the system organ class and preferred term variables, respectively.

All AEs will be listed.

5.13.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, urinalysis, chemistry, coagulation, and hormone (ACTH, TSH, cortisol) parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

A summary of the number of abnormal parameter values will also be provided. All laboratory data will be listed, with a separate listing only including abnormal (i.e. out of range) values.

5.13.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (degrees Celsius)
- Body weight (kg)

[redacted]

In addition, a separate table presenting BMI and waist circumference will also be provided. A listing will be provided including all measurements.

For blood pressure and pulse rate, the orthostatic changes will be calculated as standing minus sitting readings. At each visit, the number of patients meeting the criteria for orthostatic hypotension as described in Section 5.2.11 will be summarized. Orthostatic changes will be listed separately, including a flag to identify cases of hypotension.

5.13.4 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each follow-up:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation as provided by the central reader (Normal, Abnormal Not Clinically Significant (NCS), and Abnormal Clinically Significant (CS)) from baseline to each follow-up visit will be presented.

All ECG data, including details of any abnormalities, will be listed. For analysis purposes, the worst overall interpretation as recorded across triplicate assessments from the investigator will be reported. .

5.13.5 Physical Examination

The body systems within the physical examination data throughout the study will be summarized by treatment (Normal, Abnormal NCS, Abnormal CS). A shift table will be also presented, with shift from baseline to each post-baseline visit.

All PE data will also be listed.

5.13.6 Placebo-Control Reminder Script (PCRS)

Date and time of administration of the PCRS will be listed only.

5.13.7 C-SSRS

Suicidal ideation and suicidal behavior as measured by the C-SSRS will be summarized using frequencies and percentages by treatment group and timepoint. All C-SSRS data will also be listed.

[redacted]

[redacted]

5.13.8 Simpson-Angus Scale (SAS)

Observed and change from Baseline values for the SAS will be provided by treatment group. Total scores as well as individual question responses and scores will be listed.

5.13.9 Abnormal Involuntary Movement Scale (AIMS)

Observed and change from Baseline values for the AIMS will be provided by treatment group. Total scores as well as individual question responses and scores will be listed.

5.13.10 Barnes Akathisia Rating Scale (BARS)

Observed and change from Baseline values for the BARS will be provided by treatment group. Total scores as well as individual question responses and scores will be listed.

5.13.11 Pregnancy Test

Serum and urine pregnancy test data will be listed only.

6 INTERIM ANALYSIS

No interim analyses are planned.

7 DATA AND SAFETY MONITORING BOARD ANALYSIS

No DSMB is planned for this study. A Safety Review Committee (SRC) has been established to review ongoing safety data, and details for this are provided in a separate reporting plan.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

The following changes were made compared to the protocol:

- Primary Estimand (Section 2.3): 'Treatment Discontinuation prior to Week 4' is no longer a relevant ICE and as such it has been removed from the estimand definition (see Table 1 and Table 2)
- Primary Estimand (Section 2.3): the primary analysis set has been changed to the ITT analysis set, with the caveat that should there be a substantial overlap with the mITT, the latter will instead be used as primary analysis set.
- Analysis Sets (Section 5.1): the PP Analysis Set and all associated analyses and summaries have been removed as non-informative.
- Site effect (Section 5.11.4.2): the rules for pooling study sites for analysis purposes have been slightly modified and the provision to formally test interactions has been removed (only summaries will be produced).
- Adverse Events (Section 5.13.1): the Poisson regression was changed to a log-binomial regression due to convergence and estimation issues observed when initially fitting the model,

[redacted]

[redacted]

due to data sparsity (i.e. SOCs/PTs with 0 subjects across most treatment arms showing the event).

[redacted]

9 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA Phoenix™ WinNonlin® (Version 8.3.4 or higher, Certara, L.P.)
2. SAS Institute Inc., Cary, NC, 27513, USA
3. Little RJA, Rubin DB. Statistical analysis with missing data. Third edition. Hoboken, NJ: Wiley; 2020.

10 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Patient Disposition – ITT Analysis Set	IP	
14.1.1.2	Screen Failures – Screened Set	IP	
14.1.1.3	Analysis Sets – ITT Analysis Set	IP	
14.1.1.4	Visit Attendance – Safety Analysis Set	IP	
14.1.1.5	Protocol Deviations – Safety Analysis Set	IP	
14.1.2	**Demographics**		
14.1.2	Demographics - Safety Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1	Previous Medical History – Safety Analysis Set	IP	
14.1.3.2	Medical History Ongoing at Screening – Safety Analysis Set	IP	14.1.3.1
14.1.3.3	Prior Medications – Safety Analysis Set	IP	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Primary Analysis – ITT Analysis Set	Stat IP	
14.2.1.2	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Supportive Analysis – mITT Analysis Set	Stat IP	14.2.1.1
14.2.1.3	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Sensitivity Analysis #1 (Re-mapped ET Assessments) – ITT Analysis Set	Stat IP	14.2.1.1
14.2.1.4	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Sensitivity	Stat IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Analysis #2 (Tipping-Point Analysis) – ITT Analysis Set		
14.2.1.5	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Sensitivity Analysis #3 (Copy-Reference Imputation) – ITT Analysis Set	Stat IP	
14.2.1.6	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, by Baseline BMI – ITT Analysis Set	Stat IP	
14.2.1.7	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, by Baseline PANSS – ITT Analysis Set	Stat IP	14.2.1.6
14.2.1.8	Primary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Total Score, Site Effect – ITT Analysis Set	Stat IP	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1.1	Secondary Efficacy Endpoint, Change from Baseline to Week 4 in the CGI-S Score – ITT Analysis Set	Stat IP	14.2.1.1
14.2.2.1.2	Secondary Efficacy Endpoint, Proportion of CGI-S Score Responders– ITT Analysis Set	Stat IP	
14.2.2.2	Secondary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Positive Subscale Score – ITT Analysis Set	Stat IP	14.2.1.1
14.2.2.3	Secondary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Negative Subscale Score – ITT Analysis Set	Stat IP	14.2.1.1
14.2.2.4	Secondary Efficacy Endpoint, Change from Baseline to Week 4 in the PANSS Marder Factor Scores – ITT Analysis Set	Stat IP	
14.2.2.5.1	Secondary Efficacy Endpoint, Proportion of PANSS Responders at Week 4 (Main Analysis) – ITT Analysis Set	Stat IP	
14.2.2.5.2	Secondary Efficacy Endpoint, Proportion of PANSS Responders at Week 4 (Sensitivity Analysis) – ITT Analysis Set	Stat IP	14.2.2.5.1
14.2.3	**Exploratory Endpoints**		
14.2.3	Exploratory Efficacy Endpoint, Change from Baseline to Week 4 in CogState Tests Total Scores – ITT Analysis Set	Stat IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events – Safety Analysis Set	IP	
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set	IP	
14.3.1.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Poisson Regression – Safety Analysis Set	Stat IP	
14.3.1.4	Treatment Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.1.5	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.1.6	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Severity – Safety Analysis Set	IP	
14.3.1.7	Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Strongest Relationship – Safety Analysis Set	IP	
14.3.1.8	Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Analysis Set	IP	14.3.1.2
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Deaths – Safety Analysis Set	IP	
14.3.2.2	Serious Adverse Events – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4	Abnormal Laboratory Values – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.5.1	Treatment Exposure – Safety Analysis Set	IP	
14.3.5.2	Treatment Compliance – Safety Analysis Set	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs – Safety Analysis Set	IP	
14.3.6.2	BMI and Waist Circumference – Safety Analysis Set	IP	14.3.6.1

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.6.3	Incidence of Orthostatic Hypotension – Safety Analysis Set	IP	
14.3.6.4	Physical Examination – Safety Analysis Set	IP	
14.3.6.5	Shift Table of Physical Examination to Day 28 – Safety Analysis Set	IP	
14.3.7	**Other Safety**		
14.3.7.1	Hematology – Safety Analysis Set	IP	14.3.6.1
14.3.7.2	Shift Table of Hematology – Safety Analysis Set	IP	
14.3.7.3	Chemistry – Safety Analysis Set	IP	14.3.6.1
14.3.7.4	Shift Table of Chemistry – Safety Analysis Set	IP	14.3.7.2
14.3.7.5	Urinalysis – Safety Analysis Set	IP	
14.3.7.6	Coagulation – Safety Analysis Set	IP	14.3.6.1
14.3.7.7	Hormones – Safety Analysis Set	IP	14.3.6.1
14.3.7.8	12-Lead ECG – Safety Analysis Set	IP	
14.3.7.9	Shift Table of 12-Lead ECG – Safety Analysis Set	IP	
14.3.7.10	Columbia – Suicidal Severity Rating Scale (C-SSRS) – Safety Analysis Set	IP	
14.3.7.11	Summary of Simpson-Angus Scale (SAS) Total Score – Safety Analysis Set	IP	
14.3.7.12	Summary of Abnormal Involuntary Movement Scale (AIMS) Total Score – Safety Analysis Set	IP	14.3.7.11
14.3.7.13	Summary of Barnes Akathisia Rating Scale (BARS) Global Score – Safety Analysis Set	IP	14.3.7.11
14.3.8	**Concomitant Medication**		
14.3.8	Concomitant Medications by ATC Level 2 and Preferred Name – Safety Analysis Set	IP	14.1.3.3
14.4	**PK Tables**		
14.4.1	Serum Concentrations, Descriptive Statistics – Pharmacokinetic Analysis Set	IP	
14.4.2	PK Parameters, Descriptive Statistics – Pharmacokinetic Analysis Set	IP	
14.4.3	Dose-Proportionality, Power Model Analysis – Pharmacokinetic Analysis Set	Stat IP	
14.5	**PD Tables**		
14.6	**Other Data**		

[redacted]

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1	Primary Efficacy Endpoint, Line Plot of LS Means of Change from Baseline in PANSS Total Score – ITT Analysis Set	Stat IP	
14.2.1.2	Primary Efficacy Endpoint, Line Plot of LS Means of Change from Baseline in PANSS Total Score – mITT Analysis Set	Stat IP	14.2.1.1
14.2.1.3	Primary Efficacy Endpoint, Change from Baseline in PANSS Total Score at Week 4, Forest Plot of Subgroups Analysis – ITT Analysis Set	Stat IP	
14.4	**PK Data**		
14.4.1	Serum Concentrations, Mean Profiles on Linear Scale – Pharmacokinetic Analysis Set	IP	
14.4.2	Serum Concentrations, Mean Profiles on Semi-Logarithmic Scale – Pharmacokinetic Analysis Set	IP	
14.4.3	Serum Concentrations, Individual Profiles on Linear Scale – Pharmacokinetic Analysis Set	IP	
14.4.4	Serum Concentrations, Individual Profiles on Semi-Logarithmic Scale – Pharmacokinetic Analysis Set	IP	

[redacted]

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Patient Data Listings**		
16.2.1	**Discontinued Patients**		
16.2.1.1	Patient Disposition – ITT Analysis Set	IP	
16.2.1.2	Screen Failures – Screened Set	IP	
16.2.1.3	Visit Attendance – Safety Analysis Set	IP	
16.2.2	**Protocol Deviations**		
16.2.2	Protocol Deviations – Safety Analysis Set	IP	
16.2.3	**Patients Excluded from The Efficacy Analyses**		
16.2.3	Analysis Sets – ITT Analysis Set	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographics – Safety Analysis Set	IP	
16.2.4.2	MINI 7.0.2 and BPD Module – Safety Analysis Set	IP	
16.2.4.3	Serology – Safety Analysis Set	IP	
16.2.4.4	Previous Medical History – Safety Analysis Set	IP	
16.2.4.5	Medical History Ongoing at Screening – Safety Analysis Set	IP	
16.2.4.6	Inclusion Criteria – Failures – Safety Analysis Set	IP	
16.2.4.7	Exclusion Criteria – Failures – Safety Analysis Set	IP	
16.2.4.8	Prior Medications – Safety Analysis Set	IP	
16.2.4.9	Concomitant Medications – Safety Analysis Set	IP	16.2.4.8
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Study Drug Administration – Safety Analysis Set	IP	
16.2.5.2	Treatment Compliance – Safety Analysis Set	IP	
16.2.5.3	PK Concentration Data – Pharmacokinetic Analysis Set	IP	
16.2.5.4	PK Parameters – Pharmacokinetic Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Positive and Negative Symptoms Scale (PANNS) – ITT Analysis Set	IP	
16.2.6.2	Clinician Global Impression-Severity (CGI-S) – ITT Analysis Set	IP	
16.2.6.3	CogState Tests – ITT Analysis Set	IP	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Events – Safety Analysis Set	IP	
16.2.7.2	Adverse Events Leading to Study Discontinuation – Safety Analysis Set	IP	16.2.7.1
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Abnormal Laboratory Values – Safety Analysis Set	IP	
16.2.8.2	Hematology – Safety Analysis Set	IP	
16.2.8.3	Chemistry – Safety Analysis Set	IP	16.2.8.2

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.4	Urinalysis – Safety Analysis Set	IP	16.2.8.2
16.2.8.5	Coagulation – Safety Analysis Set	IP	16.2.8.2
16.2.8.6	Hormones – Safety Analysis Set	IP	
16.2.8.7	Pregnancy Test – Safety Analysis Set	IP	
16.2.8.8	12-Lead ECG – Safety Analysis Set	IP	
16.2.8.9	Vital Signs – Safety Analysis Set	IP	
16.2.8.10	Orthostatic Vital Signs – Safety Analysis Set	IP	
16.2.8.11	Physical Examination – Safety Analysis Set	IP	
16.2.8.12	Placebo-Control Reminder Script (PCRS) – Safety Analysis Set	IP	
16.2.8.13	Columbia – Suicidal Severity Rating Scale (C-SSRS) – Safety Analysis Set	IP	
16.2.8.14	Simpson-Angus Scale (SAS) – Safety Analysis Set	IP	
16.2.8.15	Abnormal Involuntary Movement Scale (AIMS) – Safety Analysis Set	IP	
16.2.8.16	Barnes Akathisia Rating Scale (BARS) – Safety Analysis Set	IP	