CLINICAL STUDY PROTOCOL

PROTOCOL 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
STUDY NUMBER:	[redacted]
IND NUMBER:	137581
SPONSOR:	LB Pharmaceuticals Inc 575 Madison Avenue New York, NY 10022 Phone: (646) 588-8175
ORIGINAL PROTOCOL VERSION AND DATE:	Final Version 1.0, 17 July 2023
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NCT#	NCT06179108

CONFIDENTIAL

SPONSOR APPROVAL FORM

Protocol 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

Study No: [redacted]

Original Protocol Version and Date: Version 1.0, 17 July 2023

Previous Protocol Version and Date: Version 2.0, 23 Nov 2023

Amended Protocol Version and Date: Version 3.0, 08 February 2024

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the study drug. Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Signature	*Date (DD/MMM/YYYY)*
[redacted]	

Signature	*Date (DD/MMM/YYYY)*
[redacted]	

Signature	*Date (DD/MMM/YYYY)*
[redacted]	

[redacted]

Signature *Date (DD/MMM/YYYY)*

Investigator Name (printed) *Site Number*

STUDY SYNOPSIS

Protocol 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

Study Number: [redacted]

Clinical Phase: Phase 2

Investigator(s)/ Study Center(s): This study will [redacted] will oversee operational aspects of this study on behalf of LB Pharmaceuticals Inc, the Sponsor of the study.

Objectives: The objectives of this study are as follows:

Primary 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 Positive and Negative Syndrome Scale (PANSS) total score, compared to placebo.

Secondary Objectives

- 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.

Exploratory Objectives

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

Study Design: This is a Phase 2 randomized, double-blind, placebo-controlled, fixed dose, multicenter study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of LB-102 50 mg once daily (QD), LB-102 75 mg QD, and LB-102 100 mg QD versus placebo QD for

the treatment of adult patients with an acute exacerbation of schizophrenia. [redacted] patients will be randomized to receive 1 of 4 study treatments in a 3:3:3:1 ratio: placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg for 28 days.

- Placebo group [redacted]
- LB-102 50 mg group [redacted]
- LB-102 75 mg group [redacted]
- LB-102 100 mg group [redacted]

Re-screening may be permitted on a case-by-case basis with the approval of LB Pharmaceuticals Inc and Medical Monitors.

Study participation will last approximately 8 weeks and includes a 7-day inpatient screening phase (up to a 7-day extension of the screening phase is allowed, if necessary, with the approval of the Medical Monitor), 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.

Duration of Treatment: 28-day inpatient Study Treatment Period.

Planned Sample Size: [redacted] patients will be randomized into the study.

Target Population: The patient population will include males and females, 18 to 55 years of age with a current diagnosis of schizophrenia as defined by criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and confirmed by the Mini International Neuropsychiatric Interview version 7.0.2 (MINI 7.0.2) for Schizophrenia and Psychotic Disorders, with a total PANSS score between 80 and 120 inclusive, and a score of ≥4 (moderate or greater) for ≥2 or more of the following Positive Scale (P) items: Item 1 (P1; delusions), Item 2 (P2; conceptual disorganization), Item 3 (P3; hallucinatory behavior), Item 6 (P6; suspiciousness/persecution), and a score of ≥4 on the CGI-S. Eligible patients will include those who would benefit from hospitalization or continued hospitalization for the treatment of a current acute exacerbation of psychotic symptoms (defined as 6 weeks prior to Screening).

Eligibility Criteria: **Inclusion Criteria**

Patients will be eligible for inclusion in the study if they meet all of the following criteria:

1. Patient, who is able to provide written informed consent (as required by Institutional Review Board [IRB]) prior to the initiation of any protocol-required procedures. Ability, in the opinion of the Principal Investigator (PI), to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medication, and to be reliably rated on assessment scales.

2. Must be willing to be hospitalized for the duration of the inpatient period of the study, and willing to comply with instructions from the Investigator and study staff.

3. Have stable living environment when not in a hospital, as demonstrated by the ability to provide contact information for themselves or family/friend(s)/caregiver(s).

4. Male and female patients 18 to 55 years of age inclusive at the time of informed consent with a diagnosis of schizophrenia as defined by DSM-5 criteria and confirmed by the MINI 7.0.2 for Schizophrenia and Psychotic Disorders Studies.

5. Body mass index (BMI) must be ≥18 and ≤40 kg/m^2.

6. Patient who is:

   - experiencing an acute exacerbation of psychotic symptoms, with onset ≤6 weeks before Screening AND the patient requires hospitalization for this acute exacerbation of psychotic symptoms.

   OR

   - if already an inpatient at Screening, has been hospitalized for onset ≤2 weeks for the current exacerbation.

7. Patients who are experiencing an acute exacerbation of psychotic symptoms and marked deterioration of usual function as demonstrated by meeting ALL of the following criteria at the Screening and Baseline visits:

   - Total PANSS score between 80 and 120, inclusive, and

- Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items: Item 1 (P1; delusions), Item 2 (P2; conceptual disorganization), Item 3 (P3; hallucinatory behavior), Item 6 (P6; suspiciousness/persecution), and

- CGI-S score ≥4 (moderately to severely ill).

8. Have received previous antipsychotic treatment (dose and duration as per the label) and who showed a previous good response to such antipsychotic treatment (other than clozapine) in the last 12 months, according to the Investigator's opinion.

9. Have history of relapse and/or exacerbation of symptoms when they were not receiving antipsychotic treatment, according to the Investigator's opinion.

10. Patients willing to discontinue all prohibited psychotropic medications prior to Screening, if determined to be clinically appropriate by the Investigator, and not for the sole purpose of inclusion in the trial.

Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

Sex and Reproductive Status

1. Sexually active females of childbearing potential and male patients who are not practicing 2 different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who would not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use 2 of the following precautions: oral contraceptives, patch contraceptives, injection contraceptives, implantable hormonal contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the patient's current practice. Contraceptive requirements do not apply to patients who are in same sex relationship, who are medically or surgically sterilized (e.g., bilateral tubal ligation, bilateral oophorectomy, hysterectomy); or practice sexual abstinence during this study.

2. Females who are breastfeeding or who have a positive pregnancy test result prior to receiving trial medication.

Target Disease

3. Patients who presented with a first episode of schizophrenia based on the clinical judgment of the Investigator and patients with diagnosed schizophrenia equal to or less than a year.

4. Improvement of ≥20% in total PANSS score between the Screening and Baseline assessments.

5. History of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (dose and duration as per the label) or required clozapine within the last 12 months.

6. Current DSM-5 Axis I diagnosis other than schizophrenia including, but not limited to, schizoaffective disorder, major depressive disorder, bipolar disorder, post-traumatic stress disorder, anxiety disorders, delirium, dementia, amnestic or other cognitive disorders, as determined by the MINI 7.0.2. Also, patients with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder, as determined by the MINI 7.0.2 and Mini International Neuropsychiatric Interview with Borderline Personality Disorder Module version 7.0.2 (MINI-Plus BPD 7.0.2).

7. Risk for suicidal behavior during the study as determined by the Investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS) as confirmed by the following: answers "Yes" on items 4 or 5 (C-SSRS – Ideation) with the most recent episode occurring within the 6 months before Screening, or answers "Yes" to any of the 5 items (C-SSRS – Suicidal Behavior) with an episode occurring within the 12 months before Screening. This assessment will be repeated at Baseline Visit (at baseline "Since Last Visit" version of the CSSR-S scale should be used). Non-suicidal self-injurious behavior is not exclusionary.

8. Risk of violent or destructive behavior based on the Investigator's opinion and homicidal ideation based on responses to SCI- PANSS interview questions or statements made by the patient at any other times during the Screening or Baseline visits.

9. Patients with clinically significant tardive dyskinesia determined by a score of ≥3 on Item 8 of the Abnormal Involuntary Movement Scale (AIMS) at Screening.

10. Patients with a score of ≥3 on the Barnes Akathisia Rating Scale (BARS) global clinical assessment of akathisia at Screening.

Medical History and Concurrent Diseases

11. Patients who met DSM-5 criteria for substance abuse or dependence within the past 1 year, including alcohol and benzodiazepines, but excluding caffeine and nicotine. Previous occasional use of alcohol or cannabis is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to Screening, and the use of alcohol or cannabis is not considered to be the precipitating factor of the current psychotic episode in the opinion of the Investigator; subjects are required to abstain from alcohol and cannabis use during the trial.

12. Patients with hypothyroidism or hyperthyroidism (unless the condition had been stabilized with medications for at least the past 90 days) and/or clinically significant abnormal thyroid function (abnormal thyroid-stimulating hormone [TSH] levels followed by free T3 and T4 levels), as assessed by the Investigator, in discussion with the study Medical Monitor.

13. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results. Positive result at Screening for hepatitis B surface antigen (HbsAg), hepatitis C virus, or human immunodeficiency virus- (HIV)-1 or -2. Patients with chronic hepatitis B or hepatitis C may be included after discussion with the Medical Monitor provided that their condition is stable and values for liver function test meet the specified criteria of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2 × upper limit of normal (ULN). The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation.

14. Patients with insulin-dependent diabetes mellitus (i.e., any patient using insulin) are excluded. Patients with non-insulin-dependent diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:

    - Glycosylated hemoglobin (HbA1c) <7.0%, and

- Screening glucose must have been ≤125 mg/dL or ≤6.94 mmol/L (fasting) or <200 mg/dL or <11.1 mmol/L (non-fasting). If the non-fasting Screening glucose was ≥200 mg/dL or ≥11.1 mmol/L, patients must have been retested in a fasted state and the retest value must have been ≤125 mg/dL or ≤6.94 mmol/L, and

- Patient had been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to Screening or diabetes had been well controlled by diet for at least 28 days prior to Screening, and

- Patient had no hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, and

- Patient's diabetes should not be newly diagnosed during Screening for the trial.

15. Patients with uncontrolled hypertension (diastolic blood pressure [DBP] >95 mmHg or systolic blood pressure [SBP] >145 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension defined as a decrease of ≥20 mmHg in SBP and/or a decrease of ≥10 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, OR development of symptoms. NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a patient based on the criteria noted above.

16. Patients with known ischemic heart disease or any history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery.

17. Patients with epilepsy or a history of seizures (with the exception of febrile seizure).

Physical and Laboratory Results

18. Patients with a positive urine drug screen or a positive blood alcohol test. Detectable levels of marijuana, barbiturates, benzodiazepines or opiates in the drug screen are not exclusionary if, in the Investigator's documented opinion, the patient does not meet DSM-5 criteria for substance abuse or

dependence, in the Investigator's documented opinion, the positive test does not signal a clinical condition that would impact the safety of the patient or interpretation of the trial results, and approval was granted by the Medical Monitor prior to treatment.

19. Patients with a history of alcohol use disorder, substance use disorder (by DSM-5 criteria) within 12 months of Screening or a positive screen for drugs of abuse at Screening (unless consistent with current prescription for medical condition).

20. The following laboratory test results are exclusionary:

    - Platelets ≤75,000/μL or ≤75×10^9/L
    - Hemoglobin ≤9 g/dL or ≤90 g/L
    - Neutrophils, absolute ≤1000/μL or ≤1×10^9/L
    - AST >2 × ULN
    - ALT >2 × ULN
    - Creatine phosphokinase >3 × ULN, unless discussed with and approved by the Medical Monitor
    - Creatinine ≥2 mg/dL or ≥176.8 μmol/L
    - Estimated neytrine clearance of <45 mL/min, calculated using the Cockcroft-Gault equation, at Screening
    - HbA1c ≥7.0%
    - Abnormal free T4 (during Screening), unless discussed with and approved by the Medical Monitor (Note: Free T4 will be measured only if the result for TSH is abnormal).

21. Clinically significant abnormal finding on the triplicate set of electrocardiograms (ECGs) or evidence of any of the following cardiac conduction abnormalities at Screening (mean values will be used for the following criteria):

    - Heart rate <40 beats per minute (bpm) and >110 bpm (based on the ECG reading). NOTE: The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation

- Interval between Q and T wave corrected for heart rate using Fridericia's formula (QTcF) interval >450 msec for males and females
- PR interval ≥200 msec
- Intraventricular conduction delay with QRS duration >120 msec
- Evidence of second- or third-degree atrioventricular block
- Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB

Prohibited Therapies or Medications

22. Patients who are currently taking oral antipsychotic medications, monoamine oxidase inhibitors (MAOIs), anticonvulsants (e.g., lamotrigine, Depakote), tricyclic antidepressants (e.g., imipramine, desipramine), selective serotonin reuptake inhibitors, and any other antidepressants or any other psychoactive medications (except lorazepam, zolpidem, zaleplon, eszopiclone, or similar benzodiazepines, diphenhydramine, benztropine, and propranolol). Patients taking prohibited psychotropic medications may be eligible for inclusion in the study if it is clinically appropriate to discontinue the medication before the Baseline Visit (in the opinion of the Investigator). The prohibited psychotropic agent must be discontinued and washed out at least 5 half-lives prior to Baseline. Subjects taking a depot antipsychotic could not have received a dose of medication for at least 1 and a half injection cycles before Baseline. The medications should not be discontinued solely to make the patient eligible for enrollment in the study.

23. Patients who received electroconvulsive therapy within 90 days of Screening.

24. Patients who received Transcranial Magnetic Stimulation (TMS) within 90 days of Screening.

Allergies and Adverse Drug Reactions

25. Patients with a history of neuroleptic malignant syndrome.

26. Patients with a history of allergic response (defined as hypersensitivity reactions such as flushing, rash, wheezing,

abdominal cramps, hypotension, seizure, etc., not intolerance) to more than 1 class of medications.

Others

27. Prisoners or patients who were compulsorily detained (involuntarily hospitalized) for treatment of either a psychiatric or physical illness or have been in the last 6 months prior to the Screening Visit must not be enrolled into this study.

28. Patients who have participated in another clinical study in which they received an experimental or investigational drug agent within 3 months of Screening.

Study Drug(s): [redacted] patients will be randomized to receive 1 of 4 study treatments in a 3:3:3:1 ratio: placebo, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD for 28 days. LB-102 and placebo will be administered as visually matched tablets for the treatment of adult patients with an acute exacerbation of schizophrenia[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Primary Endpoint: The primary endpoint is the change from Baseline to Week 4 in the PANSS total score, compared to placebo

Secondary Endpoints: Secondary efficacy endpoints will be as follows:

- 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

Exploratory Endpoint:

- Effect of LB-102 on Cogstate test score

Safety Outcome Measures:

Safety will be assessed by the following:

- AE reporting
- Physical examination
- Vital signs
- Body weight, 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), HbA1c, cortisol, adrenocorticotropic hormone (ACTH), TSH and total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)
- 12-lead ECGs
- Assessments of extrapyramidal side effects (EPS): the Simpson-Angus Scale (SAS), the AIMS, the BARS
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetic Analyses

PK analyses [redacted] randomized in the study regardless of cohort. PK blood samples will be collected on Day 1, 8, and 21 at the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours. On Day 1 only, a pre-dose PK blood sample will be collected.

Statistical Procedures:

[redacted]

[redacted] The sample size was estimated via Monte Carlo simulations using 10,000 simulated trials.

A formal and detailed statistical data analysis plan will be prepared before database lock. The primary endpoint will be the change from Baseline to Week 4 on the PANSS total score. Formal statistical testing for comparison of the LB-102 50 mg and 75 mg treatment groups to placebo will be performed for the primary endpoint only, using appropriate procedures for multiplicity adjustment. In addition, descriptive statistics for safety, efficacy, and PK variables will be provided for all treatment groups. Shift tables for safety parameters will be prepared for appropriate categorical variables and change from Baseline and effect sizes will be calculated for efficacy measures.

The primary efficacy analysis will be performed using a Mixed Model for Repeated Measures (MMRM) using the modified Intent-to-Treat population as analysis set. The model will include treatment, site, visit, and treatment by visit interaction as categorical covariates and Baseline PANSS as continuous covariate. Within-patient correlation will be accounted for using an unstructured correlation. A similar model will be considered for continuous secondary endpoints. The response rate endpoint will be analyzed using a logistic regression model with treatment as categorical covariate and Baseline PANSS total score as continuous covariate.

Safety: Safety variables to be examined in this study will include AEs, physical examinations, vital signs, body weight, BMI (derived programmatically from body weight and height measurements), waist circumference, clinical laboratory tests (hematology, serum chemistry [including prolactin]), urinalysis, pregnancy tests, PT, aPTT, INR, HbA1c, cortisol, ACTH, TSH, total cholesterol, triglycerides, HDL, and LDL, ECGs, and an evaluation of extrapyramidal symptoms using the SAS, AIMS, and BARS. The C-SSRS will be used to assess and classify reported suicidal behavior.

Pharmacokinetics: Plasma concentrations of LB-102 [redacted] will be measured during the study and PK parameters derived using noncompartmental or compartmental methods as appropriate. The following PK parameters (as appropriate) will be calculated: 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 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 ($t_{½}$).

No value for λ_z, $AUC_{0\text{-inf}}$, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for patients with no detectable concentrations for 2 or fewer time points.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

PK parameters of LB-102 and metabolites will be summarized by cohort using descriptive statistics (sample size, arithmetic means, geometric means, SD, % coefficient of variation, minimum, median, and maximum). Figures will be created to display mean and individual patient LB-102 [redacted] Dose proportionality will be assessed using linear regression, or another acceptable approach.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
$5HT_7$	5-hydroxytryptamine (serotonin) receptor 7
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-12}	area under the concentration-time curve from time of dosing up to 12 hours
AUC_{0-24}	area under the concentration-time curve from time of dosing up to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to time
$AUC_{\%extrap}$	area under the concentration-time curve extrapolated from time t to infinity as a percentage of the total AUC
AVB	atrioventricular block
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BPD	Borderline Personality Disorder
bpm	beats per minute
CGI-S	Clinical Global Impressions-Severity of Illness scale
CI	confidence interval
CL/F	oral clearance
CLss/F	apparent clearance at steady state
C_{max}	maximum concentration
C_{min}	minimum concentration

Abbreviation	Definition
CMO	chief medical officer
CPK	creatine phosphokinase
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome p450
d	day(s)
D_2	dopamine receptor 2
D_3	dopamine receptor 3
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EPS	extrapyramidal side effects
EoS	end of study
EoT	end of treatment
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour(s)
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Integrated response technology
ITT	intent-to-treat
IU	international units
IXRS	interactive response system
[redacted]	[redacted]
LBBB	left bundle branch block
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LS	least squares
λ_z	terminal elimination rate constant
MAD	multiple ascending doses
MAR	Missing At Random
MD	medical doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute(s)
MI	Multiple Imputation
MINI 7.0.2	Mini International Neuropsychiatric Interview version 7.0.2
MINI-Plus 7.0.2	Mini International Neuropsychiatric Interview-Plus version 7.0.2
MINI-Plus BPD 7.0.2	MINI International Neuropsychiatric Interview with Borderline Personality Disorder Module version 7.0.2
mITT	modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
MTD	maximum tolerated dose
ng/mL	nanogram per milliliter
OTC	over-the-counter
PANSS	Positive and Negative Syndrome Scale
PCRS	Placebo-Control Reminder Script
PD	protocol deviation
PET	positron emission tomography
PhD	Doctor of Philosophy

Abbreviation	Definition
PI	Principal Investigator
PK	pharmacokinetic
PP	per-protocol
PR	interval between the beginning of the P wave and the beginning of the next QRS complex
PT	prothrombin time
QD	once daily
QRS	duration of ventricular depolarization and contraction interval
QT	interval between Q and T wave
QTcF	interval between Q and T wave corrected for heart rate using Fridericia's formula
RAUC	ratio AUC after the first and last dose
RBBB	right bundle branch block
RBC	red blood cells
RC_{max}	accumulation ratio based on C_{max} after the first dose and last dose
RO	receptor occupancy
RR	interval between 2 R waves on the electrocardiogram tracing
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SBP	systolic blood pressure
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SD	standard deviation
SGAs	second generation antipsychotics
SoA	schedule of assessments
SOC	system organ class
SOP	standard operating procedure
SRC	Safety Review Committee
SS	steady state
$t_{½}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TSH	thyroid-stimulating hormone

Abbreviation	Definition
ULN	upper limit of normal
UK	United Kingdom
US	United States
VCT	Verified Clinical Trials
WBC	White blood cells
[redacted]	[redacted]

1 INTRODUCTION AND RATIONALE

1.1 Background

Schizophrenia is a chronic and debilitating mental illness that affects approximately 1% of the population. Hallucinations and delusions are the most striking characteristic positive symptoms of schizophrenia; however, more subtle negative symptoms (e.g., social withdrawal and lack of emotion, energy, and motivation) may also be present. Patients with schizophrenia have a 3.5 times higher rate of mortality compared to the general population.[1] A study in 2013 of over 6 million Swedish adults (including 8300 patients with schizophrenia) found that females and males with schizophrenia died 12 and 15 years earlier than their counterparts in the general population, respectively.[1] Schizophrenia patients suffer a profoundly reduced quality of life and are 10 times more likely to commit suicide than the general population.[1] Half of the suicides among patients with schizophrenia occur within the first 2 years of disease onset,[1] pointing to the urgency for behavioral and pharmaceutical intervention. Schizophrenia is a lifelong disease for the majority of patients. The course of schizophrenia is highly variable with periods of psychosis and stabilization of varying duration and intensity. Sustained remission of both positive and negative symptoms occurs in a minority of patients even with prolonged antipsychotic therapy. Many patients, even when stable, suffer disability due to the cognitive impairments that occur despite adequate antipsychotic therapy. Compliance with long-term medication is a significant problem due to dissatisfaction with antipsychotic side effects or self-discontinuation of medication as a result of feeling better and no longer perceiving the need for continuous medication. Both of these issues contribute to relapse among schizophrenia patients.[1]

1.2 Current Treatment Options for Schizophrenia

There are currently 26 Food and Drug Administration (FDA) approved drugs to treat schizophrenia, all of which rely on dopamine inhibition to at least a degree. Despite the plethora of approved drugs most schizophrenia patients do not experience adequate resolution of their symptoms and switching medication or, worse, going off medication is common. Common side effects of schizophrenia drugs include extrapyramidal side effects (EPS), interval between Q and T wave (QT) prolongation, sedation, and weight gain. In preclinical and clinical studies LB-102 demonstrated greater dopamine receptor occupancy (RO) than equivalent doses of [redacted] which could translate into a better tolerated drug.

1.3 Background on LB-102

LB-102 [redacted] was designed to be an improved version of the safe and effective benzamide antipsychotic [redacted] increasing its permeability across the blood-brain-barrier.[1] This potentially decreases the plasma concentrations needed to achieve efficacy, thereby decreasing the magnitude and frequency of adverse events (AEs) typically observed in patients treated with [redacted].[1] In vitro studies have confirmed that [redacted] (LB-102) is better able than [redacted] to passively penetrate a Parallel Artificial Membrane Permeability Assay membrane and exhibits similar activity and selectivity toward central nervous system receptors (dopamine receptor 2 [D_2], dopamine receptor 3 [D_3], and 5-hydroxytryptamine (serotonin) receptor 7 [$5HT_7$]) [redacted].[1] In vivo studies have demonstrated that LB-102 has a

favorable pharmacokinetic (PK) profile in rats and mice, [redacted] as well as a similar [redacted] (apomorphine induced climbing, novel object recognition, and locomotor activity) covering 3 aspects of schizophrenia.[1]

In summary, LB-102 is a proprietary molecule having similar physicochemical and biological characteristics equivalent to or better than [redacted], an antipsychotic with an established decades-long clinical track record.

1.4 Summary of Clinical Experience, Pharmacology, and Safety

LB-102 was well tolerated with all treatment-emergent adverse events (TEAEs) either mild or moderate severity in a Phase 1, randomized double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and PK of LB-102 in healthy volunteers. The most notable safety result was mildly elevated prolactin levels, which was expected to occur based on LB-102's mechanism of action as a dopamine antagonist and that it is a commonly reported AE for drugs of this class.[1] At the highest dose ([redacted] LB-102) minor interval between Q and T wave corrected for heart rate using Fridericia's formula (QTcF) prolongation was noted; however, predefined QT stopping criteria were not reached. In addition, a single incidence of acute dystonia was observed at [redacted] LB-102 once daily (QD) as well as a single incidence at ~~75 mg~~ [redacted] LB-102 BID. There were no serious adverse events (SAEs) during the course of the study. The Columbia-Suicide Severity Rating Scale (C-SSRS) score did not change during study treatment[redacted]-Study LB-102-001 achieved its objectives of identifying the safety, tolerability, and PK of a single oral dose and multiple oral doses of LB-102 in healthy volunteers.

LB-102 was rapidly absorbed and LB-102 concentration generally declined from peak in an apparent biphasic manner. Exposure increased in a slightly greater than dose-proportional manner. Apparent clearance appeared to decrease as dose increased. Minor (as defined by the FDA)[1] amounts [redacted], approximately 2.5% of LB-102, were detected in plasma samples. The plasma concentrations [redacted] at lower doses were within several fold of lower limit of quantification (LLOQ) making descriptive PK analysis tenuous. For PK results in Part B (multiple ascending doses [MAD]), trough concentrations of LB-102 [redacted] plateaued before the morning dose on Day 4. After multiple doses, there was slight to moderate accumulation of LB-102 across dose levels.

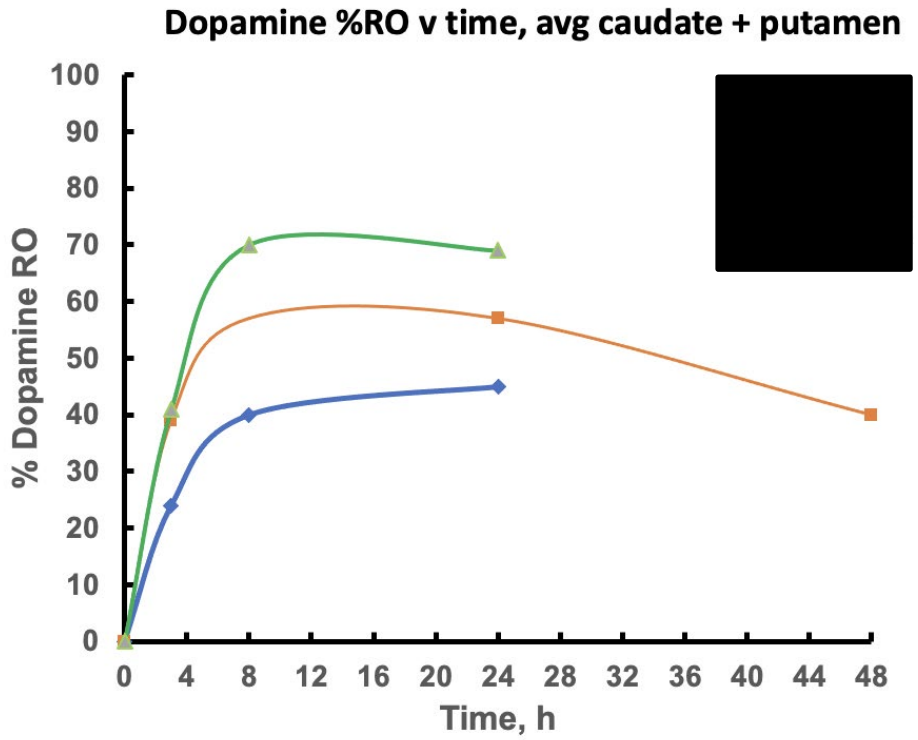
An open-label positron emission tomography (PET) study was conducted to evaluate dopamine RO of LB-102 administered orally to healthy volunteers. This was a Phase 1, open-label study with 4 cohorts consisting of 4 patients each. Eligible patients received 1 dose of LB-102 on Day 1; patients in the final cohort were dosed for 4 days QD on an inpatient basis. Blood samples for PK and safety assessments were collected at Screening, immediately pre-dose, and during, before, and after the PET scan. Patients enrolled in the inpatient cohort were monitored daily. Follow-up after discharge consisted of a phone call the next day to check on patients. This was an adaptive study and doses in Cohorts 2 to 4 were determined after PET data from Cohort 1 were obtained. For Cohort 1 and 2 dynamic, ^{11}C raclopride PET scans were obtained at Baseline, 2.5, 7.5, and 23.5 hours after LB-102 administration. For Cohort 3 dynamic, ^{11}C raclopride PET scans were obtained at Baseline, 2.5, 7.5, 23.5, and 47.5 hours after LB-102 administration. For

Cohort 4 dynamic, ^{11}C raclopride PET scans were obtained at Baseline, 2.5, 7.5, and 23.5 hours post-fourth day dosing.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Striatal RO, as measured as the average of the caudate and putamen, are presented in Figure 1.1.

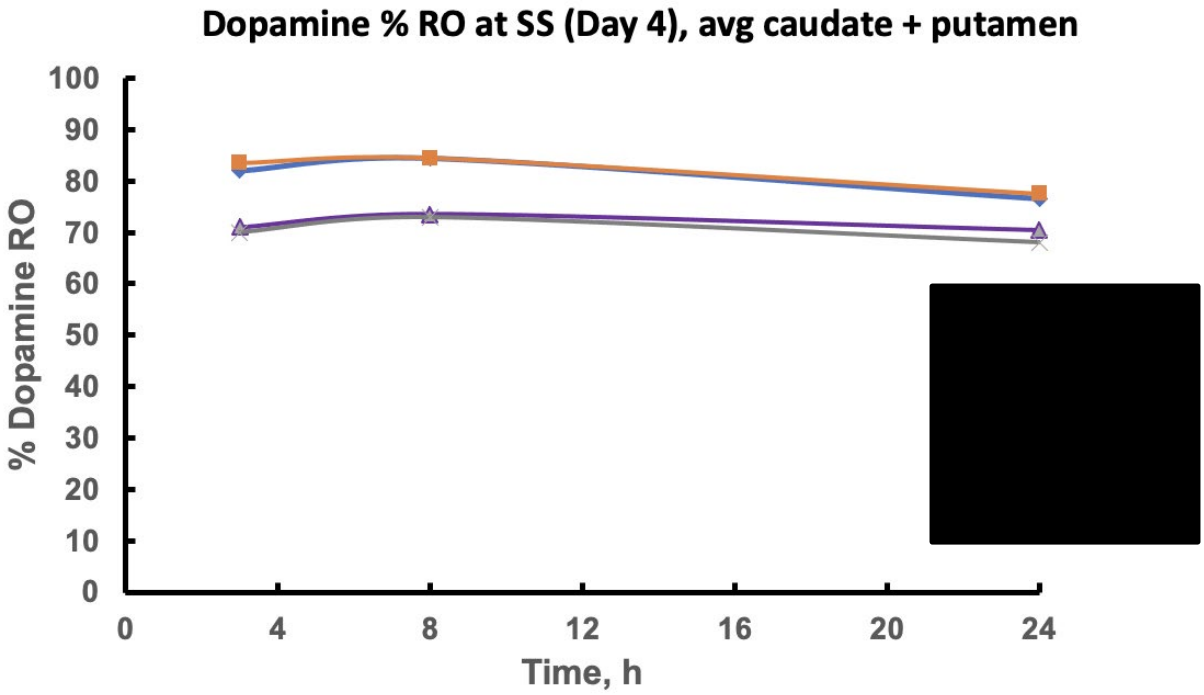
Figure 1.1: Striatal dopamine RO from single dose cohorts of LB-102-002



Abbreviations: h = hour; RO = receptor occupancy

Striatal RO for subjects who received multiple QD doses, i.e., steady state (SS) conditions, of LB-102, either [redacted] are presented in Figure 1.2.

Figure 1.2: Striatal dopamine RO from single dose cohorts of [redacted]



Abbreviations: h = hour; RO = receptor occupancy; SS = steady state.

There were no SAEs in this study. Results of this study showed that LB-102 afforded dopamine RO in the desired range to treat schizophrenia, under SS conditions, as doses as low as [redacted]. A correlation between dopamine RO and plasma LB-102 concentration could not be established.

Further information on the Phase 1 trials can be found in the Section 14.2.

1.5 Study Rationale

The current Phase 2 study is part of the LB-102 clinical development program designed to demonstrate the efficacy and safety of LB-102 for the treatment of patients with acutely exacerbated schizophrenia. A 4-week double-blind Treatment Period is of adequate length to determine whether an antipsychotic effect has been demonstrated. Since efficacy in schizophrenia is dependent on both treatment duration and dose, a fixed dose approach represents the optimal study design to evaluate efficacy. To facilitate enrollment of acutely ill patients and optimize treatment compliance, a 4-week inpatient hospitalization is required following the initial screening phase.

1.6 Dose Rationale

Based on the mechanism of action of LB-102 at dopamine D_2 and $5HT_7$ receptors, data from animal models, and PET dopamine RO data, it is hypothesized that LB-102 will have antipsychotic effects at [redacted]

1.7 Study Endpoint Rationale

The scale utilized for the primary study endpoint, Positive and Negative Syndrome Scale (PANSS) is validated and widely used in this patient population.

1.8 Risks and Benefits for Patients

1.8.1 Risks

Administration of second generation antipsychotics (SGAs) (including the metabolite of LB-102, [redacted]) can result in extrapyramidal symptoms, weight gain, elevations in lipids and blood sugar, sedation, dry mouth, constipation, dizziness, and falls due to low blood pressure, QTcF prolongation, cognitive impairment, and prolactin elevation.[1]

Electrocardiograms (ECGs) and clinical laboratory tests will be conducted throughout the study.

The effect of LB-102 on pregnant women and fetal development is unknown. Therefore, women who are pregnant or lactating will be excluded from this study, and highly effective contraception will be required of all female participants of childbearing potential and of male participants with sexual partners of childbearing potential. Pregnancy tests will also be required of female participants of childbearing potential before the start of treatment.

1.8.2 Benefits

In the 2 clinical trials conducted to date, LB-102 was shown to have an overall safety profile that was similar to other SGAs.

Schizophrenia is a chronic and debilitating mental illness that affects approximately 1% of the population. Schizophrenia manifests in hallucinations and delusions, dysfunctional thinking, social withdrawal and lack of emotion, energy, and motivation. Schizophrenia patients suffer a profoundly reduced quality of life and are 10 times more likely to commit suicide than the general population.[1] Despite a seeming surfeit of available drugs to treat schizophrenia, adequate treatment of schizophrenia remains a challenge.[1] LB-102 was designed to be an improved version of [redacted] and in vitro studies have demonstrated that it has an increased membrane permeability, which could potentially decrease the magnitude and frequency of AEs typically observed in patients treated with [redacted].[1] LB-102 may offer improved clinical benefit relative to the currently available treatments for schizophrenia.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine whether 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.

2.2 Secondary Objectives

The 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.

2.3 Exploratory Objectives

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

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

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

3.2 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

3.3 Exploratory Endpoint

- Effect of LB-102 on Cogstate test score

3.4 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)

- C-SSRS

4 STUDY PLAN

4.1 Study Design

This Phase 2 randomized, double-blinded, placebo-controlled, fixed dose, multicenter clinical study is designed to evaluate the efficacy, safety, tolerability, and 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.

An informed consent form (ICF) form must be signed by the patient before any study-related procedures are performed.

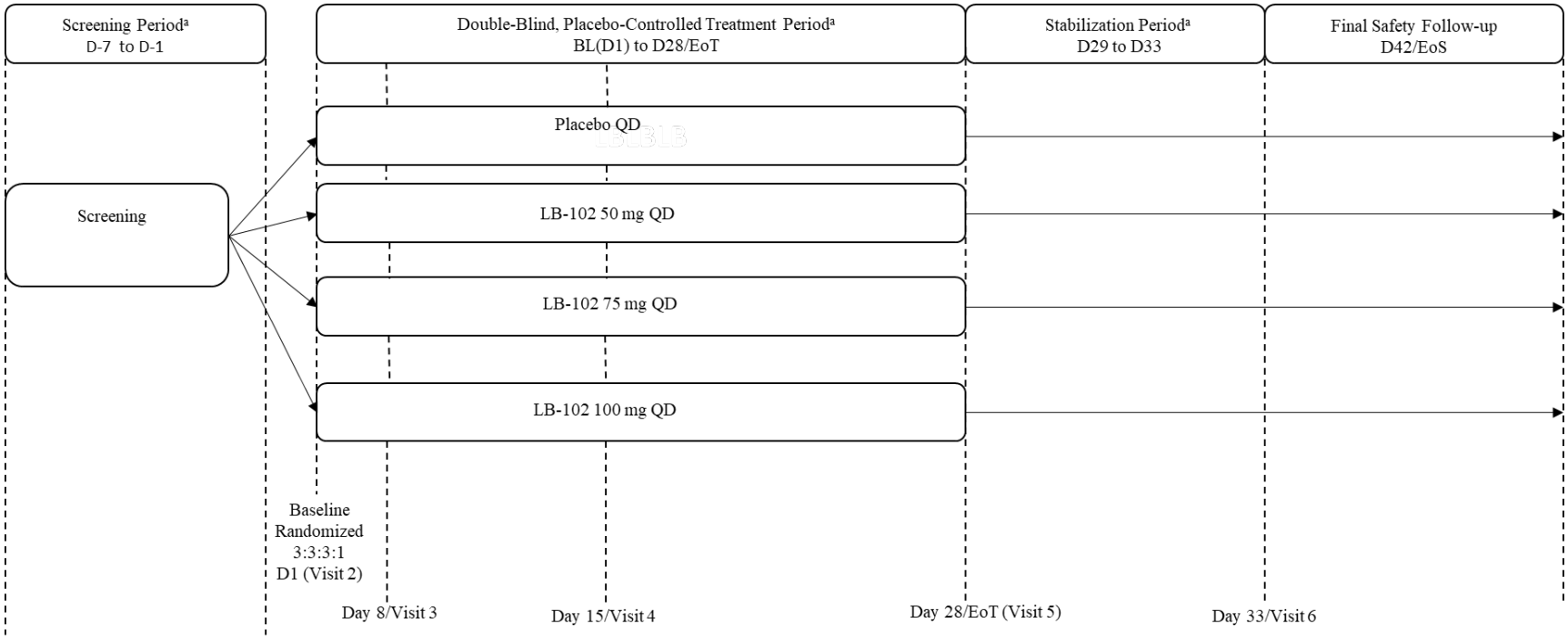
[redacted] patients will be randomized to receive 1 of 4 study treatments in a 3:3:3:1 ratio: placebo QD, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD, for 28 days. Re-screening may be permitted on a case-by-case basis with the approval of LB Pharmaceuticals and Medical Monitors. The study will be conducted in [redacted] study centers.

Study participation will last approximately 8 weeks and includes a 7-day inpatient screening phase (up to a 7-day extension of the screening phase is allowed, if necessary with the approval of the Medical Monitor), 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.

Patients will be evaluated at Baseline and periodically thereafter using the PANSS, CGI-S, SAS, BARS, AIMS, C-SSRS, 12-lead ECG, vital signs, clinical laboratory values, body weight/waist circumference, total cholesterol, triglycerides, HDL, and LDL and reported/observed AEs. In addition, blood samples will be collected for PK analysis.

The study is summarized graphically in Figure 4.1.

Figure 4.1: Study Schematic



[a] Inpatient
Abbreviations: D = Day; EoS = end of study; EoT = end of treatment; mg = milligram; QD = once daily

4.1.1 Stopping Criteria

4.1.1.1 Individual Patient Stopping Criteria

Dosing of an individual patient will cease if any of the following criteria are met:

- SAE regardless of association to LB-102 or placebo according to the Principal Investigator (PI) and notification to the Medical Monitor.
- Any other event that is deemed by the Investigator or Sponsor to pose an unacceptable risk to the patient.

4.1.1.2 QT Prolongation Stopping Criteria

Dosing of an individual patient will cease if any of the following criteria are met:

- An increase in QTcF to >500 msec for male and female patients.

OR

- An increase in QTcF of >60 msec over Baseline.

A confirmation of an abnormal finding meeting the stopping criteria will be required within 15 minutes of the initial QTcF reading.

4.2 Study Duration

The duration of participation for each individual patient in this study will be approximately 8 weeks, including a 7-day inpatient screening phase (up to a 7-day extension of the screening phase is allowed, if necessary with the approval of the Medical Monitor), a 28-day inpatient Study Treatment Period and up to 5-day inpatient Stabilization Period, and the Final Safety Follow-up approximately 2 weeks after the completion of the Treatment Period.

[redacted] sites are planned to randomly assign [redacted] patients over a 18-month period.

4.3 Safety Review Committee

A Safety Review Committee (SRC) will be established to review available safety data; details are included in the safety data plan.

Detailed roles, responsibilities, and administrative conduct of the SRC will be documented in the [redacted] Safety Review Committee Plan. The plan will define the roles and responsibilities of the SRC, its membership, and purpose and timing of its meetings. The plan will also describe procedures for communication, documentation, and an outline of data that will be provided to the SRC for review.

5 STUDY POPULATION

Patients must meet all inclusion criteria and have none of the exclusion criteria at Baseline to be enrolled in the study. No deviations will be permitted from the inclusion or exclusion criteria. The Investigator may contact the Medical Monitor to discuss eligibility of any given patient.

To ensure the inclusion of appropriate patients, the information collected during the screening phase that pertains to the diagnosis of schizophrenia, evaluation of the level of disease severity and exacerbation, and the distinction between symptoms of exacerbated schizophrenia and comorbid conditions will be recorded (e.g., using an audio recording device). In addition, the Mini International Neuropsychiatric Interview version 7.0.2 (MINI 7.0.2), Placebo-Control Reminder Script (PCRS) and Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) will be audio recorded. The information and recorded interviews will be submitted for review by an experienced independent central reviewer to confirm that the patient is appropriate for inclusion in the study. In addition, at Baseline and final endpoint, SCI-PANSS will be evaluated by a local rater with central supervision via independent, central review. In addition, SCI-PANSS is audio recorded at all applicable visits when they are administered; however, the patient withdrawal or refusal of consent for recording will not preclude participation in the study.

Specific entry criteria are detailed in Section 5.1 and Section 5.2.

5.1 Inclusion Criteria

Patients will be eligible for inclusion in the study if they meet all of the following criteria:

1. Patient, who is able to provide written informed consent (as required by Institutional Review Board [IRB]) prior to the initiation of any protocol-required procedures. Ability, in the opinion of the PI, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medication, and to be reliably rated on assessment scales.

2. Must be willing to be hospitalized for the duration of the inpatient period of the study, and willing to comply with instructions from the Investigator and study staff.

3. Have stable living environment when not in hospital, as demonstrated by the ability to provide contact information for themselves or family/friend(s)/caregiver(s).

4. Male and female patients 18 to 55 years of age inclusive at the time of informed consent with a diagnosis of schizophrenia as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and confirmed by the MINI 7.0.2 for Schizophrenia and Psychotic Disorders Studies.

5. BMI must be ≥18 and ≤40 kg/m^2.

6. Patient who is:

   - experiencing an acute exacerbation of psychotic symptoms, with onset ≤6 weeks before Screening AND the patient requires hospitalization for this acute exacerbation of psychotic symptoms.

   OR

   - if already an inpatient at Screening, has been hospitalized for onset ≤2 weeks for the current exacerbation.

7. Patients who are experiencing an acute exacerbation of psychotic symptoms and marked deterioration of usual function as demonstrated by meeting ALL of the following criteria at the Screening and Baseline visits:

   - Total PANSS score between 80 and 120, inclusive, and

   - Score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale (P) items: Item 1 (P1; delusions), Item 2 (P2; conceptual disorganization), Item 3 (P3; hallucinatory behavior), Item 6 (P6; suspiciousness/persecution), and

   - CGI-S score ≥4 (moderately to severely ill).

8. Have received previous antipsychotic treatment (dose and duration as per the label) and who showed a previous good response to such antipsychotic treatment (other than clozapine) in the last 12 months, according to the Investigator's opinion.

9. Have history of relapse and/or exacerbation of symptoms when they were not receiving antipsychotic treatment, according to the Investigator's opinion.

10. Patients willing to discontinue all prohibited psychotropic medications prior to Screening, if determined to be clinically appropriate by the Investigator, and not for the sole purpose of inclusion in the trial.

5.2 Exclusion Criteria

Patient will be excluded from the study if they meet any of the following criteria:

Sex and Reproductive Status

1. Sexually active females of childbearing potential and male patients who are not practicing 2 different methods of birth control with their partner during the trial and for 30 days after the last dose of trial medication or who would not remain abstinent during the trial and for 30 days after the last dose. If employing birth control, each couple must use 2 of the following precautions: oral contraceptives, patch contraceptives, injection contraceptives, implantable hormonal contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal

ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the patient's current practice. Contraceptive requirements do not apply to patients who are in same sex relationship, who are medically or surgically sterilized (e.g., bilateral tubal ligation, bilateral oophorectomy, hysterectomy); or practice sexual abstinence during this study.

2. Females who are breastfeeding or who have a positive pregnancy test result prior to receiving trial medication.

Target Disease

3. Patients who presented with a first episode of schizophrenia based on the clinical judgment of the Investigator and patients with diagnosed schizophrenia equal to or less than a year.

4. Improvement of ≥20% in total PANSS score between the Screening and Baseline assessments.

5. History of treatment resistance to schizophrenia medications defined as failure to respond to 2 adequate courses of pharmacotherapy (dose and duration as per the label) or required clozapine within the last 12 months.

6. Current DSM-5 Axis I diagnosis other than schizophrenia including, but not limited to schizoaffective disorder, major depressive disorder, bipolar disorder, post-traumatic stress disorder, anxiety disorders, delirium, dementia, amnestic or other cognitive disorders as determined by the MINI 7.0.2. Also, patients with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder, as determined by the MINI 7.0.2 and Mini International Neuropsychiatric Interview with Borderline Personality Disorder Module version 7.0.2 (MINI-Plus BPD 7.0.2).

7. Risk for suicidal behavior during the study as determined by the Investigator's clinical assessment and Columbia-Suicide Severity Rating Scale (C-SSRS) as confirmed by the following: answers "Yes" on items 4 or 5 (C-SSRS – Ideation) with the most recent episode occurring within the 6 months before Screening, or answers "Yes" to any of the 5 items (C-SSRS – Suicidal Behavior) with an episode occurring within the 12 months before Screening. This assessment will be repeated at Baseline Visit (at baseline "Since Last Visit" version of the CSSR-S scale should be used). Non-suicidal self-injurious behavior is not exclusionary.

8. Risk of violent or destructive behavior based on the Investigator's opinion and homicidal ideation based on responses to SCI-PANSS interview questions or statements made by the patient at any other times during the Screening or Baseline visits.

9. Patients with clinically significant tardive dyskinesia determined by a score of ≥3 on Item 8 of the AIMS at Screening.

10. Patients with a score of ≥3 on the BARS global clinical assessment of akathisia at Screening.

Medical History and Concurrent Diseases

11. Patients who met DSM-5 criteria for substance abuse or dependence within the past 1 year, including alcohol and benzodiazepines, but excluding caffeine and nicotine. Previous occasional use of alcohol or cannabis is allowed as long as the level of use does not meet DSM-5 criteria for any moderate or severe substance use disorder within the 12 months prior to Screening, and the use of alcohol or cannabis is not considered to be the precipitating factor of the current psychotic episode in the opinion of the Investigator; subjects are required to abstain from alcohol and cannabis use during the trial.

12. Patients with hypothyroidism or hyperthyroidism (unless condition had been stabilized with medications for at least the past 90 days) and/or clinically significant abnormal thyroid function (abnormal TSH levels followed by free T3 and T4 levels), as assessed by the Investigator, in discussion with the study Medical Monitor.

13. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results. Positive result at Screening for hepatitis B surface antigen (HbsAg), hepatitis C virus, or human immunodeficiency virus- (HIV)-1 or -2. Patients with chronic hepatitis B or hepatitis C may be included after discussion with the Medical Monitor provided that their condition is stable and values for liver function test meet the specified criteria of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2 × upper limit of normal (ULN). The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation.

14. Patients with insulin-dependent diabetes mellitus (i.e., any patients using insulin) are excluded. Patients with non-insulin-dependent diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:

    - Glycosylated hemoglobin (HbA1c) <7.0%, and

    - Screening glucose must have been ≤125 mg/dL or ≤6.94 mmol/L (fasting) or <200 mg/dL or <11.1 mmol/L (non-fasting). If the non-fasting Screening glucose was ≥200 mg/dL or ≥11.1 mmol/L, patients must have been retested in a fasted state and the retest value must have been ≤125 mg/dL or ≤6.94 mmol/L, and

    - Patient had been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to Screening or diabetes had been well controlled by diet for at least 28 days prior to Screening, and

    - Patient had no hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, and

    - Patient's diabetes should not be newly diagnosed during Screening for the trial.

15. Patients with uncontrolled hypertension (diastolic blood pressure [DBP] >95 mmHg in any position or systolic blood pressure [SBP] >145 mmHg) or symptomatic hypotension, or orthostatic hypotension defined as a decrease of ≥20 mmHg in SBP or a decrease of ≥10 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, OR development of symptoms. NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a patient based on the criteria noted above.

16. Patients with known ischemic heart disease or any history of myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery.

17. Patients with epilepsy or a history of seizures (with the exception of febrile seizure).

Physical and Laboratory Results

18. Patients with a positive urine drug screen or a positive blood alcohol test. Detectable levels of marijuana, barbiturates, benzodiazepines or opiates in the drug screen are not exclusionary if, in the Investigator's documented opinion, the patient does not meet DSM-5 criteria for substance abuse or dependence, in the Investigator's documented opinion, the positive test does not signal a clinical condition that would impact the safety of the patient or interpretation of the trial results, and approval was granted by the Medical Monitor prior to treatment.

19. Patients with a history of alcohol use disorder, substance use disorder (by DSM-5 criteria) within 12 months of Screening or a positive screen for drugs of abuse at Screening (unless consistent with current prescription for medical condition).

20. The following laboratory test results are exclusionary:

    - Platelets ≤75,000/μL or ≤75×10^9/L
    - Hemoglobin ≤9 g/dL or ≤90 g/L
    - Neutrophils, absolute ≤1000/μL or ≤1×10^9/L
    - AST >2 × ULN
    - ALT >2 × ULN
    - Creatine phosphokinase >3 × ULN, unless discussed with and approved by the Medical Monitor
    - Creatinine ≥2 mg/dL or ≥176.8 μmol/L
    - Estimated creatinine clearance of <45 mL/min, calculated using the Cockcroft-Gault equation, at Screening

- HbA1c ≥7.0%

- Abnormal free T4 (during Screening), unless discussed with and approve by the Medical Monitor (Note: Free T4 will be measured only if the result for TSH is abnormal)

21. Clinically significant abnormal finding on the triplicate set of ECGs or evidence of any of the following cardiac conduction abnormalities at Screening (mean values will be used for the following criteria):

    - Heart rate <40 beats per minute (bpm) and >110 bpm (based on the ECG reading). NOTE: The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation

    - Interval between Q and T wave corrected for heart rate using Fridericia's formula (QTcF) interval >450 msec for males and females

    - PR interval ≥200 msec

    - Intraventricular conduction delay with QRS duration >120 msec

    - Evidence of second- or third-degree atrioventricular block

    - Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB

Prohibited Therapies or Medications

22. Patients who are currently taking oral antipsychotic medications, monoamine oxidase inhibitors (MAOIs), anticonvulsants (e.g., lamotrigine, Depakote), tricyclic antidepressants (e.g., imipramine, desipramine), selective serotonin reuptake inhibitors, and any other antidepressants or any other psychoactive medications (except lorazepam, zolpidem, zaleplon, eszopiclone, or similar benzodiazepines, diphenhydramine, benztropine, and propranolol). Patients taking prohibited psychotropic medications may be eligible for inclusion in the study if it is clinically appropriate to discontinue the medication before the Baseline Visit (in the opinion of the Investigator). The prohibited psychotropic agent must be discontinued and washed out at least 5 half-lives prior to Baseline. Subjects taking a depot antipsychotic could not have received a dose of medication for at least 1 and a half injection cycles before Baseline. The medications should not be discontinued solely to make the patient eligible for enrollment in the study.

23. Patients who received electroconvulsive therapy within 90 days of Screening.

24. Patients who received Transcranial Magnetic Stimulation (TMS) within 90 days of Screening.

Allergies and Adverse Drug Reactions

25. Patients with a history of neuroleptic malignant syndrome.

26. Patients with a history of allergic response (defined as hypersensitivity reactions such as flushing, rash, wheezing, abdominal cramps, hypotension, seizure, etc., not intolerance) to more than 1 class of medications.

Others

27. Prisoners or patients who are compulsorily detained (involuntarily hospitalized) for treatment of either a psychiatric or physical illness or have been in the last 6 months prior to the Screening Visit must not be enrolled in this study.

28. Patients who have participated in another clinical study in which they received an experimental or investigational drug agent within 3 months of Screening.

5.3 Patient Withdrawal/Discontinuation Criteria

All patients are free to withdraw from participation in this study at any time for any reason and without prejudice.

A patient will be considered to have completed the study when they complete the End of Study (EoS) Visit (Visit 7). If a patient is discontinued at any time after randomization into the study, the Investigator will make every effort to follow the patient and complete the follow-up procedures at an Early Termination (ET) Visit as follows:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Full physical examination
- Bodyweight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the schedule of assessments (SoA) (Table)
- Urine pregnancy test for all females of childbearing potential
- Assessment and recording of AEs
- PANSS, PCRS must be administered before PANSS
- CGI-S

- C-SSRS
- AIMS
- BARS
- SAS
- Cogstate test

Patients may be replaced; however, this must be assessed on a case-by-case basis and be approved by the Sponsor or their designee.

The data on ET will be captured in electronic case report form (eCRF) that should be collected for every patient who receives study drug, whether or not the patient completes the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a patient discontinuing early should be selected from the following standard categories:

- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the Investigator for the best interest of the patient, are grounds for discontinuation. These events include SAEs and nonserious AEs regardless of relation to the study drug.
- *Lack of Efficacy:* Worsening of psychotic symptoms.
- *Non-compliance with study drug according to the PI.*
- *Protocol Deviation*: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug non-compliance, failure to return for defined number of visits).
- *Withdrawal of Consent*: The patient desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw – if consent is withdrawn, the patient must be questioned by the Investigator or site staff whether the withdrawal is due to an AE, lack of efficacy, personal or family reasons, or whether the patient withdrew consent and refused all EoS procedures including refusing to give a reason; these reasons must be documented in the eCRF, consistent with FDA recommendations. If the patient gave a reason for withdrawing, it should be recorded in the eCRF.
- *Investigator Decision*: In the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- *Death*: The patient died.
- *Lost to Follow-up*: The patient stopped coming for visits and study personnel were unable to contact the patient.
- *Study Terminated by Sponsor.*

- *Other*: The patient was discontinued for a reason other than those listed above, such as theft or loss of study drug. The reason must be clearly documented in the eCRF in order to determine whether the withdrawal was associated with an AE or lack of efficacy.

If a patient is withdrawn from dosing before completing the study, the reason for withdrawal will be entered in the appropriate eCRF. Whenever possible and reasonable, evaluations scheduled for study completion should be performed at the time of premature discontinuation of dosing. All patients who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.

6 STUDY TREATMENT AND MANAGEMENT

6.1 Description

Information about the study drugs is provided in 1.

Table 6.1: Details of Study Drug

	Preparations to Be Administered	
	LB-102	**Placebo**
Active Agent	[redacted]	Not applicable
Manufacturer	[redacted]	[redacted]
Dose(s)	[redacted]	Not applicable
Route	[redacted]	Oral
Formulation	[redacted]	Tablet
Strength(s)	[redacted]	Not applicable

Abbreviations: API = Active Pharmaceutical Ingredient; UK = United Kingdom

6.1.1 Formulation and Preparation

[redacted]

6.1.2 Labeling

Study drugs will be packaged [redacted] in accordance with applicable regulatory requirements.

6.1.3 Storage

Study drug must be stored at secure and locked location at temperature ranges between 20°C – 25°C (68°F – 77°F) with acceptable excursions to 15°C – 30°C (59°F and 86°F) is allowed.

Verbal and written instructions for proper storage, handling, and administration of the study drug will be given to the patient and will include instructions to contact the study site immediately if they experience problems with the study drug and/or administration.

Site storage conditions should be monitored by the site personnel and reviewed by the monitor during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor.

Complete instructions for proper study drug storage and handling will be provided in the Pharmacy Manual.

6.2 Shipment, Blinding, and Unblinding

6.2.1 Shipment

All study drugs will be supplied by the Sponsor [redacted]. No study drug will be shipped to a site until authorization has been given by the Sponsor or its representative. The study drug will be shipped under ambient conditions.

6.3 Treatment Assignment

This is a randomized, double-blind, placebo-controlled study.

Patients will be randomized in a 3:3:3:1 ratio to either placebo, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD. An unblinded biostatistician [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 hyphen and a 3-digit consecutive number).

PK analyses will include [redacted] patients randomized regardless of cohort and PK blood samples will be collected on Day 1, 8, and 21 during the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours. On Day 1 only, a pre-dose PK blood sample will be collected. Refer to Section 8.3 for PK windows.

6.3.1 Blinding and Unblinding Treatment Assignments

This study will be conducted under double-blind conditions such that neither the patient nor the Investigator or study staff members working directly with patients will know the identity of each patient's treatment.

Each site will assign a dedicated unblinded pharmacist and/or applicable unblinded study team member for the preparation of LB-102 or placebo. The knowledge of the patients assigned treatment will only be available to assigned unblinded pharmacist/unblinded study staff member. The unblinded pharmacist/unblinded staff team member ensures the treatment assignment is not shared with any study staff having direct patient contact and that no other unblinding occurs.

Clinical sites should follow site specific procedures/processes to ensure the blind is maintained.

Treatment assignment for an individual patient is restricted. In an emergency situation the Investigator may unblind the patient via the IRT when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the patient.

If possible, the Investigator should notify the Medical Monitor and/or Chief Medical Officer (CMO) before unblinding, but priority should be given to the treatment of the patient.

Study drug unblinding is restricted to the designated unblinded pharmacist/unblinded study team member [redacted] and is provided electronically from the IRT.

Breaking of the blind, other than as described above, will be considered as a protocol violation. Any patient whose study drug treatment is unblinded will be discontinued, and the date, time, and reason for the unblinding will be documented. Additionally, the Investigator/designee will need to update the patient's status in the IRT.

6.4 Dose and Administration

[redacted] patients will be randomized to receive 1 of 4 study treatments in a 3:3:3:1: placebo, LB-102 50 mg QD, LB-102 75 mg QD, or LB-102 100 mg QD for 28 days. LB-102 and placebo will be administered as visually matched tablets for the treatment of adult patients with an acute exacerbation of psychotic symptoms of schizophrenia. LB-102 tablets [redacted] The placebo tablets will match [redacted] in appearance [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

6.5 Accountability

The unblinded pharmacist/unblinded study staff member at the investigational site must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of patients (patient number and initials) who received the study drug. The assigned unblinded pharmacist/unblinded staff member ensures the treatment assignment is not shared with any study staff having direct patient contact and that no other unblinding occurs. Unblinding treatment assignment documentation must be stored in a secured manner that restricts access to the blinded team members.

The unblinded pharmacist/unblinded study staff member will not supply the study drug to any person except those named as Investigators and Sub-Investigators on the FDA 1572, designated staff, and patients in this study. The unblinded pharmacist/unblinded study staff member will not dispense study drug from any sites other than those listed on the FDA 1572.

The Investigator must keep an accurate accounting of the number of study drug units delivered to the site, dispensed to patients, returned to the Investigator by the patient, and returned to the Sponsor or other disposition during and at the completion of the study. The study drug must be dispensed to patients only by an appropriately qualified person. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of the Investigator. Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all study drug received at the site before final disposition.

Upon completion of the study, unused supplies of study drug will be reconciled. The used and unused drug supply will be destroyed on-site, as per the site procedure, with approval of the Sponsor or, if not allowed, returned to the Sponsor or designee.

6.6 Treatment Compliance

Administration of study drug will be supervised by study personnel to ensure compliance.

6.7 Prior and Concomitant Medications

All prescription, nonprescription medications (e.g., over-the-counter [OTC]) drugs and herbal supplements) and non-medical treatments starting from 30 calendar days before Screening until end of the study must be recorded in source documents and the eCRF. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units, and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit. All as-needed prescriptions should be converted to reflect actual dose taken per day.

Starting on the first day of the screening phase, after written informed consent for the study has been provided, all antipsychotic or other psychotropic medications will be stopped with clinically appropriate titration down as per the Investigator’s clinical judgment. Patients will be

instructed not to take any medication(s) during the conduct of the study unless approved by the Investigator. Any patient unable to be safely discontinued from current antipsychotic therapy or other psychotropic medications will not be eligible for the study. Any treatment other than the study treatment given will be considered a concomitant medication and will be documented in the eCRF. Any patient requiring emergency treatment with prescription or nonprescription medication during the screening phase through the EoS Visit will be approved by the Investigator. If the Investigator determines that the patient requires medication during the study, the Medical Monitor must be contacted within 24 hours.

Psychotropic medications are prohibited except for lorazepam as needed for agitation, restlessness, irritability, or hostility; zolpidem, zaleplon, or eszopiclone for insomnia; diphenhydramine or benztropine for EPS; and propranolol for akathisia.

Within the daily limits shown in 2, lorazepam, benztropine, and propranolol are not allowed on as needed basis; every administration must be considered and approved by the Investigator prior to administration.

The AE associated with the need for lorazepam, benztropine, or propranolol should be recorded on the Adverse Events in the eCRF. The amount and timing for each lorazepam, benztropine, or propranolol administration should be recorded for each patient.

Table 6.2: Permitted concomitant medications

Medication	Study Period	Dose Permitted	Timing Restriction
Lorazepam	Screening phase through Day 7	Maximum of 6 mg/day	Not within 12 hours prior to PANSS
	Day 8 though Day 14	Maximum of 4 mg/day	
	Day 15 through Day 28	Maximum of 2 mg/day On no more than 4 days/Week	
Benztropine	Screening phase Through Day 28	Maximum 4 mg/day	Not within 12 hours prior to SAS, BARS, or AIMS
Propranolol	Screening phase Through Day 28	Maximum of 40 mg/day	
Sleep Medication zolpidem, zaleplon, or eszopiclone for insomnia	Day 1 and Day 28	No restrictions [a]	Not within 8 hours prior to Cogstate test

[a] Allow nighttime use only (prn); exclude regular use; exclude daytime use; exclude use within 12 hours of a study visit
Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; mg = milligram; PANSS = Positive and Negative Syndrome Scale; SAS = Simpson-Angus Scale

During the End of Stabilization period, the use of lorazepam, benztropine, and propranolol is not restricted.

Smoking is allowed, under supervision.

Table 6.3 below provides a select list of CYP2D6 inhibitors and CYP3A4 inhibitors and inducers that are prohibited within 14 days of randomization and for the duration of the trial.

Table 6.3: Selected CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers Prohibited During the Trial

Selected CYP2D6 Inhibitors	
Celecoxib	Methadone
Chloroquine	Moclobemide
Chlorpheniramine	Paroxetine
Clemastine	Pyrilamine
Clomipramine	Quinidine
Fluoxetine	Terbinafine
Halofantrine	Tripelennamine
Hydroxyzine	
Selected CYP3A4 Inhibitors	
Amiodarone	Fluvoxamine
Amprenavir	Indinavir
Aprepitant	Itraconazole
Chloramphenicol	Ketoconazole
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole (if used orally)	Quinupristin/Dalfopristin
Delavirdine	Ritonavir
Diltiazem	Saquinavir
Erythromycin	Troleandomycin
Fluconazole	Verapamil
Selected CYP3A4 Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifampin
Nevirapine	St. John’s Wort
Oxcarbazepine	Troglitazone
Phenobarbital	

Abbreviations: CYP = cytochrome P450

6.7.1 Acceptable Contraceptive Methods

For females of childbearing potential who may participate in the study, the following methods of contraception, if used properly and used for the duration of the study and for 30 days after the last dose of study medication, are generally considered reliable; however, if employing birth control, each couple must use 2 of the following precautions: oral contraceptives, patch contraceptives, injection contraceptives, implantable hormonal contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the patient's current practice. Contraceptive requirements do not apply to patients who are in same sex relationship, who are medically or surgically sterilized (e.g., bilateral tubal ligation, bilateral oophorectomy, hysterectomy); or practice sexual abstinence during this study.

These methods of contraception also apply to female partners of male patients.

The Investigator and each patient will determine the appropriate method of contraception for the patient during participation in the study. This will be documented at the Screening Visit in the patient's source documentation/medical record.

Male patients or male partners of female patients should not donate sperm until 90 calendar days after the last dose of study drug.

7 STUDY CONDUCT

Unless otherwise indicated, all assessments will be performed by the Investigator or designated study personnel.

After signing the ICF, each patient will be screened to ensure eligibility for the study.

7.1 Schedule of Assessments

The study consists of a 7-day inpatients screening phase (up to a 7-day extension of the screening phase is allowed, if necessary with the approval of the Medical Monitor), Study Treatment Period (Days 1 to Day 28 including Baseline [Day 1]), Stabilization Period (up to 5 days, Days 29 to 33), and EoS Visit (Visit 7 [Day 42] ± 2 days). Therefore, the maximal study duration for an individual patient will be approximately up to 8 weeks.

Note, this is an inpatient study from Screening to the end of the Stabilization Period. The procedures to be performed throughout the study are outlined in the SoA (Table).

Table do: Schedule of Assessments

Event	Screening Phase	Baseline	Study Treatment Period								End of Stabilization Period	End of Study Visit
	Up to 7 days[a]	Day 1	Days 2-7	Day 8 ± 1	Days 9-14	Day 15 ± 1	Days 16-20	Day 21 ± 1	Days 22-27	Day 28 or ET	33[c]	Day 42± 2
Visit Number	**1**	**2**	**NA[b]**	**3**	**NA[b]**	**4**	**NA[b]**	**5**	**NA[b]**	**6**	**7**	**8**
Entrance/Screening Criteria												
Informed Consent[a]	X											
Admission to Inpatient Unit[a]	X											
Inclusion/Exclusion Criteria Review[a]	X	X										
Screening Adjudication Form(s) and Recordings[d]	X											
Medical History[e]	X											
MINI-Plus BPD 7.0.2	X											
Prior Medication Washout[f]	X											
Hepatitis/HIV	X											
Urine Drug and Blood Alcohol Screen[g]	X[g]											
Randomization		X										
Efficacy												
(PCRS) SCI-PANSS and CGI-S	X[h]	X[h]		X		X		X		X[h]		
Cogstate Test	X[i]	X[i]								X[i]		
Safety												
Prior and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[j]	X	X		X		X		X		X		X
AIMS	X	X[k]		X[k]		X[k]		X[k]		X[k]		
SAS	X	X[k]		X[k]		X[k]		X[k]		X[k]		
BARS	X	X[k]		X[k]		X[k]		X[k]		X[k]		
C-SSRS	X[l]	X[m]		X[m]		X[m]		X[m]		X[m]	X[m]	X[m]
BMI and Waist Circumference[n]	X	X		X		X		X		X		

Event	Screening Phase	Baseline	Study Treatment Period								End of Stabilization Period	End of Study Visit
	Up to 7 days[a]	Day 1	Days 2-7	Day 8 ± 1	Days 9-14	Day 15 ± 1	Days 16-20	Day 21 ± 1	Days 22-27	Day 28 or ET	33[c]	Day 42± 2
Visit Number	**1**	**2**	**NA[b]**	**3**	**NA[b]**	**4**	**NA[b]**	**5**	**NA[b]**	**6**	**7**	**8**
Urine Pregnancy Test[o]	X	X								X	X	
Clinical Laboratories (for Screening and exclusionary purposes)[p]	X											
Hematology, Serum Chemistry including Prolactin, Urinalysis[q]	X	X		X		X		X		X		
TSH[r]	X									X		
PT, aPTT, and INR	X	X								X		
ACTH and Cortisol		X								X		
Resting 12-lead ECG[s]	X	X		X		X		X		X		
Vital Signs[t]	X	X		X		X		X		X		
Adverse Events[u]	X	X	X	X	X	X	X	X	X	X	X	X
Other												
Study Drug Dosing		X	X	X	X	X	X	X	X	X		
PK Sample Collection[v]		X		X				X				
Restart Standard Antipsychotic[w]											X	

a. Screening begins when the ICF is signed and will take place between Day −7 and Day −1; up to a 7-day extension of the screening phase is allowed, if necessary with the approval of the Medical Monitor; screening procedures should be initiated with a sufficient amount of time allotted in order to obtain central laboratory results and ECG results from the central reader prior to randomization. Review of inclusion/exclusion criteria at Baseline will be based on assessments performed during Screening. Hospitalization will begin with the signing of the ICF for patients who are not already hospitalized at the initial Screening Visit.

b. Each patient may receive the QD administration of study treatment. No other assessments are scheduled; however, AEs observed or reported, and concomitant medications may be recorded. In case of an AE, an unscheduled visit may be conducted at the discretion of the PI.

c. Stabilization Period is up to 5 days.

d. The Screening assessments to be audio recorded include the MINI 7.0.2, PCRS and SCI-PANSS and are submitted to an independent central reviewer for review and eligibility confirmation.

e. Includes full psychiatric history, DSM-5 diagnosis of schizophrenia, and MINI 7.0.2.

f. Washout of prohibited medications begins after signing the ICF and after diagnosis of Schizophrenia is confirmed by MINI. Details of medications requiring washout and guidance for washout time required are provided in Appendix 14.4. Prohibited and restricted medications are listed in Table 6.3: .

g. Urine drug screen (full panel including opioids) and a blood alcohol test are required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the Investigator.

h. At Screening, Baseline, and final endpoint, SCI-PANSS and CGI-S will be evaluated by a local site rater with central supervision via independent, central review. SCI-PANSS will be audio recorded at any visit where they are administered. SCI-PANSS assessment should be preceded by the PCRS. Patients with improvement of ≥20%

in total PANSS score between the Screening and Baseline assessments will be excluded from study participation. SCI-PANSS will be administered first on visits before any other scales, when SCI-PANSS and CGI-S are being administered with the exception of Screening where MINI-Plus BPD 7.0.2 will be administered first.
The Placebo-Control Reminder Script© Hassman and Cohen, 2019, Version 5.0 educates clinical trial subjects of key causes of the placebo and nocebo effects, level setting of the subject's study expectations, reminding subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with clinical providers. The PCRS informs subjects that they are to be honest about their symptoms and that the site staff have no expectations of symptom improvement or worsening and will not be disappointed by the subject's responses, and asks subjects to explain in their own words PCRS content to ensure comprehension. The PANSS Rater will read the PCRS before administering the PANSS at each study visit.

i. During Screening, patients will undergo a practice assessment of the Cogstate test. On Day 1 and Day 28, the actual Cogstate testing will be performed. Note: Cogstate Battery test creot be done within 8 hours of receiving a benzodiazepine or sleep medication.

j. To include height at the Screening Visit only. A full physical examination will be conducted at the Screening Visit and at EoT Visit. At each other study visit, patients will be assessed for continued dosing and any possible physical symptoms and a targeted physical examination may be performed, if indicated.

k. On Days 1, 8, 15, 21, and 28, the SAS, BARS, and AIMS assessments are to be conducted 3 to 6 hours after the administration of study treatment with the exception of ET Visit.

l. If the administration of C-SSRS at Screening highlights the risk of suicide not previously known, in the opinion of the Investigator, the patient should be excluded from the trial. At this visit the "Baseline/Screening" version of the C-SSRS scale will be used.

m. At all other study visits the "Since Last Visit" version of the C-SSRS scale should be used.

n. BMI; derived programmatically from body weight and height measurements.

o. All positive urine pregnancy test results must be confirmed by a serum test. Patients with positive urine and serum pregnancy test results at Screening must not be enrolled. Patients with positive urine and serum pregnancy test results during the trial must discontinue treatment and be withdrawn from the trial. Pregnancy tests can be performed at any point during the trial if pregnancy is suspected.

p. Clinical laboratory samples at Screening for exclusionary purposes are to be taken after a fast of at least 8 hours. Vital signs and ECG should be completed before any blood samples are collected. Clinical laboratory test results drawn within ± 24 hours of the scheduled timepoint may be used. Clinical laboratory tests will include the following (see Table 14.2: and Section 8.2.4):

- Hematology Screening assessments (excluded test result) will include measurement of hemoglobin (≤9 g/dL or ≤90 g/L), platelets (≤75,000/µL or ≤75×10^9/L), neutrophils (absolute ≤1000/µL or ≤1×10^9/L).
- Clinical chemistry tests for exclusionary purposes are for ALT (>2 × ULN), AST (>2 × ULN), creatinine (≥2 mg/dL or ≥176.8 µmol/L), CPK (≥3 × ULN, unless discussed with the Medical Monitor), HbA1c (≥7.0%), TSH. Important note: Free T4 will be measured only if the result for TSH is abnormal.
- Creatinine clearance will be calculated at Screening using the Cockcroft-Gault equation; estimated creatinine clearance of <45 mL/min is exclusionary.

q. Clinical laboratory samples are to be taken after a fast of at least 8 hours. Vital signs and ECG should be completed before any blood samples are collected. Clinical laboratory test results drawn within ± 24 hours of the scheduled timepoint may be used. Routine clinical laboratory tests to be monitored throughout the study will include the following:

- Hematology will include measurement of hematocrit, RBC, reticulocytes, and WBC with differential.
- Clinical chemistry will include measurement of albumin, ALT, ALP, amylase, AST, bicarbonate, bilirubin-total, blood urea nitrogen, calcium, creatine kinase, creatinine, gamma-glutamyl transpeptidase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, prolactin, sodium, total protein, total cholesterol, triglycerides, HDL, LDL and uric acid.
- Urinalysis: pH of freshly voided specimen, specific gravity, protein, glucose, ketones, blood, and microscopic examination of the sediment.

r. Important note: Free T4 will be measured only if the result for TSH is abnormal.

s. Standard 12-lead ECGs (in triplicate) will be performed after the patient has been supine and at rest for ≥5 minutes. The captured ECGs must be separated by at least 1 minute. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Any Screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the patient from the trial. Patients will be randomized based on Screening ECG results from the central reader and Baseline ECG results from the trial site. If the Baseline ECG results from the central reader, when available, indicate a QTcF >450 msec at Baseline, the Investigator must contact the Medical Monitor to discuss the patient's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

t. Vital signs will include body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting and standing after the patient has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood sample have to be completed before blood is drawn.

u. The recording of AEs is to start immediately after the ICF is signed and up to 14 days after the end of EoT.
v. PK analyses will include the ~~first 60~~ randomized patients regardless of cohort. PK blood samples will be collected on Day 1, 8, and 21 during the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours. See protocol Section 8.3. On Day 1 only, a pre-dose PK blood sample will be collected. Samples are collected after ECGs and vital signs. The total volume of blood to be collected during the Screening, treatment, and End of Stabilization period is 161 mL. Approximately 21 mL of blood will be collected during the Screening Visit, 130 mL will be collected during the 28-day Treatment Period, and 10 mL will be collected during the End of Stabilization period.
w. On Day 29 patients are to be started on standard antipsychotic medication as prescribed by the Investigator.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; CGI-S = Clinical Global Impressions-Severity of Illness scale; CPK = creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; EoT = end of treatment; ET = early termination; HDL = high-density lipoprotein, HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; LDL = low-density lipoprotein; MINI 7.0.2 = Mini International Neuropsychiatric Interview version 7.0.2; MINI-Plus BPD 7.0.2 = Mini International Neuropsychiatric Interview with Borderline Personality Disorder Module version 7.0.2; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PCRS = Placebo-Control Reminder Script; PK = pharmacokinetic; PT = prothrombin time; QD = once daily; QTcF = interval between Q and T wave corrected for heart rate using Fridericia's formula; RBC = red blood cells; SAS = Simpson-Angus Scale; SBP = systolic blood pressure; SCI-PANSS= Structured Clinical Interview for the Positive and Negative Syndrome Scale; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WBC = white blood cells.

7.2 Study Procedures by Time Point

7.2.1 Visit 1 (Screening – up to 7 Days)

The Screening Visit is to occur within 7 calendar days prior to the start of study drug administration. After the patient has signed the ICF, the following assessments will be performed and recorded in the patient's source documentation/medical record and in the eCRF:

- Administration of informed consent
- Subjects will also be asked to provide additional consent for their participation in a secure, proprietary research subject database administered by Verified Clinical Trials ([VCT], Garden City, NY). The database will utilize partially identified subject information to review subjects' research study history within the database. Participants who are identified as verification failures by VCT, should not be enrolled without documented approval from LB Pharmaceuticals [redacted] At the last subject contact, VCT staff will automatically close out the subject (safety follow-up, ET, or complete) based on the Interactive Response System (IXRS)
- Admission to inpatient unit
- DSM-5 diagnosis of schizophrenia
- MINI 7.0.2
- MINI-Plus BPD 7.0.2
- Review of inclusion and exclusion criteria
- Recording of medical history
- Recording of prior and current medications (e.g., prescription and nonprescription medications)
- Washout of prohibited psychotropic medications (after signing of ICF)
- PANSS, PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- Collection of demographic information
- Physical examination including height
- Body weight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)

- Collection of blood and urine samples for clinical laboratory tests. Lab results that are exclusionary are presented in Table 14.2 and other information is presented in the footnotes to the SoA (Table)
- Urine pregnancy test for all females of childbearing potential
- Assessment and recording of AEs
- Urine drug screen/blood alcohol test
- AIMS
- BARS
- SAS
- Submission of applicable data to the Endpoint Adjudication Committee for confirmation of eligibility
- Cogstate test - practice assessment

7.2.2 Visit 2 (Baseline, Study Day 1)

At this visit, the following assessments will be performed and recorded in the patient's source documentation/medical record and in the eCRF:

- Review of inclusion and exclusion criteria
- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Targeted physical examination (if applicable)
- Body weight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table)
- Urine pregnancy test for all females of childbearing potential
- Assessment and recording of AEs
- PANSS- patients with improvement of ≥20% in total PANSS score between the Screening and Baseline assessments will be excluded from study participation. PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- Randomization
- Pre-dose PK blood sample will be collected
- Study drug administration

- PK sample collection for the ~~first 60~~ patients randomized regardless of cohort at the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours
- AIMS, 3 to 6 hours post-dose
- BARS, 3 to 6 hours post-dose
- SAS, 3 to 6 hours post-dose
- Cogstate test

7.2.3 Study Days 2 Through 7

On Days 2, 3, 4, 5, 6, and 7 each patient may receive the QD administration of study treatment. No other assessments are scheduled; however, AEs observed or reported, and concomitant medications may be recorded. If any assessments are required in order to evaluate an AE, an unscheduled visit may be conducted, at the discretion of the PI.

7.2.4 Visit 3 (Study Day 8)

The following Study Day 8 assessments can be performed on Day 8 ± 1 day; however, they should all be performed on the same day:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Targeted physical examination (if applicable)
- Body weight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table)
- Study drug administration
- PK sample collection [redacted] patients randomized regardless of cohort at the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours
- Assessment and recording of AEs
- PANSS, PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- AIMS, 3 to 6 hours post-dose
- BARS, 3 to 6 hours post-dose

- SAS, 3 to 6 hours post-dose

7.2.5 Study Days 9 Through 14

On Days 9, 10, 11, 12, 13, and 14 each patient may receive the QD administration of study treatment. No other assessments are scheduled. However, any AEs observed or reported, and concomitant medications may be recorded. If any assessments are required in order to evaluate an AE, an unscheduled visit may be conducted, at the discretion of the PI.

7.2.6 Visit 4 (Study Day 15)

The following Study Day 15 assessments can be performed on Day 15 ± 1 day; however, they should all be performed on the same day:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Targeted physical examination (if applicable)
- Bodyweight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table)
- Study drug administration
- Assessment and recording of AEs
- PANSS, PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- AIMS, 3 to 6 hours post-dose
- BARS, 3 to 6 hours post-dose
- SAS, 3 to 6 hours post-dose

7.2.7 Study Days 16 Through 20

On Days 16, 17, 18, 19, 20, each patient may receive QD administration of study treatment. No other assessments are scheduled. However, any AEs observed or reported, and concomitant medications may be recorded. If any assessments are required in order to evaluate an AE, an unscheduled visit may be conducted, at the discretion of the PI.

7.2.8 Visit 5 (Study Day 21)

The following Study Day 21 assessments can be performed on Day 21 ± 1 day; however, they should all be performed on the same day:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Targeted physical examination (if applicable)
- Bodyweight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table)
- Study drug administration
- PK sample collection ~~first 60~~ patients randomized regardless of cohort at the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours
- Assessment and recording of AEs
- PANSS, PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- AIMS, 3 to 6 hours post-dose
- BARS, 3 to 6 hours post-dose
- SAS, 3 to 6 hours post-dose

7.2.9 Study Days 22 Through 27

On Days 22, 23, 24, 25, 26, and 27 each patient may receive the QD administration of study treatment. No other assessments are scheduled. However, any AEs observed or reported, and all concomitant medications may be recorded. If any assessments are required in order to evaluate an AE, an unscheduled visit may be conducted, at the discretion of the PI.

7.2.10 Visit 6 (Study Day 28)

On Study Day 28, all assessments should be performed on the same day; the last day of study drug dosing is Day 28 and, if possible, when any patient discontinues prior to this visit, the following assessments will be performed:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)

- Full physical examination (if applicable)
- Bodyweight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table)
- Study drug administration
- Urine pregnancy test for all females of childbearing potential
- Assessment and recording of AEs
- PANSS. PCRS must be administered before PANSS
- CGI-S
- C-SSRS
- AIMS, 3 to 6 hours post-dose
- BARS, 3 to 6 hours post-dose
- SAS, 3 to 6 hours post-dose
- Cogstate test

7.2.11 Stabilization Period (Study Days 29 Through 33)

Patients are to remain inpatient and be restabilized on standard-of-care antipsychotics, which may be started on Day 29. No other assessments are scheduled, and therefore no formal visits are shown in the SoA. However, any AEs observed or reported and concomitant medications may be recorded. If any assessments are required in order to evaluate an AE, an unscheduled visit may be conducted at the discretion of the PI.

7.2.12 Visit 7 (Study Day 33)

On Study Day 33 (or the last day of stabilization if it occurs before Day 33) the following assessments will be conducted:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Urine pregnancy test for all females of childbearing potential (Table)
- Assessment and recording of AEs
- C-SSRS

Based on known PK properties of LB-102, it is expected that within 5 days of the end of the Study Treatment Period, plasma concentration of LB-102 and its metabolites is expected to be minimal.

7.2.13 Visit 8 (End of Study)

At Visit 8 ± 2 days, the following procedures will be conducted:

- C-SSRS
- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Targeted physical examination (if applicable)
- Assessment and recording of AEs

7.2.14 Study Procedures for Early Termination and Withdrawal

If a patient is discontinued at any time after randomization into the study, the Investigator will make every effort to follow the patient and complete the follow-up procedures at an ET Visit as follows:

- Recording of concomitant medications (e.g., prescription and nonprescription medications)
- Full physical examination
- Bodyweight, BMI (derived programmatically from body weight and height measurements), and waist circumference
- Vital signs
- Resting 12-lead ECG (triplicate, further information in Section 8.2.3)
- Collection of blood and urine samples for clinical laboratory tests. Additional information is presented in the footnotes to the SoA (Table 7.1)
- Urine pregnancy test for all females of childbearing potential
- Assessment and recording of AEs
- PANSS
- CGI-S
- C-SSRS
- AIMS
- BARS

- SAS
- Cogstate test

8 DESCRIPTION OF ASSESSMENTS

All assessments will be performed throughout the study as noted in the SoA (Table).

8.1 Efficacy Assessments

8.1.1 Screening Assessments

8.1.1.1 Mini International Neuropsychiatric Interview Version 7.0.2 and Mini International Neuropsychiatric Interview With Borderline Personality Disorder Module Version 7.0.2.

The MINI 7.0.2 is a brief structured interview for the major Axis I psychiatric disorders in the DSM-5 and the International Statistical Classification of Diseases and Related Health Problems, Version 10. Seventeen diagnostic modules consisting of screening and a series of secondary questions are to be answered with "yes" or "no" responses. If the patient answers "yes" to a screening question, the interviewer proceeds to questions in the module. If the patient answers "no" to a screening question, the interviewer will move forward accordingly to the subsequent module, following instructions in the structured interview. The Mini International Neuropsychiatric Interview-Plus version 7.0.2 (MINI-Plus 7.0.2) contains additional modules beyond what is included in the MINI 7.0.2. For this study, the MINI-Plus 7.0.2 module for Borderline Personality Disorder will be used.

The MINI 7.0.2 is intended to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and has an administration time of approximately 20-30 minutes[8]. At Screening, the patients will be assessed for Schizophrenia as well as the lack of exclusionary psychiatric diagnoses by the MINI 7.0.2 and the MINI-Plus BPD 7.0.2.

8.1.1.2 Positive and Negative Syndrome Scale

The PANSS consists of 3 subscales containing a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. The symptom constructs for each subscale are as follows:

1. Positive subscale (7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility)

2. Negative subscale (7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking)

3. General psychopathology subscale (16 symptom constructs: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance)

The PANSS will be administered using the clinician rated semi-structured interview via the SCI-PANSS. Instructions for administering this instrument will be provided to the site. PANSS will be administered first on visits when PANSS and CGI-S are being administered.

8.1.1.3 Placebo-Control Reminder Script

The PCRS© Hassman and Cohen, 2019, Version 5.0 educates clinical trial subjects of key causes of the placebo and nocebo effects, level setting of the subject's study expectations, reminding subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with clinical providers. The PCRS informs subjects that they are to be honest about their symptoms and that the site staff have no expectations of symptom improvement or worsening and will not be disappointed by the subject's responses and asks subjects to explain in their own words PCRS content to ensure comprehension. The PANSS Rater will read the PCRS before administering the PANSS at each study visit.

8.1.1.4 Clinical Global Impressions-Severity of Illness Scale

The severity of illness for each patient will be rated using the CGI-S. To perform this assessment, the rater or Investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

8.1.1.5 Cogstate Computerized Battery of Tests

The Cogstate Computerized Schizophrenia Battery of Tests is a measure of cognitive ability in subject with Schizophrenia in both the acute and chronic stages and will take approximately 22 to 35 minutes to complete. Patients will have 1 practice session during the Screening Visit and complete the actual test on Day 1 (Baseline) and Day 28 (Visit 6) ET Visit). For each Cogstate test, the construct validity for cognitive impairment in Schizophrenia and sensitivity to change in cognition in such patients have been demonstrated in scientific literature. Patients perform the test on a provided laptop and then it is uploaded via a web-based portal.

8.2 Safety Assessments

Tolerability will be assessed by reported and observed AEs. Frequency and severity of AEs will be summarized.

Routine safety assessments will be performed throughout the study, with a final assessment performed when a patient completes the study on Day 42/Visit 7 or patient discontinues. (See in the SoA Table).

8.2.1 Physical Examination and Height

When required, a full physical examination will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes,

extremities, and nervous system. An AE form must be completed for all changes identified as clinically noteworthy. Height without shoes will be recorded in inches. At other time points as noted in the SoA, a brief or targeted exam that is focused on any changes since the previous exam may be conducted.

8.2.2 Vital Signs and Body Weight

Vital signs will include body temperature, SBP, DBP, and heart rate. Blood pressure and heart rate will be measured in the following order: supine, sitting and standing after the patient has been in each position for at least 3 minutes. Vital signs scheduled for the same visit as blood sample have to be completed before blood is drawn.

Body weight without shoes will be recorded in pounds.

An AE form must be completed for all changes identified as clinically noteworthy.

8.2.3 Electrocardiogram

Standard 12-lead ECGs (in triplicate) will be performed after the patient has been supine and at rest for ≥5 minutes. The captured ECGs must be separated by at least 1 minute. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. Any Screening ECG with abnormal result(s) considered to be clinically significant should be repeated to confirm the finding(s) before excluding the patient from the trial. Patients will be randomized based on Screening ECG results from the central reader and Baseline ECG results from the trial site. If the Baseline ECG results from the central reader, when available, indicate a QTcF>450 msec at Baseline, the Investigator must contact the Medical Monitor to discuss the patient's continued participation in the trial. ECGs scheduled for the same visit as blood samples are to be completed before blood is drawn.

8.2.4 Clinical Laboratory Tests

The following clinical laboratory tests (samples are to be taken after an overnight fast of at least 8 hours) are to be performed as indicated in the SoA (Table):

- *Hematology:* hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count (with differential), and platelet count
- *Coagulation:* PT, aPTT, and INR
- *Chemistry:* albumin, albumin/globulin ratio, ALT, alkaline phosphatase, AST, bilirubin-direct, bilirubin-indirect, bilirubin-total, blood urea nitrogen, blood urea nitrogen/creatinine ratio, calcium, chloride, creatine kinase, creatinine, gamma-glutamyl transpeptidase, globulin, glucose, HbA1c, lactate dehydrogenase, phosphate, potassium, prolactin, sodium, total cholesterol, triglycerides, HDL, LDL, and uric acid
- *Urinalysis:* pH of freshly voided specimen, specific gravity, protein, glucose, ketones, blood, and microscopic examination of the sediment

- *Pregnancy tests*: urine or serum pregnancy tests, only required for female patients of childbearing potential (e.g., not postmenopausal or surgically sterile [hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy])
- *Other:* urine drug screen/blood alcohol test andTSH
- ACTH and cortisol

Laboratory samples will be analyzed by a central laboratory to ensure consistent interpretation of results. Additional details on the processing and shipment of specimens are provided in the Laboratory Manual. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

8.2.5 Adverse Events

All AEs occurring after the patient signs the ICF and up to 14 days after the end of the Treatment Period will be recorded.

See Section 9 for additional information.

8.2.6 Simpson-Angus Scale

The SAS is a measure of 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. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (see Section 6.7). Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration in the eCRF.

8.2.7 Barnes Akathisia Rating Scale

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the Investigator, subjective feelings of restlessness by the patient, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, patients will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (e.g., while engaged in neutral conversation or engaged in activity on the ward) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration (Section 6.7). Investigators are encouraged to delay scale administration until 12 hours have

elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration in the eCRF.

The BARS global score is defined as the global clinical assessment of akathisia.

8.2.8 Abnormal Involuntary Movement Scale

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the patient is at rest (e.g., in the waiting room), and the Investigator will also make global judgments on the patient's dyskinesias (items 8 through 10). 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). For this scale, the patient is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the patient's dental status. 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). Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 12 hours of scale administration. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration in the eCRF.

8.2.9 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS.

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior during participation in a clinical trial of centrally acting drugs. The C-SSRS is composed of 5 questions addressing suicidal ideation, with sub-questions assessing the severity of ideation as well as 5 suicidal behavior categories (Completed Suicide, Actual Attempt, Interrupted Attempt, Aborted Attempt, and Preparatory Acts or Behavior). The tool is administered via interview with the patient (by a trained operator/interviewer). All attempts will be made to use the same interviewer for the same patient throughout the study.

This study will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the patient with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all patients at the Screening Visit to determine eligibility (prior to the first dose). Risk for suicidal behavior during the study as determined by the Investigator's clinical assessment and C-SSRS as confirmed by the following: answers "Yes" on items 4 or 5 (C-SSRS – Ideation) with the most recent episode occurring within the 6 months before Screening, or answers "Yes" to any of the 5 items (C-SSRS – Suicidal Behavior) with an episode occurring within the 12 months before Screening. This

assessment will be repeated at Baseline Visit (using the Since Last Visit" C-SSRS). The "Since Last Visit" C-SSRS form will be completed at all post-Screening visits.

8.3 Pharmacokinetic Assessments

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

These samples will not be used to assess biomarkers or genetic markers.

PK plasma samples will be analyzed for concentrations of LB-102 [redacted], as applicable based on randomization. PK analyses will include the [redacted] randomized in the study regardless of cohort and PK blood samples will be collected on Day 1, 8, and 21 at the following timepoints after the morning dose: 15 minutes, 30 minutes, 1, 2, 3, 4, 8, and 24 hours. On Day 1 only, a pre-dose PK blood sample will be collected.

The following windows for PK collection are allowed:

- Pre-dose PK can be drawn up to 60 minutes prior to first dose.
- ± 5 minutes window on the 15 minutes, 30 minutes, 1, 2, 3, 4, 8 hours, PK collection times.
- ±15 minutes window on 24-hour PK collection time.

Note: The 24-hour PK must be drawn prior to next applicable dose.

Plasma concentrations of LB-102 [redacted] will be measured during the study and PK parameters derived using noncompartmental or compartmental methods as appropriate. The following PK parameters (as appropriate) will be calculated: 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 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 ($t_{½}$).

No value for λ_z, AUC_{0-inf}, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for patients with detectable concentrations for 2 or fewer time points.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

PK parameters of LB-102 [redacted] will be summarized by cohort using descriptive statistics (sample size, arithmetic means, geometric means, standard deviation [SD], % coefficient of variation [CV], minimum, median, and maximum). Figures will be created to

display mean and individual patient LB-102 [redacted] concentration-time curves in plasma on both a linear and logarithmic scale. Dose proportionality will be assessed using linear regression, or another acceptable approach.

9 ADVERSE EVENT REPORTING

9.1 Definitions and Criteria

9.1.1 Adverse Events

Per International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A,[2] an AE is "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product."

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs.

9.1.2 Serious Adverse Events

An SAE or a serious adverse drug reaction (ADR) is any untoward event that at any dose meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received study drug
- Other: important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

An AE is life-threatening if the patient was at immediate risk of death from the event; it does not refer to an event that hypothetically might have caused death if it were more serious. For

example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

All AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AEs (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either "serious" or "nonserious" according to the criteria outlined above.

An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Any serious, untoward event that occurs subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

9.1.3 Unexpected Adverse Drug Reactions

An unexpected ADR is a reaction for which the nature or severity is not consistent with the applicable product information (Investigator's Brochure [IB]). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis, and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 9.2.

9.1.4 Clinical Laboratory Changes

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the Baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study drug
- Has accompanying or inducing symptoms or signs
- Is judged by the Investigator as clinically significant

Combined elevations of aminotransferases and bilirubin, either serious or nonserious, and whether or not causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥2 × ULN with simultaneously ALT or AST ≥3 × ULN) should always be reported to the Sponsor as soon as possible following the procedures outlined in Section 9.2.2 for SAE reporting, with the Investigator's assessment of seriousness, causality, and a detailed narrative.

9.1.5 Assessment of Severity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the patient's normal level of functioning.
Moderate:	The AE produces some impairment of functioning, but is not hazardous to the patient's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health.

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself may be of relatively minor medical significance (such as severe headache). Severity is not the same as "seriousness," which is based on patient/event outcome at the time of the event.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience should be noted. If the severity category changes over several days, those changes should be recorded as separate AEs (with distinct onset dates).

9.1.6 Assessment of Relationship

Each AE will be assessed as to its relationship to the study drug, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the study drug will be assumed sufficient for at least plausible association.

Not related:	No causal relationship exists between the study drug and the AE, but an obvious alternative cause exists, e.g., the patient's underlying medical condition or concomitant therapy.
Possibly related:	A connection with the administration of the study drug appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the study drug.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the study drug.

When assessing the relationship to the study drug, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping the suspect study drug, in absence of other intervention or treatment)

- Known class effect
- Biological plausibility
- Lack of alternative explanation (e.g., a concomitant drug or disease)

9.1.7 Action Taken Regarding Study Drug

The action taken regarding the study drug as a result of an AE should be selected from 1 of the categories listed below and recorded in the eCRF:

- Dose Not Changed: No change in study drug dose was made.
- Drug Interrupted: The study drug was temporarily stopped.
- Drug Withdrawn: The study drug was permanently stopped.
- Not Applicable: Patient died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to the start of treatment.
- Unknown.

9.1.8 Other Action Taken for Event

Other action(s) taken as a result of the AE should be selected from 1 of the categories listed below and recorded in the eCRF:

- None (i.e., no treatment was required)
- Therapy(ies) required (i.e., prescription and/or OTC medication was required to treat the AE)
- Hospitalization or prolongation of hospitalization required (i.e., hospitalization was required or prolonged because of the AE, whether medication was required)
- Other

9.1.9 Adverse Event Outcome

The outcome of the AE should be selected from 1 of the categories listed below and recorded in the eCRF:

- Recovered/Resolved (i.e., the patient fully recovered from the AE with no residual effect observed)
- Recovering/Resolving (i.e., the AE improved but has not fully resolved)
- Not Recovered/Not Resolved (i.e., the AE is still present and observable)

- Recovered/Resolved with Sequelae (i.e., the residual effects of the AE are still present and observable, including sequelae/residual effects)
- Fatal (i.e., "fatal" should be used when death is a direct outcome of the AE)
- Unknown

9.2 Reporting Procedures and Requirements

9.2.1 Adverse Events

Each time the patient is seen or contacted by the Investigator or the study staff, be it at the study clinic, hospital, or over the telephone, the Investigator will determine whether any AE has occurred by evaluating the patient. AEs may be directly observed, reported spontaneously by the patient, or by questioning the patient at each contact. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. If AEs occur, the first concern will be the safety of the study patients. All AEs will be followed until resolved or stable and the outcome documented in the patient's source documentation/medical record, and in the eCRF.

Any AE that occurs after the patient signs the ICF until 14 days after the end of the Treatment Period will be recorded in the patient's source documentation/medical record and on the AE page of the eCRF. If the Investigator detects an AE in a patient after the last scheduled study visit and considers the event possibly related or related to prior study treatment, the Investigator should report it to the Sponsor or designated representative.

Illnesses that are present at the time informed consent is given are to be regarded as concomitant illnesses and recorded in the medical history. Investigators should document all significant illnesses that the patient has experienced within 30 days of Screening as a prior illness. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs.

All clinical laboratory results, vital signs, and ECG results or findings should be evaluated by the Investigator to determine their clinical significance. Isolated abnormal clinical laboratory test results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

9.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 9.1.2). If the AE is considered serious, the Investigator should report this even[redacted] to the IRB according to its standard operating procedures (SOPs).

If the Investigator detects an SAE in a study patient after the last scheduled study visit, and considers the SAE related or possibly related to this study's study drug administration, the Investigator should report it to Sponsor or designated representative.

The Investigator must report [redacted] all SAEs on the eCRF page within 24 hours of learning about the event regardless of relationship to study drug. If the site experiences a temporary disruption of the eCRF system, a back-up paper SAE Report Form will be available for site staff to complete.

At minimum, the initial report of the SAE should include the following information:

- AE description
- Study code/protocol number
- Patient number and year of birth
- Study drug
- Reporter name and contact information
- Relationship to the study drug

If the eCRF system is not available, the site staff will complete the back-up paper SAE Report Form and e-mail it within 24 hours to the following address: ~~drugsafety@worldwide.com~~.

In cases where the email system is unavailable, site staff will transmit the back-up paper SAE Report Form by fax to[redacted]

If notification is made via email or fax, site staff must enter the SAE information into the eCRF system as soon as the system becomes available. The original paper SAE Report Form submitted should be kept at the study site with the patient's source documentation/medical record or in the site's study files.

If the SAE has not resolved at the time the Investigator submits an initial SAE report, the Investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing). Additional follow-up information must be reported in the eCRF within 24 hours of awareness following Investigator (or site) awareness of the information. The Investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported per the reporting procedures described above.

All SAEs shall be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE eCRF page shall be updated. Additionally, any relevant laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information that has been gathered about the event shall be transmitted to the Sponsor and maintained in the patient's source documentation/medical record.

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. For reported deaths, the Investigator should supply [redacted] the IRB with any additional requested information

(e.g., autopsy reports and terminal medical reports). Additionally, any such reports shall be maintained in the patient's source documentation/medical record.

The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

Any suspected unexpected serious adverse reaction must be reported according to applicable regulatory requirements.

9.2.3 Pregnancy During the Study

If a patient, or the female partner of a male patient, becomes pregnant during the study, the Investigator will notify the Sponsor or designated representative immediately after the pregnancy is confirmed. The Investigator will report any pregnancies using the eCRF Pregnancy Reporting Form within 24 hours of becoming aware of the event. The Investigator will also (1) notify the patient's physician that the patient was being treated with LB-102, and (2) follow the progress of the pregnancy and document the outcome of the pregnancy. Pregnancy outcome information should be forwarded to Sponsor or designated representative when available.

Patients who become pregnant during the study will not be eligible for any further study treatments, the study drug will be discontinued immediately, and the patient will complete an ET Visit. The Investigator should make every effort to follow the patient until completion of the pregnancy and complete the Exposure in Utero (EIU) Reporting Form eCRF with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that of an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.2.2. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following the reporting guidelines as outlined in Section 9.2.2.

For reports of pregnancy in the female partner of a male patient, the eCRF Pregnancy Report Form and EIU Reporting form (or SAE form if applicable) should be completed with the patient's identification number and year of birth, and details regarding the female partner should be entered in the narrative section. The pregnancy outcome of the female partner should be followed and the reporting procedures outlined above (for pregnant patients) should be followed; however, consent should be received prior to the collection of any information via a pregnant partner ICF. The male partner may continue in the study after re-education and confirmation that recommended birth control methods per exclusion criteria are being used.

10 STATISTICS

10.1 General Procedures

The statistical analysis will be undertaken [redacted] in collaboration with LB Pharmaceuticals Inc.

A detailed Statistical Analysis Plan (SAP) will be finalized and signed before database lock and before analysis of the study being carried out. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, SD, minimum, and maximum). For categorical variables, frequencies and percentages will be presented by treatment. Baseline is defined as the last observation prior to initiation of study medication. Details of the statistical analyses will be provided in the SAP.

10.2 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] 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.

10.3 Analysis Populations

The following analysis populations are planned:

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

- Intent-to-treat (ITT) Analysis Set: all randomized patients, irrespective of whether they receive the drug or not.

- Modified Intent-to-treat (mITT) Analysis Set: all randomized patients with at least 1 dose of study drug. This will be the main analysis population for efficacy analysis purposes and patients will be analyzed based on the treatment they were randomized to.

- Per-Protocol (PP) Analysis Set: all patients included in the mITT Analysis Set that do not have a major protocol violation. The PP Analysis Set will be used for supportive analyses of the primary and key secondary efficacy endpoints.

10.4 Statistical Methods

10.4.1 Protocol Deviations

All protocol deviations (PDs) will be assessed and documented on a case-by-case basis before database lock. PDs should be collected by site and grouped into different categories, such as:

- Those who entered the study even though they did not satisfy the entry criteria;
- Those who developed withdrawal criteria during the study but were not withdrawn;
- Those who received the wrong treatment or incorrect dose;
- Those who received a prohibited concomitant treatment.

PDs that are considered to have an impact on the primary and some secondary efficacy variables, will be considered to be major PDs and will lead to exclusion of the patient from the PP Analysis Set. The deviations that might lead to this exclusion will be detailed in a Protocol Deviation Handling Plan and a full list of such occurrences will be provided in the Appendix 16.2 of the CSR (clinical study report).

10.4.2 Patient Disposition

Details for the reasons and number of the Screening failures will be tabulated. Patient disposition will include the number of patients who enroll in the study and the number and percentage of patients included in each analysis set by treatment group. The frequency and percentage of patients who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, as well as of those who complete the study, will be summarized by treatment group.

In addition, for the PP Analysis Set only, the reason for exclusion from this analysis set will also be tabulated.

10.4.3 Demographic and Baseline Characteristics

Treatment groups will be compared with respect to patient demographics and baseline characteristics using descriptive statistics only. Demographics and Baseline characteristics, including age, sex, race, weight, height, BMI, and disease history (duration, etc.) will be summarized by treatment group for the Safety Analysis Set.

10.4.4 Analysis of Efficacy

10.4.4.1 Estimand

For the definition of the main study estimand, the following intercurrent events (ICEs) have been deemed as relevant:

a) Taking a prohibited medication prior to Week 4

b) Starting an emergency treatment prior to Week 4

The primary estimand for all the above events will follow the treatment-policy strategy, to estimate the difference in means (population-level summary) between any active dose of LB-102 and placebo (treatment) in adult patients with acute schizophrenia as defined by the inclusion/exclusion criteria (population) for change from Baseline to Week 4 in the PANSS total score (variable) regardless of the occurrence of the above-mentioned ICEs.

10.4.4.2 Primary Efficacy Endpoint

The primary endpoint is the change from Baseline to Week 4 in the PANSS total score. The null and alternative hypothesis for each dose level are as follows:

H_0: the difference in the change from Baseline to Week 4 in the PANSS total score between LB-102 active treatment and placebo is equal to 0;

H_1: the difference in the change from Baseline to Week 4 in the PANSS total score between LB-102 active treatment and placebo is different from 0.

All efficacy endpoints will be analyzed for the mITT Analysis Set, and the primary endpoint will also be analyzed for the PP Analysis Set.

Principal Analysis

In line with the estimand definition, all data collected after the occurrence of an ICE will be included in the primary efficacy analysis. As a primary analysis, all missing data due to study discontinuation for lack of efficacy or drug-related AEs will be imputed assuming a Missing Not At Random (MNAR) mechanism and assuming that after withdrawal the subjects 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.

The primary efficacy endpoint (change from Baseline to Week 4 on the PANSS total score) will be analyzed using a Mixed Model for Repeated Measures (MMRM) approach, including site, visit, treatment, and their interaction as categorical covariates and Baseline PANSS as continuous covariates. Within -patient correlation across repeated measures will be accounted for by using an unstructured correlation, or the best fit structure should an unstructured matrix cause convergence issues. The differences between active treatment groups and placebo at Week 4 will be estimated alongside confidence intervals (CIs) and *P* values. The model will be fit separately for each imputed dataset and results pooled using Rubin's rules to derive one treatment effect estimate.

This analysis will be performed for the mITT and repeated for the PP Analysis Set. Should the mITT and ITT differ substantially (e.g., by at least 10%) the primary analysis will be performed for the ITT and the mITT only be regarded as supportive information.

A strategy for pooling sites enrolling a limited number of patients will be specified in the SAP prior to unblinding, and the derived 'pooled study site' variable used in all relevant statistical analyses.

Sensitivity Analysis

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 results. Details of the MI model for this and the main analysis as well as further sensitivity analyses will be provided in the SAP.

The analysis model will be the same as for the primary analysis, with results obtained on each imputed dataset that will be pooled to provide a single measure of treatment effectiveness (alongside 95% CI and *P* values).

Exploratory Analysis

Further exploratory assessments might be performed to investigate heterogeneity of treatment effects across investigational sites, by summarizing the primary endpoint separately by study site. Subgroup Analysis

Subgroups of interest will be defined based on BMI and severity of disease at Baseline (as measured by the PANSS total score). The primary and secondary endpoints will be descriptively analyzed within the relevant subgroup strata.

10.4.4.3 Secondary Efficacy Endpoint(s)

All continuous secondary efficacy variables will be analyzed using similar approaches to what was described for the primary endpoint, using the appropriate Baseline measurement instead of the Baseline PANSS score, without any data imputation.

The secondary efficacy endpoints to analyze in this way are the following:

- Change from Baseline to Week 4 in 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

The MMRM model for the above endpoints will allow to estimate the least square (LS) means and their difference between each active dose and placebo alongside their 95% CI and *P* values, which will only be displayed for informative/descriptive purposes (i.e., no multiplicity correction will be implemented).

An additional exploratory endpoint is clinical response, defined as a reduction of ≥20% from Baseline in PANSS total score at Week 4. This will be analyzed consistently with a "composite

strategy" estimand, where a patient will be considered a responder if the criteria for clinical response are met and none of the ICEs mentioned above has occurred. For the purposes of this endpoint, only study discontinuations related to the treatment (e.g., lack of efficacy, AE related to the underlying condition such as worsening, etc.) will be considered as relevant ICEs and thus contribute to a non-responder status if occurring.

This endpoint will be analyzed using a logistic regression model including treatment and Baseline PANSS score as covariates to estimate the odds ratio of response of any active dose vs placebo.

10.4.4.4 Exploratory Efficacy Endpoint

The Cogstate Computerized Battery of Tests scores will be analyzed using an Analysis of Covariance (ANCOVA) model including site and treatment as categorical covariates and Baseline Cogstate score as continuous covariate. No imputations will be performed for missing data and similar quantities to compare treatments as for the primary analysis model (LS means and their differences across arms) will be presented.

10.4.4.5 Multiplicity

Results from the analysis of the primary endpoint 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 comparing the larger *P* value against 0.05 and if this hypothesis is rejected then even the other one is rejected, otherwise the smaller *P* values is tested against 0.025.

10.4.5 Analysis of Safety

All safety analyses will be performed using the Safety Analysis Set.

10.4.5.1 Extent of Exposure

Extent of exposure will be summarized by treatment as number of drug administrations received and the overall duration of the exposure (from first to last dose) in days.

10.4.5.2 Adverse Events

AEs will be characterized by type, severity, seriousness, and relationship to treatment. AEs will be coded by preferred term and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

The incidence of TEAEs (number and percent of patients reporting the AE at least once during the study), SAEs, AEs related to study treatment, SAEs related to treatment, and AEs leading to study discontinuation will be summarized by treatment.

A TEAE is defined 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.

Any AE commencing after the last dose of study drug plus 14 calendar days will not be considered treatment-emergent.

The incidence of TEAEs and treatment-related AEs will also be summarized by maximum severity and strongest relationship to study drug by MedDRA primary SOC and preferred term. The summary will include the total number and percentage of patients reporting a particular event as well as the total number of events. In counting the number of events reported, a continuous event, i.e., reported more than once and which did not cease, will be counted only once; noncontinuous AEs reported several times by the same patient will be counted as multiple events.

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 SOC/preferred term will be calculated for each LB-102 dose vs placebo alongside 95% CI and *P* values. For such analysis, a Poisson regression model with a log-link and a robust error variance will be considered, using the binary indicator for the presence of a given SOC/preferred term (or any AE) as response and treatment as the only covariate whose betas will be exponentiated to return the associated relative risk.

10.4.5.3 Electrocardiogram

A list of patients with abnormal 12-lead ECG parameters will be presented. Baseline and change from Baseline in ECG parameters (heart rate, cardiac rhythm, PR interval, QRS interval, QT interval, and QTc interval) will be summarized at each post-Baseline time point.

10.4.5.4 Vital Signs

Summary statistics for absolute vital sign value and the changes from Baseline will be presented by treatment group for each visit.

10.4.5.5 Physical Examination

Physical examination data will be listed only.

10.4.5.6 Clinical Laboratory Tests

Mean changes from Baseline at each post-Baseline time point for each laboratory variable will be presented. In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables for the Baseline and follow-up measurements will be presented.

10.4.5.7 Other Variables Related to Safety

Other safety variables include the SAS, the BARS, the AIMS, and the C-SSRS.

These scales will be summarized by treatment group and visit including, where appropriate, change from Baseline measures.

10.4.6 Pharmacokinetics

Data from patients who participated in the study will be included in the PK analysis. Patients with missing sample concentrations will be included in the PK analyses, provided their PK parameters can be adequately characterized based upon the remaining data.

Deviation from procedures described in this protocol that impact the quality of data required to meet the objectives of the study will be documented and may result in the exclusion of PK data from the analyses for a particular patient. This includes any deviations or events that would invalidate the evaluation of the PK. Examples of deviations and events that could result in the exclusion of PK data from the analyses include emesis after dosing (within the predetermined time), sample processing, or assay errors that lead to inaccurate bioanalytical results. Other deviations or events that do not disqualify data from analyses may require minor adjustments to calculations. If these occur, data analyses will be adjusted and documented accordingly such that conclusions are not biased. An example of such an event includes, but is not limited to, minor deviations between the actual and scheduled time of sample collection.

Other PK analyses may be performed as appropriate.

Plasma concentrations of LB-102 [redacted] will be measured during the study and PK parameters derived using noncompartmental or compartmental methods as appropriate. The following PK parameters (as appropriate) will be calculated: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/F, C_{max}, T_{max}, λ_z, and $t_{½}$.

No value for λ_z, $AUC_{0\text{-}inf}$, CL/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for patients with no detectable concentrations for 2 or fewer time points.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

PK parameters of LB-102 ~~and metabolites~~ will be summarized by cohort using descriptive statistics [redacted] Figures will be created to display mean and individual patient LB-102 and [redacted] concentration-time curves in plasma on both a linear and logarithmic scale. Dose proportionality will be assessed using linear regression, or another acceptable approach.

10.4.7 Interim Analysis

No interim analysis is planned for this study.

11 STUDY MANAGEMENT AND RESPONSIBILITIES

11.1 Ethics

11.1.1 Good Clinical Practice

The study will be performed in accordance with this protocol, local national laws (as applicable), ICH guideline for Good Clinical Practice (GCP),[3] and the most recent guidelines of the Declaration of Helsinki.[7]

11.1.2 Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IRB. Approval is required for the study protocol, IB, protocol amendments, ICFs, patient information sheets, and advertising materials. No study drug will be shipped to a site until written IRB authorization has been received by the Sponsor or its representative.

11.1.3 Informed Consent

For each study patient, a written ICF will be obtained before any protocol-related activities are performed. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. Patients should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The PI or a designated representative will provide the Sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

Subjects will also be asked to provide additional consent for their participation in a secure, proprietary research subject database administered by VCT [Verified Clinical Trials, Garden City, NY]. The database will utilize partially identified subject information to review subjects' research study history within the database. Participants who are identified as verification failures by VCT, should not be enrolled without documented approval from LB Pharmaceuticals and ~~Worldwide~~. At the last subject contact, VCT staff will automatically close out the subject (safety follow-up, ET, or complete) based on the IXRS.

11.1.4 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor and its authorized representatives are allowed full access to the records.

11.2 Auditing and Monitoring

To ensure accurate, complete, and reliable data, [redacted] will provide instructional material to the study sites and the Sponsor at a start-up training session to instruct the Investigators and

study coordinators. This session will give instruction in the protocol, the completion of the eCRFs, and study procedures.

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. A Monitoring Plan will be developed and approved by the Sponsor [redacted] using a risk-based monitoring approach with the primary focus on critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human patients or the integrity of the study results. Monitoring may include remote monitoring, personal visits, and/or telephone communication to assure that the investigation is conducted according to the protocol, SOPs, GCP guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. As defined in the Monitoring Plan, eCRFs may be reviewed remotely or on-site for completeness, clarity, and consistency with source documents available for each patient. At the conclusion of the study, [redacted] will conduct a quality review of the database.

The study may be audited by the Sponsor, [redacted] and/or regulatory agencies at any time. Investigators will be given a notice before an audit occurs.

Medical advisors and clinical research associates or assistants may request to witness patient evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the eCRF generation, where clinically appropriate.

11.3 Data Handling, Documentation, and Record Keeping

11.3.1 Source Documentation

Note that a variety of original documents, data, and records for a given patient (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study) will be considered as source documents in this study. All study specific information obtained at each study visit must be recorded in the patient's record (source documentation), and then entered into a validated EDC database by trained site personnel.

11.3.2 Direct Access to Source Data and Documents

The Investigator/institution will provide direct access to source data and documents for trial-related monitoring, audits, IRB, and regulatory inspection.

11.3.3 Record Retention

The Investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority but should not be less than 2 years after the first marketing approval. In addition, the retention period must meet the requirements of the most stringent authority. The Investigator should take measures to prevent accidental or premature destruction of these documents.

11.3.4 Study Documentation

By signing a copy of the country-specific regulatory form(s), the PI or designated representative acknowledges that they have received a copy of the IB on LB-102 and assures the Sponsor that they will comply with the protocol and the provisions stated in the country-specific regulatory form(s). No changes in this protocol can be made without the Sponsor's written approval.

11.4 Indemnification

The Sponsor's indemnification of the Investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

11.5 Amendments

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified within 5 calendar days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study patient, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

11.6 Study Discontinuation

Both the Sponsor and the PI or designated representative reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, the Sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the PI or designated representative will inform the IRB of the same within the required time frame. In terminating the study, the Sponsor and the PI or designated representative will assure that adequate consideration is given to the protection of the patients' interests.

12 PUBLICATION POLICY

The Sponsor must review and approve any results of the study, abstracts or slide presentation for professional meetings prepared by the Investigator(s), before its submission. Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately. This review is required to ensure that the Sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use. Authorship of any publication will agree with any other study Investigators and the Sponsor. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors,[4] Investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those Investigators will receive a collective authorship as the “LB-102 Study Group” and will be identified in a note.

13 REFERENCES

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14 APPENDICES

14.1 Names of Study Personnel

The names of study personnel are provided in separate documentation to the site.

Role	Name and Contact Information
Sponsor:	
Medical Monitor:	
CRO:	
Central Laboratory:	
ECG Central Facility:	

Abbreviations: CRO = contract research organization; ECG = electrocardiogram

14.2 Phase 1 Clinical Data

14.2.1 Phase 1 LB-102-001 - Completed

A randomized, double-blinded, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, and PK of LB-102 administered orally to healthy volunteer (Protocol LB-102-001).

This was a Phase 1, randomized double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and PK of LB-102 in healthy volunteer. The study consisted of 2 parts: Part A – Single Ascending Dose (SAD) and Part B – MAD. There were 5 cohorts in Part A and 3 cohorts in Part B. Each cohort consisted of 8 patients (n = 6 assigned to LB-102 treatment, and n = 2 assigned to placebo treatment). In Parts A and B, eligible healthy volunteers were randomized on Day 1 (pre-dose) to placebo (n = 2) or LB-102 (n = 6) treatment. Eligible healthy volunteers received 1 dose on Day 1 (Part A) or 13 doses on Days 1 to 7 (Part B) of placebo or LB-102. In Cohort 1 (Part A), dosing of the first 2 healthy volunteers (1 active and 1 placebo) commenced at least 24 hours prior to the remaining 6 healthy volunteers. Dosing of the remaining healthy volunteers in the cohort proceeded if no safety issues were identified for the first 2 healthy volunteers. Blood samples for PK and safety assessments were collected at nominal timepoints described below. Healthy volunteers were discharged on Day 3 (Part A) or Day 9 (Part B) and returned for a Follow-up Visit (Day 8 or Day 15, respectively) for safety review. For Cohort 5 (Part A), healthy volunteers returned for an additional Follow-up Visit.

Safety Results

LB-102 was generally well tolerated with all TEAEs either mild (37) or moderate (6) severity. Out of the 64 healthy volunteers, 28 healthy volunteers (50 mg QD, N = 4; 10 mg QD, N = 2; 100 mg QD, N = 3; 200 mg QD, N = 3; 150 mg QD, N = 1; 50 mg BID, N = 2; 100 mg BID, N = 3; 75 mg BID, N = 5; placebo, N = 5) experienced at least 1 TEAE, with a total of 43 TEAEs. Out of the 43 TEAEs, 29 (50 mg QD, N = 3; 10 mg QD, N = 1; 100 mg QD, N = 3; 200 mg QD, N = 5; 150 mg QD, N = 1; 50 mg BID, N = 2; 100 mg BID, N = 5; 75 mg BID, N = 8; placebo, N = 1) were considered possibly, probably, or definitely related to treatment.

Of the TEAEs definitely related to study drug, there were 11 cases of elevated prolactin (≥100 µg/L; 50 mg QD, N = 3; 10 mg QD, N = 1; 100 mg QD, N = 1; 150 mg QD, N = 1; 50 mg BID, N = 2; 100 mg BID, N = 1; 75 mg BID, N = 2), 4 cases of moderate dystonia (200 mg QD, N = 1; 100 mg BID, N = 2; 75 mg BID, N = 1), and 1 case of mild ECG QTcF prolongation (458 msec, 200 mg LB-102 QD) that were all resolved with either no course of action (prolactin increase and QTcF interval prolongation) or concomitant medications (dystonia). Due to 2 TEAEs in the same SOC (acute dystonic reaction), treatment was halted in all healthy volunteers taking 100 mg LB-102 BID (Cohort 7) and the 2 healthy volunteers in Cohort 7 taking placebo. As a result, the SRC decided to reduce the dose for Cohort 8 to 75 mg LB-102 BID. Additionally, because QTcF interval was fairly prolonged from pre-dose values (20-46 msec) in all healthy volunteers taking 200 mg LB-102 QD (Cohort 4), the dosage for Cohort 5 was reduced to 150 mg LB-102 QD. Of the TEAEs probably or possibly related to study drug, there were 4 cases of nausea (100 mg LB-102 QD, N = 1; 200 mg LB-102, N = 1; 100 mg

LB-102 BID, N = 1; 75 mg LB-102 BID, N = 1) and 1 case of vomiting (100 mg LB-102 BID), urticaria (100 mg LB-102 QD), gastroesophageal disease (200 mg LB-102), insomnia (75 mg LB-102 BID), dizziness (75 mg LB-102 BID), and somnolence (75 mg LB-102 BID).

Vital signs and physical examination results were largely unchanged from Baseline. Other than increases in prolactin, chemistry laboratory results were also relatively unchanged throughout study treatment. C-SSRS did not change during study treatment.

Pharmacokinetics Results

In Part A (SAD), LB-102 was rapidly absorbed and LB-102 concentration generally declined from peak in an apparent biphasic manner. The estimates of mean $t_{½}$ of LB-102 generally ranged from 11.993 to 14.146 hours; exposure (as measured by C_{max}, AUC_{0-t}, and AUC_{0-inf}) increased in a slightly greater than dose-proportional manner. Mean C_{max} ranged from 24.1 ng/mL at the lowest dose of 10 mg LB-102 to 975.667 ng/mL at the highest dose of 200 mg LB-102. Mean AUC_{0-t} ranged from 221.911 h•ng/mL at the lowest dose to 6709.821 h•ng/mL at the highest dose. Mean AUC_{0-inf} ranged from 252.637 h•ng/mL at the lowest dose to 7002.109 h•ng/mL at the highest dose. Apparent clearance (CL/F) appeared to decrease as dose increased (42.44 L/h to 28.89 L/h).

In Part A (SAD), [redacted] was formed quickly over time after a single dose of LB-102 (median T_{max}, range = 2 to 3.5 hours) and generally declined with an approximate biphasic disposition of comparable shape to LB-102 but at approximately 2.5% of LB-102 abundance. The plasma concentrations of [redacted] at lower doses were within several fold of LLOQ making descriptive PK analysis tenuous. In fact, [redacted] was not detected in healthy volunteers taking 10 mg LB-102 QD (Cohort 2). Mean [redacted] $t_{½}$ ranged from approximately 8.921 to 14.614 hours. Mean C_{max} ranged from 4.167 ng/mL at the lowest detectable dose, 50 mg LB-102, to 27.747 ng/mL at the highest dose, 200 mg LB-102. Mean AUC_{0-t} ranged from 31.183 h•ng/mL at the lowest detectable dose, 50 mg LB-102, to 247.397 h•ng/mL at the highest dose, 200 mg LB-102. Mean AUC_{0-inf} ranged from 188.552 h•ng/mL at the lowest detectable dose, 100 mg LB-102, to 314.264 h•ng/mL at the highest dose, 200 mg LB-102.

In Part B (MAD), extensive PK sampling occurred on Day 6 rather than Day 7 and the last dose was given on Day 7. Thus, the PK profile for the second dose on Day 6 (including the pre-dose on Day 7) was used to calculate the PK parameter after multiple doses. For the calculation of area under the concentration-time curve from time of dosing up to 12 hours (AUC_{0-12}), Day 1, the actual time for the 12-hour sample was used in place of the nominal 12 hour since the concentration at 12 hours post-dose could not be predicted. In Part B (MAD), trough concentrations of LB-102 and [redacted] plateaued before the morning dose on Day 4. After multiple doses, there was slight to moderate accumulation of LB-102 across dose levels with mean accumulation ratio based on C_{max} after the first dose and last dose (RC_{max}) values ranged from 1.121 to 1.798 and with mean accumulation ratio based on AUC after the first and last dose (RAUC) values ranged from 1.472 to 1.925. [redacted] had a higher accumulation than LB-102 across dose levels with mean RC_{max} values ranged from 1.317 to 2.016 and with mean RAUC values ranged from 1.801 to 2.232. Exposure (as measured by C_{max}, Day 7 and AUC_{0-12},

Day 7) to LB-102 increased in a dose-proportional manner. Apparent clearance at steady state (CLss/F) to LB-102 appeared to be similar as dose increased.

Table 14.1: Summary of Key Plasma LB-102 Pharmacokinetic Parameters – Pharmacokinetic Population

PK Parameter	Statistic	10 mg LB-102 (N = 6)	50 mg LB-102 (N = 6)	100 mg LB-102 (N = 6)	150 mg LB-102 (N = 6)	200 mg LB-102 (N = 6)
C_{max} (ng/mL)	n	6	6	6	6	6
	Mean (SD)	24.1 (10.728)	176 (52.786)	348.167 (141.832)	596.5 (117.527)	975.667 (253.995)
	GM (GM CV%)	22.292 (44.5)	169.502 (30.8)	322.891 (45.6)	585.831 (21.7)	949.831 (25.4)
T_{max} (h)	n	6	6	6	6	6
	Median (min, max)	3 (3, 3)	3 (2, 4)	3.01 (1, 4)	3 (3, 4)	1.75 (1.5, 3)
λ_z (l/h)	n	6	6	6	6	6
	Mean (SD)	0.054 (0.01411)	0.0592 (0.00877)	0.0521 (0.0136)	0.0591 (0.00945)	0.0569 (0.01591)
$t_{½}$ (h)	n	6	6	6	6	6
	Mean (SD)	13.75 (3.9375)	11.933 (1.7797)	14.146 (3.9617)	11.969 (1.8897)	12.997 (3.5854)
AUC_{0-t} (ng•h/mL)	n	6	6	6	6	6
	Mean (SD)	221.911 (69.4093)	1526.08 (176.5906)	2636.04 (481.5386)	4490.161 (741.2812)	6709.821 (834.9332)
	GM (GM CV%)	212.353 (35.1)	1517.497 (11.7)	2594.86 (20.2)	4439.9 (16.5)	6668.19 (12.2)
AUC_{0-24} (ng•h/mL)	n	6	6	6	6	6
	Mean (SD)	198.807 (66.9513)	1336.105 (167.6764)	2303.664 (533.1684)	4067.23 (685.9163)	5983.093 (833.9816)
	GM (GM CV%)	189.498 (35.1)	1327.048 (12.9)	2244.225 (26.5)	4019.483 (17)	5938.059 (13.3)
AUC_{0-inf} (ng•h/mL)	n	6	6	6	6	6
	Mean (SD)	252.637 (69.857)	1595.938 (189.1599)	2809.785 (477.7622)	4363.577 (745.7299)	7002.109 (820.7252)
	GM (GM CV%)	244.171 (29.7)	1586.584 (11.9)	2773.559 (18.1)	4587.238 (16.1)	6962.173 (11.8)
CL/F (L/h)	n	6	6	6	6	6
	Mean (SD)	42.44 (12.598)	31.7 (3.794)	36.56 (6.935)	33.05 (5.25)	28.89 (3.381)

Abbreviations: AUC_{0-24} = area under the concentration-time curve up to 24 hours; AUC_{0-inf} = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve from time zero to time; CL/F = oral clearance; C_{max} = maximum concentration; CV = coefficient of variation; GM = geometric mean; h = hours; λ_z = terminal elimination rate constant; mg = milligram; ng/mL = nanogram per milliliter; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = apparent terminal half-life; T_{max} = time to reach maximum concentration

Summary – Conclusions

LB-102 was well tolerated with all TEAEs either mild or moderate severity. The most notable safety result was mildly elevated prolactin levels, which was expected to occur based on LB-102's mechanism of action as a dopamine antagonist and that it is a commonly reported AE for drugs of this class.[1] At the highest dose (200 mg LB-102), QTcF prolongation was noted; however, predefined stopping criteria were not met. In addition, acute dystonic reaction was reported in 200 mg LB-102 QD (which resulted in this dose being discontinued) and 75-100 mg LB-102 BID. There were no significant TEAEs at the lower doses.

For PK results in Part A (SAD), LB-102 was rapidly absorbed and LB-102 concentration generally declined from peak in an apparent biphasic manner. Exposure increased in a slightly greater than dose-proportional manner. Apparent clearance appeared to decrease as dose increased. Minor (as defined by the FDA)[1] amounts of [redacted], approximately 2.5% of LB-102, were detected in plasma samples. The plasma concentrations of [redacted] at lower doses were within several fold of LLOQ making descriptive PK analysis tenuous. For PK results in Part B (MAD), trough concentrations of LB-102 and [redacted] plateaued before the morning dose on Day 4. After multiple doses, there was slight to moderate accumulation of LB-102 across dose levels.

[redacted] had a higher accumulation than LB-102 across dose levels. Exposure to LB-102 increased in a dose-proportional manner. Apparent clearance at steady state to LB-102 appeared to be similar as the dose increased. LB-102 was designed to be an improved version of [redacted] by having increased permeability across the blood-brain-barrier, which would potentially decrease the plasma concentrations needed to achieve efficacy. This would thereby decrease the magnitude and frequency of AEs typically observed in schizophrenia patients treated with [redacted]. [redacted] LB-102-001 achieved its objectives of identifying the safety, tolerability, and PK of a single oral dose and multiple oral doses of LB-102 in healthy volunteer.

14.3 Exclusionary Laboratory Results for Screening

Table 14.2: Important Exclusionary Criteria for Screening

Diabetes
Patients with insulin-dependent diabetes mellitus (i.e., any patients using insulin) are excluded. Patients with non-insulin-dependent diabetes mellitus may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria: • HbA1c <7.0%, **and** • Screening glucose must have been ≤125 mg/dL or ≤6.94 mmol/L (fasting) or <200 mg/dL or <11.1 mmol/L (non-fasting). If the non-fasting Screening glucose was ≥200 mg/dL or ≥11.1 mmol/L, patients must have been retested in a fasted state, and the retest value must have been ≤125 mg/dL or ≤6.94 mmol/L, **and** • Patient had been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to Screening or diabetes had been well controlled by diet for at least 28 days prior to Screening, **and** • Patient had no hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, **and** • Patient's diabetes should not be newly diagnosed during Screening for the trial.
Laboratory
• Platelets ≤75,000/μL or ≤75×10^9/L • Hemoglobin ≤9 g/dL or ≤90 g/L • Neutrophils, absolute ≤1000/μL or ≤1×10^9/L • Aspartate transaminase (AST) >2 × ULN • Alanine transaminase (ALT) >2 × ULN • Creatine phosphokinase (CPK) >3 × ULN, unless discuss with and approve by the Medical Monitor • Creatinine ≥2 mg/dL or ≥176.8 μmol/L • Estimated creatinine clearance of <45 mL/min, calculated using the Cockcroft-Gault equation, at Screening • HbA1c ≥7.0% • Abnormal free T4 (during Screening), unless discussed with and approve by the Medical Monitor. (Note: Free T4 will be measured only if the result for TSH is abnormal.)
ECG Results
Clinically significant abnormal finding on the triplicate set of ECGs or evidence of any of the following cardiac conduction abnormalities at Screening (mean values will be used for the following criteria):

- Heart rate <40 bpm or >110 bpm (based on the ECG reading). NOTE: The Medical Monitor should be contacted in any instance where the Investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation
- QTcF interval >450 msec for males and females
- PR interval ≥200 msec
- Intraventricular conduction delay with QRS duration >120 msec
- Evidence of second- or third-degree AVB
- Electrocardiographic evidence of complete LBBB, complete RBBB, or incomplete LBBB

14.4 Half-Life of Major Psychiatric Medications

The recommended duration of the washout period should be 5 × the duration of the known half-life of the drug.

Medication	Half-life after oral administration (hours)
Antipsychotics	
Second Generation Antipsychotics	
Aripiprazole	**75-94**
Asenapine	**24**
Brexpiprazole	**91**
Cariprazine	**48-96 (parent drug)** **7-21 days (active metabolites)**
Clozapine	**12**
Iloperidone	**18-26**
Lurasidone	**29-37 (at steady state)**
Olanzapine	**30-38**
Paliperidone	**23**
Pimavanserin	**57 parent drug** **(200 for active metabolite)**
Quetiapine	**6-12**
Risperidone	**20**
Ziprasidone	**7 oral** **2-5 IM**
First Generation Antipsychotics	
Chlorpromazine	**30**
Fluphenazine	**33**
Haloperidol	**20**
Loxapine	**6-8 (parent drug)** **12 (active metabolites)**
Perphenazine	**9-12 (parent drug)** **10-19 (active metabolite)**
Pimozide	**55**
Thiothixene	**34**

Thioridazine	**4-10 (parent drug)** **21-25 (active metabolites)**
Trifluoperazine	**3-12 (parent drug)** **22 (active metabolites)**
Antidepressants	
Selective Serotonin Reuptake Inhibitors (SSRI)	
Citalopram **Escitalopram** **Paroxetine** **Sertraline**	**20-30**
Fluoxetine	**1-3 days**
Fluvoxamine	**15**
Serotonin-norepinephrine (SNRI) reuptake inhibitors	
Desvenlafaxine	**9-11**
Duloxetine	**10-12**
Levomilnacipran ER	**12**
Milnacipran	**8-10**
Venlafaxine	**5 (parent)** **11 (active metabolites)**
Tricyclics	
Amitriptyline	**9-25**
Imipramine	**19**
Clomipramine	**12-36**
Doxepin	**3-80**
Nortriptyline	**36**
Monoamine oxidase inhibitors (MAOIs)	
Tranylcypromine	**2**
Phenelzine	**12**
Isocaroxazid	**36**
Moclobemide	**2-4**
Other	
Mirtazapine	**20-40**

Agomelatine	**1-2**
Reboxetine	**13**
Vortioxetine	**66**
Benzodiazepines	
Alprazolam	**12-15**
Lorazepam	**10-20**
Oxazepam	**6-20**
Diazepam	**36-200**
Chlordiazepoxide	**3 -200**
Temazepam	**5-15**
Nitrazepam	**24-40**
Non-Benzodiazepine Anxiolytics	
Buspirone	**2-11**
Pregabalin	**6**
Antiepileptics	
Carbamazepine	**12-27**
Gabapentin	**5-7**
Lamotrigine	**15-35**
Levetiracetam	**6-8**
Oxcarbazepine	**8-15**
Pregabalin	**5-7**
Topiramate	**20-30**
Vigabatrin	**5-8**
Valproic acid	**6-17**