An Open Label Positron Emission Tomography (PET) Study to Evaluate Dopamine Receptor Occupancy of LB-102 Administered Orally to Healthy Subjects

PROTOCOL NUMBER:	LB-102-002
STUDY PHASE:	Phase 1B
IND NUMBER:	137581
PROTOCOL VERSION:	30 Sep 2020 v1.0 11 Nov 2020 v1.1
SPONSORED BY:	LB Pharmaceuticals, Inc. 575 Madison Avenue New York, NY 10022 Phone: (646) 588.8175
CONTRACT RESEARCH ORGANIZATION:	Target Health LLC 261 Madison Ave Floor 24 New York, NY 10016 Phone (212) 681-2100 (Ext 0)

This study will be performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board, or as required by law.

PROTOCOL APPROVAL

PROTOCOL TITLE: An Open Label Positron Emission Tomography (PET) Study to Evaluate Dopamine Receptor Occupancy of LB-102 Administered Orally to Healthy Subjects

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11 Nov 2020 v1.1

SPONSOR: LB Pharmaceuticals, Inc.
575 Madison Avenue
New York, NY 10022
Phone: (646)588.8175

STUDY PRODUCT: LB-102

Sponsor Approval:

Date: _____ Signature: _____
Name: Zachary Prensky
Title: CEO
LB Pharmaceuticals, Inc.

Procedures in Case of Emergency

Sponsor/CRO Contact Information

Role in Study	Name	Address and Telephone Number
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Investigator Agreement

PROTOCOL TITLE: An Open Label Positron Emission Tomography (PET) Study to Evaluate Dopamine Receptor Occupancy of LB-102 Administered Orally to Healthy Subjects

PROTOCOL NUMBER: LB-102-002

I have read the protocol and agree that it, along with the related Clinical Trial Agreement, contains all the details necessary to carry out the study. I will conduct this study according to the protocol and will complete the study in the time agreed. Potential additions or modifications to the study will be by mutual written agreement between LB Pharmaceuticals, Inc. and me and will be documented and filed, if required, with the Institutional Review Board and the United States Food and Drug Administration.

Investigator Signature: _____ Date: _____

Investigator Name (print):

Institution Name:

Institution Address:

Institution Telephone Number:

1. SYNOPSIS

Name of Sponsor/Company: LB Pharmaceuticals, Inc.

Name of Investigational Product: LB-102

Name of Active Ingredient: *N*-methyl amisulpride

Protocol Number: LB-102-002

Title of Study: An Open Label Positron Emission Tomography (PET) Study to Evaluate Dopamine Receptor Occupancy of LB-102 Administered Orally to Healthy Subjects

Estimated Number of Study Center(s): Single Center

Phase of Development: 1B

Objectives:

Primary Objective:

1. Brain Receptor Occupancy as Measured by Positron Emission Tomography

Secondary Objectives:

1. Safety and Tolerability as Measured by Number of Participants with Adverse Events

Study Design: This is a Phase 1B, open label study designed to evaluate the dopamine receptor occupancy in healthy subjects. There will be 4 cohorts consisting of 4 subjects each. Eligible subjects from Cohort 1 will receive 1 dose of LB-102 on Day 1. Subjects in the final cohort will be dosed for 4 days BID (Days 1-4) and 1 day QD (Day 5 AM; i.e. a total of 9 doses) on an inpatient basis. This will be an open label study. Blood samples for PK and safety assessments will be collected at Screening, immediately pre-dose, and during/before/after PET scan. Subjects enrolled in the inpatient cohort will be monitored daily. Follow-up after discharge will consist of a phone call the evening of discharge and the next day to check on subjects. This will be an adaptive study and doses in Cohorts 2-4 will be determined after PET data from Cohort 1 are obtained.

Cohort	Treatment
1 (n=4)	LB-102 50 mg, single dose
1 (n=4)	LB-102 XX mg, single dose
1 (n=4)	LB-102 XX mg, single dose
1 (n=4)	LB-102 XX mg, 4 x BID (Days 1-4) and 1 x QD (Day 5 AM; i.e. a total of 9 doses)

Number of Subjects (Planned): A total of 16 subjects will be enrolled with 4 subjects being enrolled in each of 4 cohorts. Each cohort must comprise at least one female and one male subject. Subjects will be considered enrolled at the point they are dosed.

Main Criteria for Eligibility:

Inclusion Criteria:

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. Competent to provide informed consent.
2. Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.
3. Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.
4. Body Mass Index (BMI) ≥ 18 and ≤ 30 kg/m^2 at screening visit.
5. Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.
6. Have normal clinical laboratory test results and ECG, which are not considered to be clinically significant by the Investigator.
7. Females participating in the study:
    a. Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's ranges; OR
    b. Females of child-bearing potential must have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:
        i. condom plus spermicide
        ii. condom plus diaphragm
        iii. condom plus cervical cap or female condom
        iv. hormonal contraceptives
        v. intrauterine device
        vi. partner vasectomy and a use of barrier contraception methods
8. If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:

a. Have had a vasectomy (at least 6 months earlier);
b. Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);
c. Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;
d. Partner use of an intrauterine device;
e. Complete abstinence from sexual intercourse;
f. Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.

9. If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.

Exclusion Criteria:

A subject will be excluded from the study if he or she meets the following criteria:

1. Are pregnant or lactating.
2. Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological or psychological/psychiatric disorders which, in the opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.
3. Clinically significant abnormal findings on physical examination or vital signs as determined by PI.
4. Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.
5. History or presence of psychiatric or neurological disease or condition, as determined by the PI.
6. History of seizures.
7. Subject with any history or current evidence of suicidal behavior.
8. Unwilling to complete any planned study assessments.
9. Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.
10. Have received treatment with an investigational drug or device within 30 days prior to Screening.
11. Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.

12. Any subject who is known to be allergic to the study drug or any components of the study drug.
13. The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.
14. The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.
15. Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:
    a. Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)
    b. QTcF interval > 450 msec for males and females
    c. PR interval ≥ 200 msec
    d. Intraventricular conduction delay with QRS duration > 120 msec
    e. Evidence of second- or third-degree atrioventricular block (AVB)
    f. Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB

Test Product, Dose, and Mode of Administration:

N-methyl amisulpride (LB-102) administered orally

Reference Therapy, Dosage and Mode of Administration: Capsules to be taken orally as described above.

Duration of Treatment: 1 day or 5 days.

Endpoint:

LB-102 binding potential and dopamine receptor occupancy measured as amount of ^{11}C raclopride displaced by LB-102 using PET at Screening (Cohorts 1-4), baseline, 2.5, 7.5, and 23.5 hours post oral dose of LB-102 (post-Day 1 dose for Cohorts 1-3. Three (3) PET scans will be done on Days 5 and 6, two on Day 5 post LB-102 dose [at times determined following Cohorts 1-3] and one on Day 6 24 h after last LB-102 dose for Cohort 4) in the caudate, putamen, thalamus, and temporal cortex. The cerebellum (devoid of Dopamine D2/D3 receptors) will be used as the reference region. Timing of scans for Cohorts 2-4 may be altered based on observations in Cohort 1.

Safety:

The following schedule represents the ideal study schedule. It should be used as guidance for study conduct. In the event there are delays at any visit days that may affect the dates of any subsequent visit, the planned days may vary. The following will be monitored to assess safety:

1. AEs:
    a. Cohorts 1-3: Days 0-2
    b. Cohort 4: Days 0-6
2. Hematology, chemistry, urinalysis at:

   a. Cohorts 1-3: Screening, Day 0, and Day 2*
   b. Cohort 4: Screening, Day 0, and Day 6*
      i. * - Only blood will be collected for laboratory tests.
3. Prolactin at:
   a. Cohorts 1-3: Screening and Day 2
   b. Cohort 4: Screening and Day 6
4. ECG
   a. Cohorts 1-3: Screening, Day 0 (prior to PET scan, ±15 min), and Day 2 (24 h post-dose, ±15 min)
   b. Cohort 4: Screening, Day 0 (prior to PET scan, ±15 min), and Day 6 (24 h post-dose, ±15 min)
5. Physical examination
   a. Cohorts 1-3: Screening and Day 0*
   b. Cohort 4: Screening and Days 0*
      i. * - If physical examination was not performed at Screening then physical examination completed at Day 0
6. Vital signs (heart rate, respiratory rate, temperature, and blood pressure)
   a. Cohorts 1-3: Screening, Day 0 (at the time of the PET scan, ±15 min), Days 1-2 (Day 1 at pre-dose, and at the time of each PET scan [±15 min, Visits 3 and 4])
   b. Cohort 4: Screening, Day 0 (at the time of the PET scan, ±15 min), Days 1-6 (Day 1 at pre-dose, and at the time of each PET scan [±15 min, Visits 3 and 4])
7. C-SSRS
   a. Cohorts 1-3: Screening and Day 2
   b. Cohort 4: Screening and Day 6

Sample Size Determination:

The sample size for the study is based on clinical dose guidance and is exploratory rather than a statistical rationale. No formal sample size calculations were made. Cohorts of 4 subjects are sufficient to characterize the dopamine receptor occupancy profile of LB-102.

Table 1: Schedule of Events, Single Dose Cohorts (Cohorts 1-3)

	Screening	Pre-Dose Scan	Check-In	Discharge	Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**
Days	**Days -14 to -1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**
Location	**Outpatient**	**Outpatient**	**Inpatient**	**Inpatient/ Outpatient**	**Outpatient**
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Medical History	X	X			
Demographics	X				
Height, Weight, BMI	X				
Physical Examination[1]	X	X[1]			
Vital Signs[2]	X	X	X	X	
Structural MRI[3]	X				
Laboratory Tests*	X	X		X*	
Serum HbA1c	X				
Serum Prolactin	X			X	
HIV, HBsAg, and HCV Labs	X				
C-SSRS	X			X	
12-Lead ECG[4]	X	X		X	
Pregnancy Test[5]	X	X	X	X	
Plasma PK[6]			X	X	
Dose Subjects[7]			X		
Concomitant Medication[8]	X	X	X	X	
Adverse Event Assessment[8]		X	X	X	
PET scan[9]		X	X	X	
Follow up by telephone[10]				X	X

Notes to the Schedule of Events:
BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; PK = Pharmacokinetic
[1] If physical examination was not performed at screening then physical examination completed at Day 0.
[2] Vital Signs will be measured at Screening, Day 0 (at the time of the PET scan, ±15 min), Day 1 at pre-dose, and at the time of each PET scan (±15 min, Visits 3 and 4).
[3] MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.
[4] ECG will be measured at Screening, Day 0 (prior to PET scan, ±15 min), and Day 2 (24 h post-dose, ±15 min).
[5] Serum pregnancy test at Screening and Urine pregnancy test on Days 0-2 for all females of childbearing potential.
[6] Plasma PK samples will be collected at Day 1 at pre-dose, and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2).
[7] Subjects are required to fast for approximately 12 hours prior to Day 1 dosing.
[8] Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.
[9] For Cohort 1-3 PET scans will be done on Day 0 and 2.5, 7.5, and 23.5 (±30 min) hours post oral dose of LB-102.

[10] Day 2 follow-up call will be done in the evening when the subject returns to their home. Day 3 follow-up call will be done in the morning.
* On Day 2, only blood will be collected for laboratory tests.

Table 2: Schedule of Events, Multiple Dose Cohort (Cohort 4)

	Screening	Pre-Dose Scan	Treatment Evaluation	Discharge	Follow-Up
Visit	**1**	**2**	**3**	**4**	**5**
Days	**Days -14 to -1**	**Day 0**	**Days 1-5**	**Day 6**	**Day 7**
Location	**Outpatient**	**Outpatient**	**Inpatient**	**Inpatient/ Outpatient**	**Outpatient**
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Medical History	X	X			
Demographics	X				
Height, Weight, BMI[1]	X				
Physical Examination	X	X[1]			
Vital Signs[2]	X	X	X	X	
Laboratory Tests*	X	X		X*	
Structural MRI[3]	X				
Serum HbA1c	X				
Serum Prolactin	X			X	
HIV, HBsAg, and HCV Labs	X				
C-SSRS	X			X	
12-Lead ECG[4]	X	X		X	
Pregnancy Test[5]	X	X	X (Day 5)	X	
Plasma PK[6]			X	X	
Dose Subjects[7]			X		
Concomitant Medication[8]	X	X	X	X	
Adverse Event Assessment		X	X	X	
PET scan[9]		X	X	X	
Follow up by telephone[10]				X	X

Notes to the Schedule of Events:
BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; PK = Pharmacokinetic
[1] If physical examination was not performed at screening then physical examination completed at Day 0.
[2] Vital Signs will be measured at Screening, Day 0 (at the time of the PET scan, ±15 min), Day 1 at pre-dose, and at the time of each PET scan (±15 min, Visits 3 and 4).
[3] MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.
[4] ECG will be measured at Screening, Day 0 (prior to PET scan, ±15 min) and after scan 4 (24 h post-dose, ±15 min).
[5] Serum pregnancy test at Screening and Urine pregnancy test on Days 0, 5, and 6 for all females of childbearing potential.
[6] Plasma PK samples will be collected on Day 1 at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2). Plasma PK samples will also be collected on Day 5 immediately pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 6)

[7] Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-4, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 5, subjects will receive 1 dose (8 AM ±1 hour).
[8] Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.
[9] One PET scan will be done on Day 0. Three PET scans will be done on Days 5 and 6, two on Day 5 post LB-102 dose (at times TBD based on first 3 cohorts) and one on Day 6 24 h after last LB-102 dose.
[10] Day 6 follow-up call will be done in the evening when the subject returns to their home. Day 7 follow-up call will be done in the morning.
* On Day 6, only blood will be collected for laboratory tests.

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2. LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
API	Active Pharmaceutical Ingredient
ASI	Application Setup Instructions
AVB	Atrioventricular Block
BID	Twice a Day
BMI	Body Mass Index
CL	Corpora Lutea
CNS	Central Nervous System
COV	Close-Out Visit
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
D_2	Dopamine (D_2) Receptors
DM	Data Management
DMP	Data Management Plan
DVP	Data Validation Plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
EPS	Extrapyramidal Side Effects
eCRF	electronic Case Report Form
eTMF	electronic Trial Master File
FDA	US Food and Drug Administration
FGA	First Generation Antipsychotics
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus

Abbreviation	Definition
HED	Human Equivalent Doses
HIPAA	Health Insurance Portability and Accounting Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LBBB	Left Bundle Branch Block
LCRA	Lead Clinical Research Associate
MAD	Multiple Ascending Doses
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-Observed-Adverse-Effect-Level
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetic
PO	Oral/by mouth
QD	Once Daily
RBBB	Right Bundle Branch Block
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGA	Second Generation Antipsychotics
SIV	Site Initiation Visit
SRC	Safety Review Committee
SOC	System Organ Class
SQV	Site Qualification Visit

3. INTRODUCTION

3.1 Background and Rationale

Schizophrenia is a chronic and debilitating mental illness that affects approximately one percent of the population. Schizophrenia manifests in delusional behavior, dysfunctional thinking, agitated body movement, social withdrawal, and depression. Schizophrenia patients suffer a profoundly reduced quality of life and are ten times more likely to commit suicide than the general population (Harris and Barraclough, 1997). Half of suicides among patients with schizophrenia occur within the first two years of disease onset (Tandon and Jibson, 2003), pointing to the urgency for behavioral and pharmaceutical intervention.

There are at least 22 drugs (both first and second generation antipsychotics) approved by the FDA indicated for the treatment of schizophrenia (HHS, 2012; FDA, 2015). Despite a seeming surfeit of available drugs to treat schizophrenia, adequate treatment of schizophrenia remains a challenge. Non-adherence and discontinuation of treatment is a major issue. A review of randomized, double-blind clinical trials involving schizophrenia or related disorders found that 53% of patients stopped their treatment at an early stage and the most prevalent reasons were poor response or psychiatric symptom worsening (Liu-Seifert et al., 2005). Discontinuation of treatment significantly increases the chance of relapse with an estimated relapse rates of approximately 80% and 95% after discontinuing treatment for 12 and 24 months, respectively (Emsley et al., 2013).

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. It is common for patients to have little or no response to an individual antipsychotic, necessitating the many therapeutic options currently available. Many patients, even when stable, suffer disability due to the cognitive and social deficits 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.

The standard pharmacologic mechanism of action for antipsychotic drugs is antagonism of dopamine (D_2) receptors in the limbic system of the brain (Meltzer and Stahl, 1976, Joyce and Meador-Woodruff, 1997, Wulff et al., 2015). This has remained largely unchanged since antipsychotics began use clinically in the 1950s. Second Generation Antipsychotics (SGAs), also known as Atypical Antipsychotics, are preferred by patients and clinicians and are used in the majority of patients. Older antipsychotics developed between 1950 and 1980 are referred to as first Generation Antipsychotics (FGAs) and are used primarily when patients have failed numerous SGAs. The primary advantage of SGAs is a lower incidence of Extrapyramidal Side Effects (EPS) that resemble the types of movement disorders that occur in Parkinson's disease. Patients who experience EPS from a specific antipsychotic will often ask for a different drug or discontinue on their own. While SGAs were an important advance, these drugs are not free of the common side effects of many CNS drugs that arise from varying degrees of antagonism of dopamine, histamine, serotonin, muscarinic, hERG, and alpha receptors. Further, these drugs distribute widely throughout the CNS due to their ability to easily cross the blood brain barrier by passive diffusion

allowing off-target effects to occur. SGA side effects as a result of off-target receptor engagement include weight gain, elevations in lipids and blood sugar, sedation, dry mouth, constipation, dizziness and falls due to low blood pressure, QT interval prolongation, cognitive impairment, and prolactin elevation. Until a disease modifying therapy is developed for schizophrenia, the ideal antipsychotic would be a drug that has selectivity for the limbic system and minimal to no engagement of receptors that cause side effects.

LB-102 was designed to be an improved version of the benzamide antipsychotic amisulpride having increased permeability across the blood-brain-barrier, potentially decreasing the plasma concentrations needed to achieve efficacy thereby decreasing the magnitude and frequency of adverse events typically observed in patients treated with amisulpride.

Amisulpride, originally developed in France in the 1980s (Thominet et al., 1983), is approved in more than 50 countries worldwide for the treatment of schizophrenia and in certain countries for the treatment of dysthymia (IMS, 2015). Amisulpride elicits its activity in part by selectively blocking the human dopaminergic D_2 (K_i 2.8 nM) and D_3 (K_i 3.2 nM) receptor with negligible affinity for the D_1, D_4, and D_5 receptor subtypes (K_i > 1,000 nM) and in part by its activity against the 5-HT_7 receptor (11.5 nM K_i). While amisulpride is a clinically effective drug, it demonstrates poor distribution to the brain. A 2014 study (Dos Santos Pereira et al., 2014), revealed that passive diffusion of amisulpride across a PAMPA membrane was the lowest of 30 psychiatric drugs tested (Figure 1).

3.2 Description

LB-102 (Figure 1) was created by adding a methyl group to the aniline nitrogen of amisulpride.

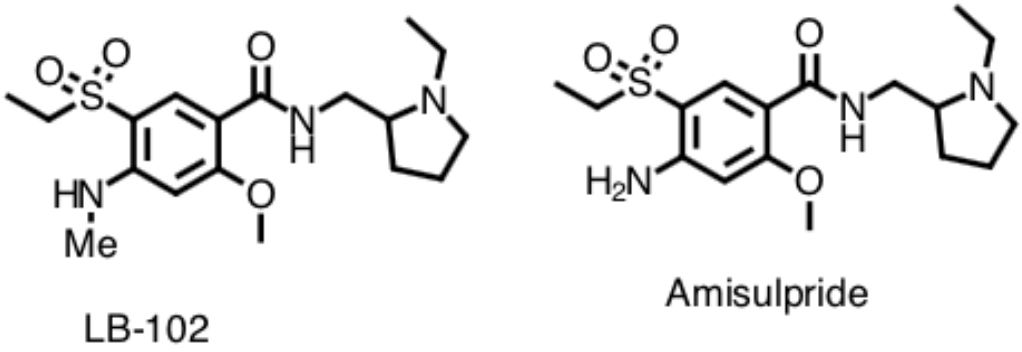

Figure 1: Structure of LB-102

Molecular Weight: 383.51

3.3 Nonclinical Pharmacology

3.3.1 Pharmacodynamics

In rodents, amisulpride preferentially blocks post-synaptic D_2 receptors in the limbic structures (responsible for affective and cognitive processes) preferentially over those in the striatum (responsible for extrapyramidal effects). In addition, amisulpride does not induce catalepsy and it does not produce D_2 hypersensitivity after repeated treatment. Amisulpride preferentially blocks pre-synaptic D_2/D_3 dopamine receptors at low doses, producing the dopamine release that is responsible for its disinhibitory effects. In animal preclinical models of schizophrenia amisulpride has been demonstrated to mimic current antipsychotics in the amphetamine induced hyperactivity (Perrault et al., 1997) and conditioned avoidance response (Natesan et al., 2008) models.

The pharmacodynamics of amisulpride are well-established (Solian Label, 2017), and based on the physicochemical attributes of LB-102 measured to date, receptor binding, pharmacokinetics, and animal behavior studies, suggest they will be similar. Phase 1 PK data of LB-102 demonstrated that, based on AUC_{inf} less than 4% of LB-102 is converted to amisulpride in humans.

A study was conducted to compare the PK of LB-102 to amisulpride in rats following a single oral dose at 3 mg/kg. The total plasma concentrations of benzamide, which includes LB-102 and its metabolite amisulpride, were found to be equivalent in LB-102- and amisulpride-treated rats (Figure 2).

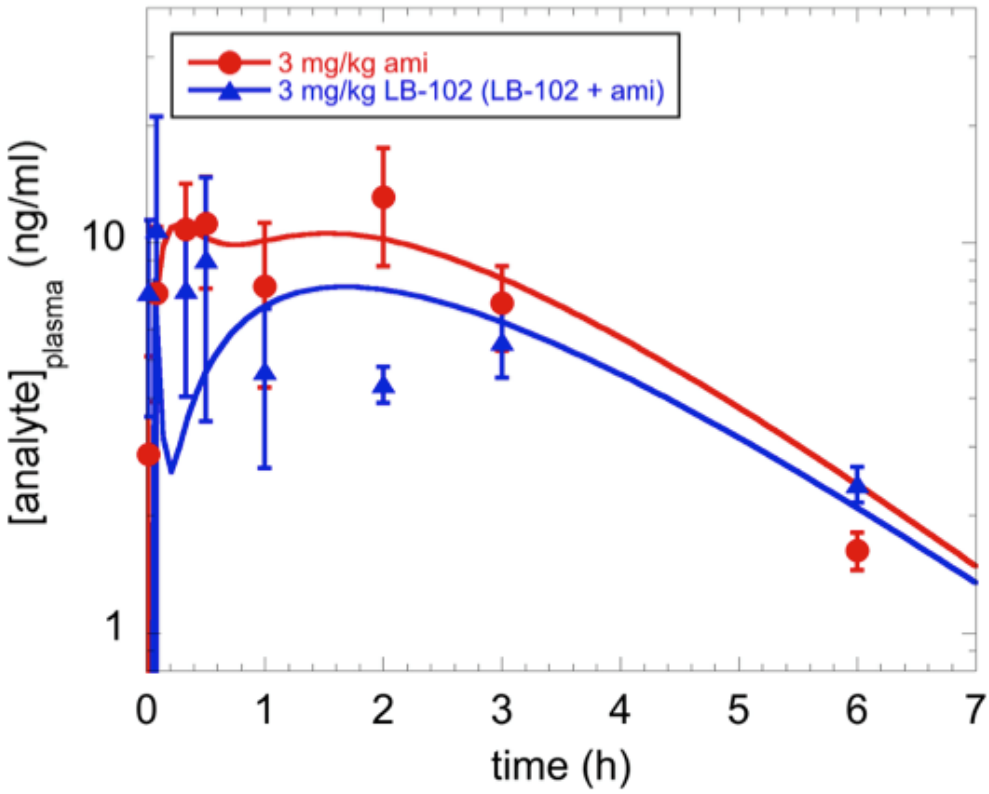

Figure 2: Plasma Concentration Vs. Time Curves Following Single Oral Dose at 3 mg/kg of LB-102 (Exposures To Amisulpride Plus LB-102) or Amisulpride (Exposures to Amisulpride) in Rats

A mouse PK study of LB-102 in mice was also conducted following a single oral dose of 30 mg/kg amisulpride or LB-102, and data for the total benzamide concentrations are depicted in Figure 3. In concordance with the rat PK data, about 50% of LB-102 is metabolized into amisulpride and the total plasma concentration of benzamide after oral dosing LB-102 was consistent with that of amisulpride.

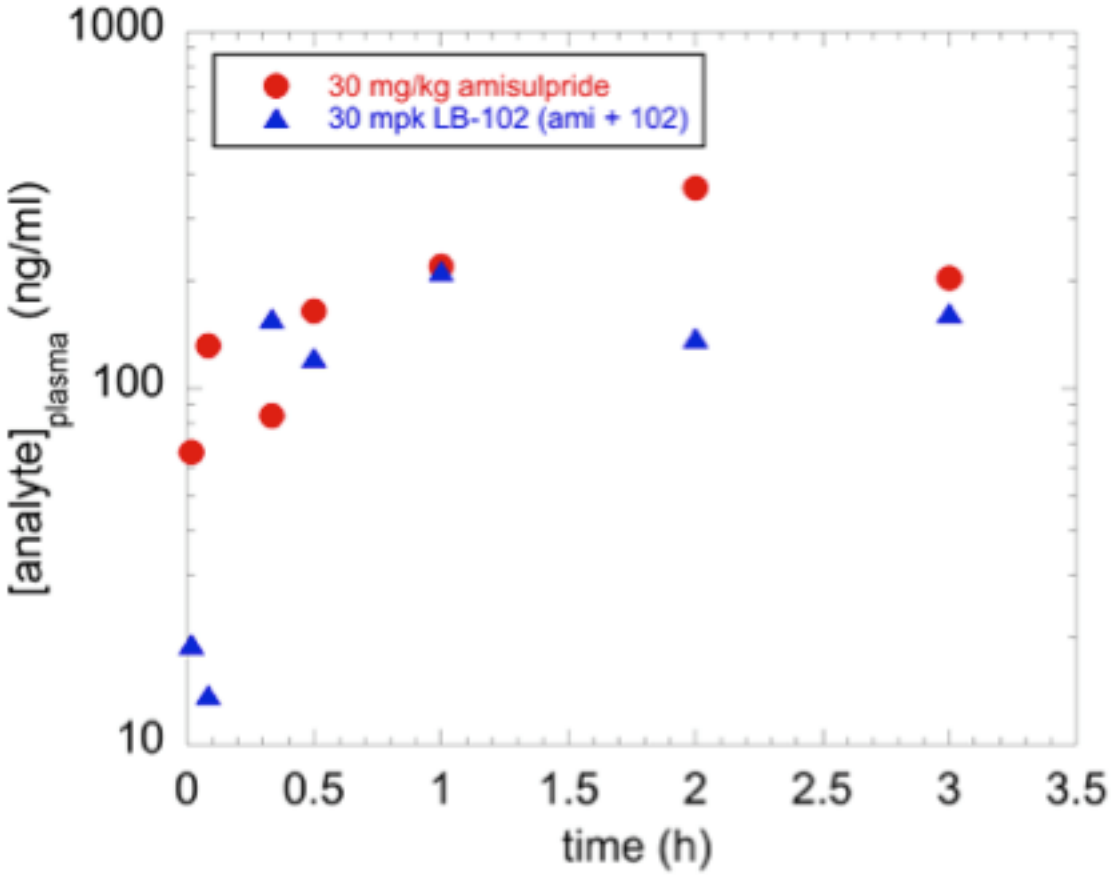

Figure 3: Pharmacokinetic Profile of 30 mg/kg Dose PO to Mice (n = 3/group)

Preliminary pharmacokinetic studies show that LB-102 behaves similarly to amisulpride in both mice and rats.

3.4 Clinical Experience and Pharmacokinetics

A phase 1, first-in-humans, clinical study of LB-102 has been completed (Note, all Phase 1 data presented are blinded). This was a single ascending dose (SAD)/multiple ascending dose study in which cohorts of 8 healthy volunteers (6 dosed with LB-102, 2 with matching placebo) are dosed

orally with LB-102. Subjects in the SAD portion of the study were dosed at 10, 50, 100, 150, and 200 mg. Subjects in the MAD portion of the study were dosed BID with 50, 75, and 100 mg (i.e. total daily doses of 100, 150, and 200 mg) over 6.5 days. The primary endpoint of this study was safety with PK/PD as secondary endpoints. Adverse event data for this study are summarized in Table 3.

Table 3: Adverse Events LB-102 Phase 1 Clinical Study

SAD

Dose (mg)	Adverse Event	n	Severity	Related to drug
10	Prolactin elevation	1	Mild	Definitely
	Abdominal cramps	1	Mild	Unrelated
50	Prolactin elevation	3	Mild	Definitely
	Diarrhea	1	Mild	Unlikely
	Upper respiratory infection	1	Mild	Unrelated
100	Prolactin elevation	1	Mild	Definitely
	Urticaria	1	Mild	Possibly
	Headache	1	Mild	Probably
	Upper respiratory infection	1	Mild	Unrelated
	Nausea	1	Mild	Probably
150	Prolactin elevation	1	Mild	Definitely
	Low back pain	1	Mild	unrelated
200	QT prolongation	1	Mild	Definitely
	Acute dystonia	1	Moderate	Definitely
	Palpitations	1	Mild	Unlikely
	Nausea	1	Mild	Possibly
	Gastroesophageal reflux	1	Mild	Possibly
	Insomnia	1	Mild	Probably
	Sore throat	1	Mild	Unrelated
	Headache	1	Mild	Unrelated

MAD

Dose (mg, BID)	Adverse Event	n	Severity	Related to drug
50	Dizziness	1	Mild	Unrelated
	Prolactin elevation	2	Mild	Definitely
75	Elevated prolactin	2	Mild	Definitely
	Abdominal cramps	1	Mild	Unrelated
	Migraine headache	1	Moderate	Possibly
	Acute dystonic reaction	1	Moderate	Definitely
	Intermittent dizziness	1	Mild	Probably
	Intermittent nausea	1	Mild	Probably
	Intermittent drowsiness	1	Mild	Probably
	Bug bite	1	Mild	Unrelated
	Insomnia	1	Mild	Possibly
	Low back pain	1	Mild	Unrelated
100	Acute dystonia	2	Moderate	Definitely
	Drowsiness	1	Mild	Unrelated
	Dry mouth	1	Mild	Unrelated
	Elevated prolactin	1	Mild	Definitely
	Nausea	1	Moderate	Probably
	Emesis	1	Mild	Possibly

While most clinical lab tests were unremarkable, there were increases in prolactin as depicted in Table 4.

Table 4: Serum Prolactin from LB-102 Phase 1 (Prolactin in ng/mL)

SAD

Dose (mg)	Screening	Day 3	Day 8*
10	9.5	47.2	
50	9.8	74	
100	8.9	50.1	
150	8.9	50.4	61.8
200	11	45.6	39.4

MAD

Dose (mg)	Screening	Day 4	Day 9
50	9.7	48.6	72.3
150	9.9	60	93.5
100	12.6	51.5	40.4

*PRL not measured at day 8 for all doses

There were no clinical observations associated with prolactin elevation depicted in Table 43. Increases in prolactin as a function of plasma concentration up to ~250 ng/mL, have been observed with amisulpride (Glatard et al 2020) and this relationship is summarized in Figure 4.

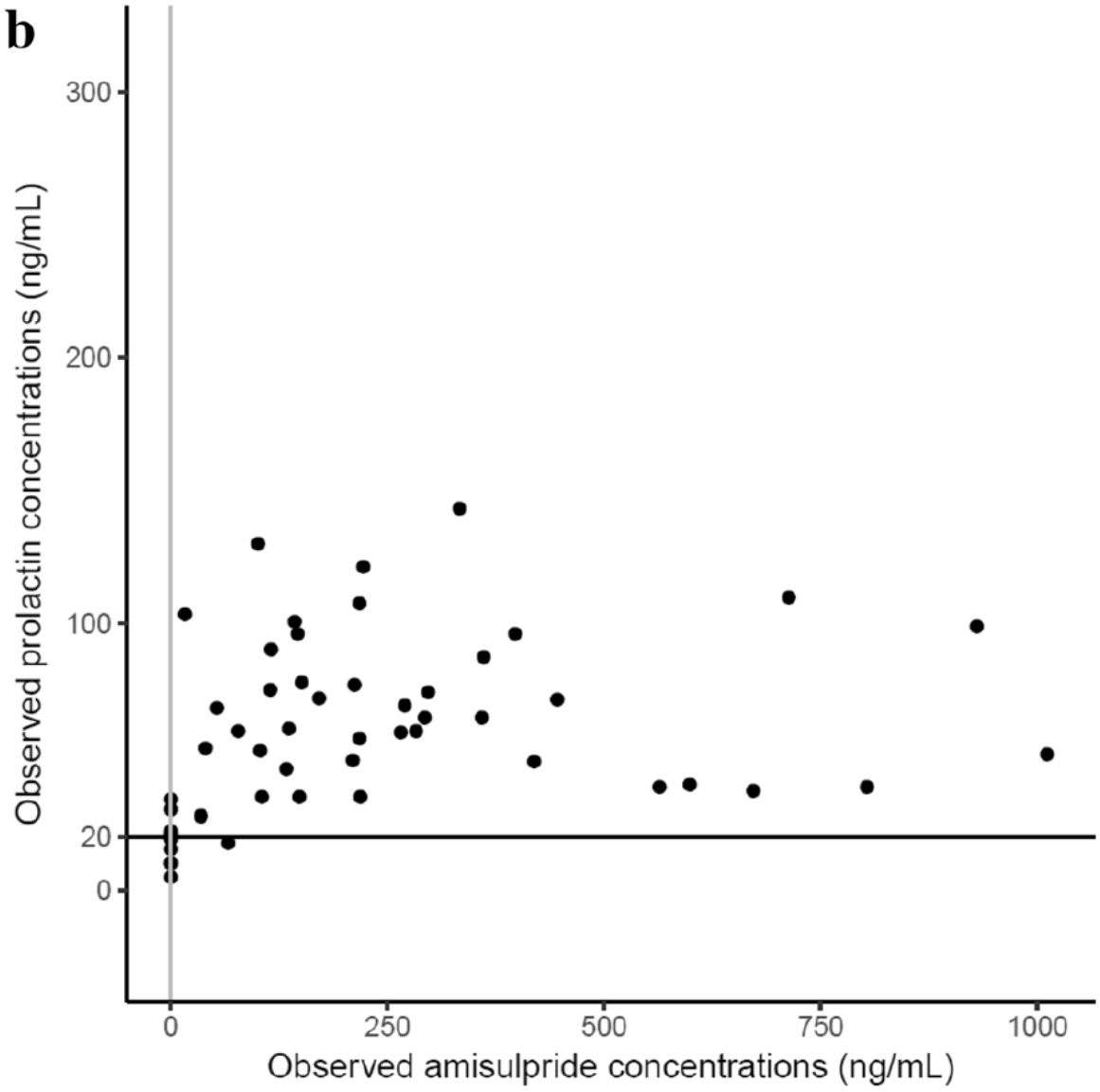

Figure 4: Relationship Between Observed Plasma Amisulpride Concentration and Prolactin Concentration (From Glatard et al 2020)

Table 5 displays PK parameters from the first four doses of the SAD clinical study of LB-102. Note from this Table that C_{max} for LB-102 exceeded 250 ng/mL between the 50 and 100 mg dose: doses that were associated with prolactin elevation.

Table 5: PK Parameters from SAD Portion of LB-102 Phase 1 Study

Dose LB-102 (mg)	Cmax (ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	$T_{1/2}$(h)
10	24	253	3	13.7
50	176	1600	3	12.3
100	349	2823	2.8	14.7
150	596.5	4650	3.2	12.6
200	976	7001	2	12.8

Plasma concentrations of LB-102 as a single dose, as a function of time, are depicted graphically in Figure 5 (Subjects with undetectable plasma LB-102 are excluded).

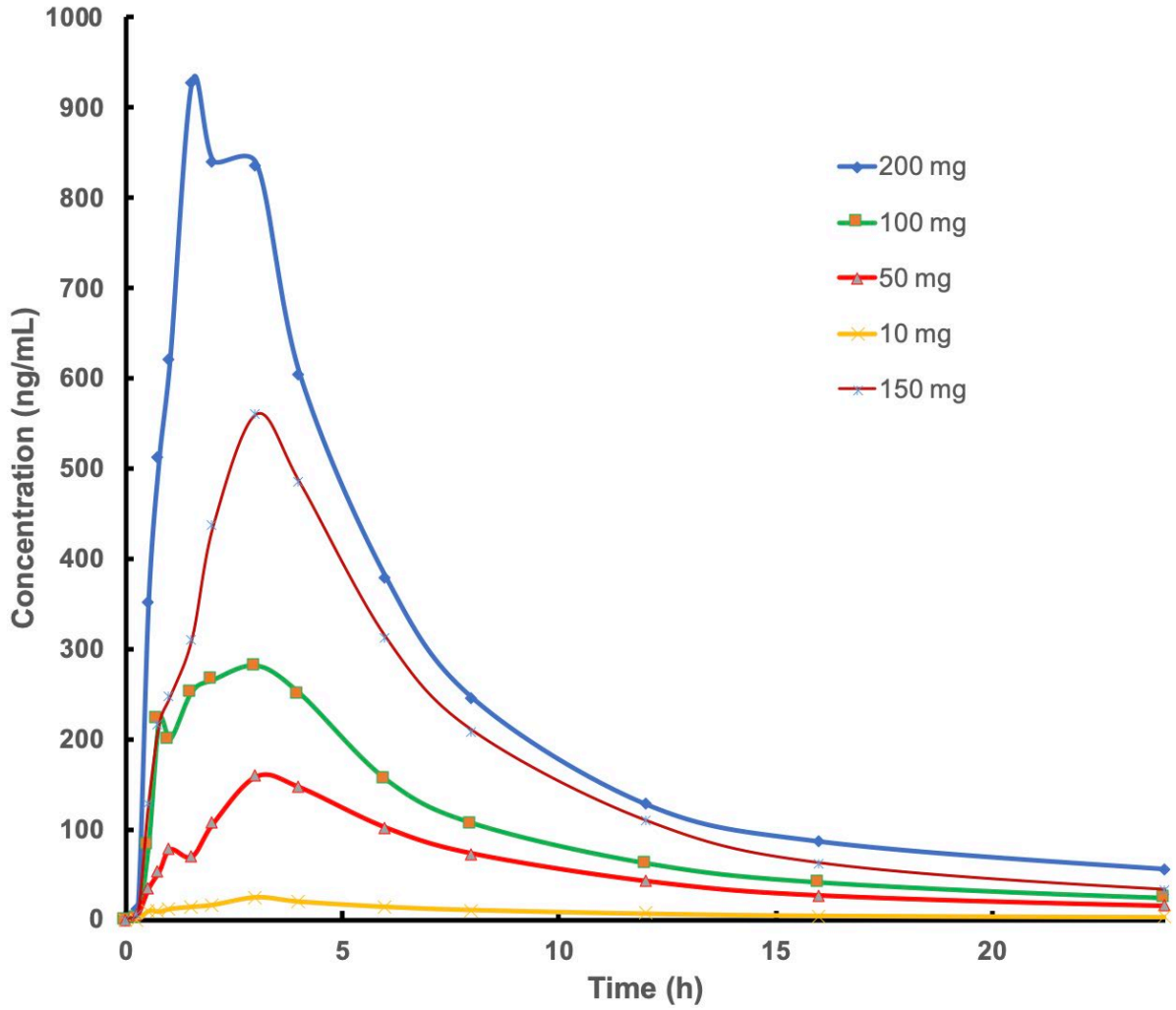

Figure 5: Plasma Concentration of LB-102 Administered as a Single Dose in Humans (n = 6/Group) Versus Time

Figure 6 shows plasma concentrations at Day 1 and Day 6 from twice daily dosing of LB-102 at 75 mg BID (150 mg/day). Note that there is evidence of accumulation of LB-102 as a result of multiple daily dosing.

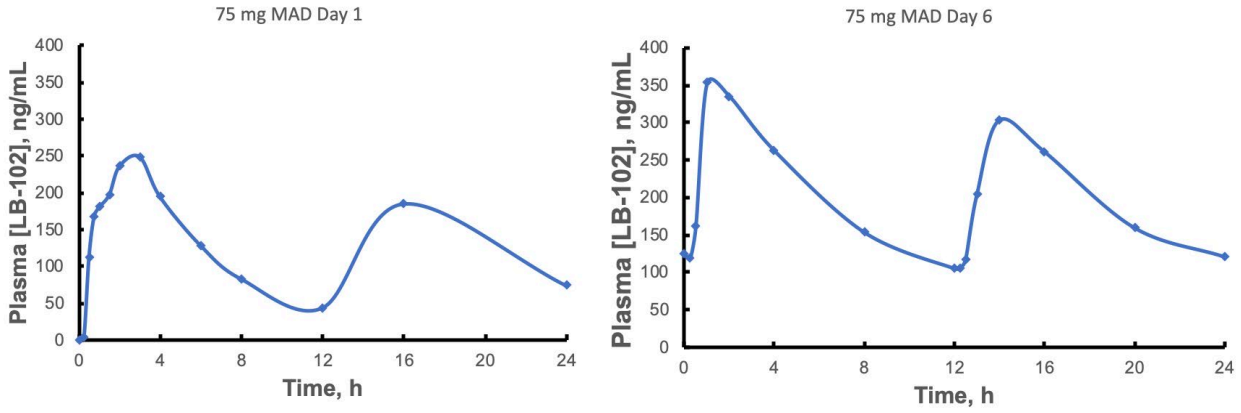

Figure 6: Plasma Concentration of LB-102 Administered as BID Over a Week in Humans (n = 6/group) Versus Time

Average increases in QT_cF from time = 0 ECG in Table 6. None of the QT interval readings met the stopping criteria of the study, specifically, and increase in QT interval of > 60 ms or an absolute value of > 500 ms.

Table 6: Increase in QT_cF (ms) From Time = 0

SAD

	2 h post-dose	4 h post-dose	6 h post-dose	Day 2
10 mg	10.8	8.1	6.1	13.8
50 mg	-1.1	-5.4	-4.1	-1.7
100 mg	7.0	4.3	2.1	4.7
150 mg	7.6	20.3	6.2	5.1
200 mg	22.3	15.9	15.3	5.9

MAD

	2 h post-dose	4 h post-dose	6 h post-dose	Day 3
50 mg	0.2	-0.6	-3.3	2.7
75 mg	10.3	6.2	4.0	8.2
100 mg	5.6	1.6	-1.4	3.9

4. OBJECTIVES

Primary Objective:

1. Brain Receptor Occupancy as Measured by Positron Emission Tomography.

Secondary Objectives:

2. Safety and Tolerability as Measured by Number of Participants with Adverse Events.

5. STUDY DESIGN

5.1 Overall Study Design and Plan

This is a Phase 1B open label study designed to evaluate dopamine receptor occupancy of LB-102 in healthy subjects by means of PET. There will be 4 dose levels, each of 4 subjects. The PK profile will include concentration of LB-102 and amisulpride. The study will be conducted at a single site.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. Competent to provide informed consent.
2. Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.
3. Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.
4. Body Mass Index (BMI) $\geq$ 18 and $\leq$ 30 kg/m^2 at screening visit.
5. Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.
6. Have normal clinical laboratory test results and ECG, which are not considered to be clinically significant by the Investigator.
7. Females participating in the study:
    a. Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's ranges; OR
    b. Females of child-bearing potential must have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:
        i. condom plus spermicide
        ii. condom plus diaphragm
        iii. condom plus cervical cap or female condom
        iv. hormonal contraceptives

v. intrauterine device

vi. partner vasectomy and a use of barrier contraception methods

8. If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:
    a. Have had a vasectomy (at least 6 months earlier);
    b. Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);
    c. Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;
    d. Partner use of an intrauterine device;
    e. Complete abstinence from sexual intercourse;
    f. Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.
9. If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets the following criteria:

1. Are pregnant or lactating.
2. Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or neurological disorders which, in the opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.
3. Clinically significant abnormal findings on physical examination or vital signs as determined by the PI.
4. Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.
5. History or presence of psychiatric or neurological disease or condition, as determined by the PI.
6. History of seizures.
7. Subject with any history or current evidence of suicidal behavior.
8. Unwilling to complete any planned study assessments,.

9. Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.
10. Have received treatment with an investigational drug or device within 30 days prior to Screening.
11. Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.
12. Any subject who is known to be allergic to the study drug or any components of the study drug.
13. The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.
14. The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.
15. Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:
    a. Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)
    b. QTcF interval > 450 msec for males and females
    c. PR interval ≥ 200 msec
    d. Intraventricular conduction delay with QRS duration > 120 msec
    e. Evidence of second- or third-degree atrioventricular block (AVB)
    f. Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB

5.3 Removal of Subjects from Therapy or Assessment

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

If a subject is withdrawn from dosing before completing the study, the reason for withdrawal will be entered on the appropriate case report form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation of dosing.

Subjects who discontinue from the study may be replaced at the discretion of the sponsor.

6. STUDY TREATMENTS

6.1 Method of Assigning Subjects to Treatment Groups

Upon confirmation of eligibility subjects will be dosed with LB-102.

In each cohort, four (4) new participants will be enrolled. Four (4) cohorts will be enrolled for a total of 12 subjects receiving a single dose and 4 subjects receiving multiple doses.

6.2 Identification of Investigational Product

LB Pharmaceuticals, Inc. will provide an adequate supply of active pharmaceutical ingredient (API) for the research site. The Pharmacist at the site will mix the API into the capsules.

6.3 Treatment Administration

Subjects will be dispensed LB-102 capsule(s) based on their assigned treatment at 8 AM (±1 hour). Subjects will take the capsule orally with 240 mL of water. Site personnel will confirm that the capsule has been taken by the study subject.

Each cohort will be dosed as follows. This will be an adaptive study and doses in Cohorts 2-4 will be determined after PET data from Cohort 1 are obtained.

Cohort	Treatment
1 (n=4)	LB-102 50 mg x 1 day
2 (n=4)	LB-102 XX x 1 day
3 (n=4)	LB-102 XX x 1 day
4 (n=4)	LB-102 XX mg, 4 x BID (Days 1-4) and 1 x QD (Day 5 AM; i.e. a total of 9 doses)

6.4 Storage

All study medication will be stored at ambient room temperature (15 to 25°C [59 to 77°F]), and in a secure area with access limited to authorized personnel.

6.5 Labeling

Each container of study drug will be labeled with study-specific information that meets all applicable regulatory requirements.

6.6 Drug Accountability

The pharmacist 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 subjects (subject number and initials) who received study drug. The pharmacist will not supply study drug to any person except those named as sub-investigators on the FDA 1572, designated staff, and subjects in this study. The pharmacist will not dispense study drug from any sites other than those listed on the FDA 1572.

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.

6.7 Selection of Dose in the Study

Comprehensive, Good Laboratory Practice (GLP)-compliant, 28-day, oral repeat-dose toxicity studies have been conducted on LB-102 in rats and dogs. For both species, LB-102 was administered using the intended clinical treatment regimen which included oral dosing twice per day approximately 12 hours apart. In rats, doses of 0, 20, 40 and 100 mg/kg/dose (0, 40, 80, and 200 mg/kg/day) and in dogs doses of 0, 0.75, 3 and 7.5 mg/kg/dose (0, 1.5, 6 and 15 mg/kg/day) were administered. For both species, a 1-month post-dose recovery period occurred following 28 days of treatment. LB-102-related effects in rats were associated with elevated levels of prolactin, which are presumed to occur with LB-102 based on its mechanism of action as a dopamine antagonist. These changes are unique to rodents, have been observed with other dopamine antagonists, were noted at all doses, and included hypertrophied corpora lutea (CLs), decreased CLs, interstitial cell hyperplasia and increased number of atretic follicles in the ovaries, mammary gland lobuloalveolar hyperplasia, and vaginal mucification in females and mammary gland atrophy and prostatic inflammation in males. Tissue changes either completely resolved or showed a trend to resolution during the recovery period. Given the species-specific nature of the response, the no-observed-adverse-effect-level (NOAEL) was determined to be 200 mg/kg/day, the highest dose administered. In dogs, the main finding was an increase in heart rate at 6 and 15 mg/kg/day. The dogs remained in sinus rhythm and, due to the lack of correlating clinical/veterinary observations, clinical pathology findings, or histopathological findings, this change was not considered to be adverse. Furthermore, no cardiovascular alterations were noted after the recovery period. The NOAEL was determined to be 15 mg/kg/day, the highest dose administered.

To determine, the initial starting dose in humans, the NOAEL doses in both species are converted to human equivalent doses (HED) using FDA's (2005) guideline entitled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." These corresponded to 32 and 8.1 mg/kg/day in rats and dogs, respectively. Dogs are the most sensitive species, therefore, applying a safety factor of 10, the initial starting dose in humans is 0.8 mg/kg/day (approximately equivalent to 50 mg/day for a 60 kg adult).

Data from the SAD portion of our Phase 1 clinical study of LB-102 have demonstrated that the drug was well-tolerated at doses up to 100 mg (Section 3.4), and data from the MAD demonstrated that the drug was well-tolerated up to 75 mg BID (150 mg/day).

6.8 Treatment Compliance

Study drug will be administered at the investigational site by site staff. A mouth check will be performed by investigational site staff to ensure study drug compliance. Dosing compliance will be recorded by the Investigator or designee at the investigational site. The date and time of study drug administration will be recorded.

6.9 Concomitant Medications

Prescription and over-the-counter medications will be prohibited throughout the study except hormonal contraception for females of childbearing potential. No concomitant drug therapy will be allowed during the study except one(s) required for the medical management of an AE. Any concomitant medication use will be evaluated on a case-by-case basis by the Investigator or a Sub-investigator. Any concomitant medications used will be recorded in the source document and on

the appropriate CRF. The medication name, dose, frequency, date, and indication for use must be recorded on the CRF. All concomitant medication use will be documented from screening through study exit/early termination.

6.9.1 Smoking

Smoking is not allowed during the time of the study.

6.9.2 Dietary and Lifestyle Restrictions

Subjects must refrain from the following dietary and/or lifestyle activities:

- Use of alcohol from 24 hours prior to Check-In through the end of the study
- Use of any THC containing product from 24 hours prior to Check-In through the end of the study

7. STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of any prohibited concomitant therapy.

The schedule of events to be performed during the study are provided in Table 1.

7.1 Single Dose Cohorts (1-3)

7.1.1 Screening (Visit 1, Days -14 to -1)

This is an open-label, single center design exploratory clinical trial examining the occupancy of LB-102 using ^{11}C-Racrlopride PET imaging.

Sixteen healthy human subjects will receive LB-102.

The following procedures will be performed:

- Administration of informed consent.
- Review inclusion and exclusion criteria.
- Record medical history, including prior and current therapies (e.g., prescription and non-prescription concomitant medications).
- C-SSRS
- Collect demographic information.
- Physical examination including weight, height, and BMI.
- Vital signs.

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).
    - *Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.
- 12-lead ECG.
- Brain Magnetic Resonance Imaging (MRI) (if not completed for research within 6 months of this visit) will be acquired after initial screening. Incidental findings will be reviewed by a qualified neuroradiologist in consultation with the PI to determine the subject's eligibility for participation in the study in light of these findings. If the MRI shows any clinically significant abnormalities, the participant will be notified by the investigator or research physician.
- Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).

7.1.2 Pre-Dose Scan (Visit 2, Day 0)

The following procedures will be performed:

- Record medical history.
- Review inclusion and exclusion criteria.
- Physical examination (If physical examination was not performed at Screening).
- Vital signs (at the time of the PET scan, ±15 min).
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen).
- 12-lead ECG (prior to PET scan, ±15 min).
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs.
- Undergo pre-dose PET/CT scan (scan 1)

7.1.3 Check-In (Visit 3, Day)

The following procedures will be performed on Day 1:

- Administer dose of study drug.

- Vital Signs (at pre-dose and at time of each PET scan, ±15 min).
- Undergo post-dose PET/CT scan (scan 2) starting at 2.5 hours post LB-102 dose (±30 min).
- Undergo post-dose PET/CT scan (scan 3) starting at 7.5 hours post LB-102 dose (±30 min).
- Plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, and 8 h.
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs if reported.
- Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day 2.

7.1.4 Discharge (Visit 4, Day 2)

The following procedures will be performed on Day 2:

- Vital Signs (at the time of the PET scan ±15 min).
- 12-lead ECG after Scan 4 (24 h post-dose, ±15 min).
- Undergo post-dose PET/CT scan (scan 4) starting at 23.5 hours (±30 min) post LB-102 dose.
- Plasma samples for PK analysis at the following time post dose (±15 min): 24 h
- Collect blood samples for clinical laboratory tests (hematology, clinical chemistry, and serum prolactin).
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs if reported.
- C-SSRS
- Follow-up telephone call.

7.1.5 Follow-Up (Visit 5, Day 3)

- Follow up will be done telephonically one day after completion of the study.

7.2 Multiple Dose Cohort (Cohort 4)

7.2.1 Screening (Visit 1, Days -14 to -1)

The following procedures will be performed:

- Administration of informed consent.
- Review inclusion and exclusion criteria.
- Record medical history, including prior and current therapies (e.g., prescription and non prescription concomitant medications).
- Collect demographic information.
- Physical examination including weight, height, and BMI.
- Vital signs.
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).
    - *Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.
- 12-lead ECG.
- Brain Magnetic Resonance Imaging (MRI) (if not completed for research within 6 months of this visit) will be acquired after initial screening. Incidental findings will be reviewed by a qualified neuroradiologist in consultation with the Investigator to determine the subject's eligibility for participation in the study. If the MRI shows any clinically significant abnormalities, the participant will be notified by the investigator or research physician.
- Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).
- C-SSRS

7.2.2 Pre-Dose Scan (Visit 2, Day 0)

The following procedures will be performed:

- Record medical history.
- Review inclusion and exclusion criteria.
- Physical examination (If physical examination was not performed at screening).
- Vital signs (at the time of the PET scan, ±15 min).

- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen).
- 12-lead ECG (prior to PET scan, ±15 min).
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs.
- Undergo pre-dose PET/CT scan (scan 1)

7.2.3 Treatment Evaluation (Visit 3, Days 1-5)

The following procedures will be performed on Days 1-5:

- Dosing at 8 AM and 8 PM (±1 hour) intervals on Days 1-5 (AM only on Day 5).
- Vital signs (at pre-dose and at time of each PET scan, ±15 min).
- Urine pregnancy test for all females of childbearing potential (Day 5 only).
- Record concomitant medication use (prior to first dose on All Days).
- Assess and record AEs (prior to first dose on All Days).
- Undergo post-dose PET/CT scan (scan 2; TBD, dependent on data from Cohorts 1-3)
- Undergo post-dose PET/CT scan (scan 3; TBD, dependent on data from Cohorts 1-3)
- Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day 6
- On Day 1 plasma samples for PK analysis at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2).
- On Day 5 plasma samples for PK analysis at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, and 8 h.

7.2.4 Discharge (Visit 4, Day 6)

The following procedures will be performed on Day 6:

- Vital signs (at the time of the PET scan, ±15 min).
- Undergo post-dose PET/CT scan (scan 4; TBD, dependent on data from Cohorts 1-3).
- 12-lead ECG after Scan 4 (24 h post-dose, ±15 min).

- On Day 6 plasma samples for PK analysis at the following times post dose (±15 min): 24 h.
- Collect blood samples for clinical laboratory tests (hematology, clinical chemistry, and serum prolactin).
- Urine pregnancy test for all females of childbearing potential.
- C-SSRS
- Record concomitant medication use.
- Assess and record AEs.
- Follow-up telephone call.

7.2.5 Follow-Up Visit (Visit 5, Day 7)

- Follow up will be done telephonically one day after completion of the study

7.3 Early Termination Visit and Withdrawal Procedures (Cohorts 1-4)

If subjects withdraw from the study early, they will complete the Follow-up procedures as an Early Termination Visit. The following procedures will be performed at the Early Termination Visit:

- Physical exam and weight measurements.
- Vital signs.
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis).
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs.

8. STUDY ASSESSMENTS

8.1 Dopamine PET Receptor Measures

The PET-CT Vision will be the primary research scanner employed (Biograph as a back-up scanner should there be any delayed down time for the former PET scan). Following a CT attenuation scan, each research subject will receive the IV bolus high specific activity ^{11}C Raclopride (15mCi) followed immediately by dynamic scans of about 30 frames in increasing length from about 20-30 sec to up to 3 minutes in length over 90 minutes in list mode and then framed up to about 30-32 frames on PET-CT vision.

Regions of interest (ROIs) will be drawn on PET images using the co-registered structural MRI. ROIs will be placed on the right and left caudate nuclei, putamen, and cerebellar cortices. Time-activity curves (TACs) will be obtained for the ROIs over the entire dynamic scan described above, and decay corrected for the time after tracer injection. Each PET scan for each of the chosen regions (caudate, putamen, thalamus and temporal cortex) will be used as the target region (highest concentration of D2/D3 receptors) and the cerebellum (devoid of Dopamine D2/D3 receptors) will be used as the reference region and a binding potential (BP_{ND}) (Innis et al., 2007) at each of the four scans using established reference tissue kinetic models as Dr. Wong has employed in the past (eg. SRTM, MRTM2, etc.) (Wong et al., 2013).

8.2 Dopamine receptor occupancy

LB-102 binding potential and dopamine receptor occupancy will be measured as the amount of ^{11}C Raclopride displaced by LB-102 using PET at baseline, and starting at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 (only post final dose for Cohort 4) in the caudate, putamen, thalamus, and temporal cortex. The cerebellum (devoid of Dopamine D2/D3 receptors) will be used as a reference region. Timing of scans for Cohorts 2-4 may be altered based on observations in Cohort 1.

Dopamine D_2 receptor occupancy (D_{2occ}) after the 2nd 3rd and 4th scans will be expressed as percent change in the ratio of the BP_{ND} at baseline (scan 1 with no drug) vs the BP_{ND} after scan 2 , scan 3, and scan 4.

$$D_{2occ} = \frac{(BP_{ND})_{\text{pre-drug}} - (BP_{ND})_{\text{post-drug}**}}{(BP_{ND})_{\text{pre-drug}}} \times 100\%$$

**post-drug BP_{ND} obtained at specified time points for each cohort

Therefore, for each of the scan start times (2.5, 7.5, and 23.5 hours post administration of the oral dose) there will be an occupancy measurement (D_{2occ}) for each of the four brain regions in quadruplicate (i.e. N=4 subjects/dose). Therefore, for each modeling method (e.g. SRTM, etc.) there will be 4 doses x 4 subjects/dose x 4 regions = 64 different occupancies in Cohorts 1, 2, 3, and 4. The dose amount and the PET scan time in Cohort 4 will be established adaptively by the results from Cohorts 1, 2, and 3. The choice of kinetic model for the final results will be established by methods and criteria previously employed by Dr. Wong and his colleagues, including information content. Also, including more than one complete kinetic model will ensure consistency and reliability of the occupancy calculations.

Thus, the BP_{ND} from each region and each of the three post-scan doses will be dynamically calculated from the entire 90-minute PET scan to calculate the occupancies D_{2occ} for each of the target brain regions above.

8.3 Pharmacokinetics

PK samples will be collected according to the lab manual.

8.4 Blood Collection

For each subject in Cohorts 1-3, up to 13 blood samples will be collected during the study for clinical and PK analysis. For each subject in Cohort 4, up to 20 blood samples will be collected during the study for clinical and PK analysis.

8.5 Analytical Procedures

8.5.1 Bioanalytical Sample Analyses

A validated LC/MS/MS procedure will be used to measure plasma concentrations of LB-102. Samples from subjects who have at least one post-dose sample will be analyzed.

Analytical results will be presented in tabular form in the final report and chromatographic and derived data will also be provided. Additionally, accuracy, precision, and linearity data for each standard curve and all quality control samples will be presented. Representative chromatograms and standard curve graphs will be included. A bioanalytical sample analysis report with quality assurance statement will be included in the final clinical study report (CSR). Copies of serially selected sample chromatograms for 20% of all samples will be included in the final report.

8.5.2 Bioanalytical Methodology

Samples will be sent to sponsor as instructed for further bioanalytical analysis. The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the LB-102 and amisulpride analytes in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

8.6 Safety

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate measured as pulse, respiratory rate, and temperature), ECG, and physical examination findings.

Any abnormal vital sign measurement, clinical laboratory test, physical examination finding, or ECG parameter deemed clinically significant by the Investigator will be repeated, including test results obtained on the final study day or upon early termination. For any test abnormality deemed clinically significant, repeat analysis will be performed during the follow-up period and until the value returns to baseline (or within normal limits) or the Investigator deems the abnormality to be of no clinical significance.

8.6.1 Dosing

Subjects in Cohort 1 will be administered a single oral dose of 50 mg and PET data will be acquired. This will be an adaptive, open-label study, and doses and PET scan times for Cohorts 2-4 will be based on observations in prior cohorts. Doses of LB-102 in this study will not exceed 150 mg.

8.6.2 Adverse Events

8.6.2.1 Adverse Event Definitions

CTCAE version 5.0 is used as a general guide while assessing AEs.

An AE is defined as any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the product, whether or not it is related to the product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the Investigator's Brochure.

An unexpected AE is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be unexpected (greater severity) if the Investigator's Brochure only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the Investigator's Brochure only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the Medical Monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

8.6.2.2 Eliciting and Documenting Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF. AEs will be collected from Check-in (Day 0) through the Day 3 (for Cohorts 1-3)/Day 7 (Cohort 4) or Early Discontinuation visit.

At each visit, subjects will be asked for any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented from any safety data collected in the eCRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

8.6.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dose, Investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the Med DRA will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The Investigator or designee must report any AE that meets the criteria for an SAE (Section 8.5.7.1) to the Medical Monitor and Safety Monitor via the eCRF within 24 hours of first becoming aware of the event by telephone. At the time of first notification, the Investigator or designee should provide at a minimum the following information if available:

- Investigator information (name, phone, fax, e-mail)
- Protocol number
- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken

Within 24 hours of the initial notification, the Investigator must submit an SAE report form in the eCRF to the Medical Monitor and Safety Monitor. Any missing or additional relevant information about the SAE should be provided in SAE follow-up reports in the eCRF. The Investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The Investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of the IRB.

The following contact information is to be used for SAE reporting:

Role in Study	Name	Address and Telephone Number
Medical Monitor	Anna Eramo, MD	LB Pharmaceuticals, Inc. 575 Madison Ave., 10th Floor New York, NY 10022 Email: anna@lbpharma.us Phone: 312-661-2021
Safety Monitor	Luxi Wang, PharmD	Target Health LLC. 261 Madison Ave, 24th Floor New York, NY 10016 Email: luwang@targethealth.com Phone: 917-660-2597

8.6.2.4 Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

Mild: Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate:	Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe:	Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.6.2.5 Assessment of Relationship

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Not related:	An AE with sufficient evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, another cause was proven.)
Unlikely/Remotely related:	An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related:	An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Probably related:	An AE with a reasonable time temporal sequence from administration of the study drug; or the AE follows a known pattern of or response to the study drug; or an alternative explanation (e.g., concomitant disease, environment factors, and/or concomitant medications) is less likely than attribution to the study drug; or the AE diminishes or disappears upon cessation of study drug.
Definitely Related:	An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

8.6.2.6 Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as "resolved," "resolved with sequelae," "ongoing," "death," "other," or "unknown."

"Death" should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

8.6.2.7 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after dosing with study drug) to a satisfactory resolution or until the Investigator deems the event to be chronic or not clinically significant or the subject to be stable. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate eCRF.

8.6.3 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, or within 30 days after the last dose of study drug/placebo, the Investigator must report the pregnancy to Target Health LLC. within 24 hours of being notified. Target Health LLC. will then forward the Exposure in Utero form to the Investigator for completion. The Investigator must obtain consent to collect pregnancy information from the female subject or female partner of a male subject (including the outcome of the pregnancy and any SAEs, if applicable).

A subject becoming pregnant while on study drug will immediately be withdrawn from further dosing but will continue to be followed throughout the duration of the study.

The subject or partner should be followed by the Investigator until completion of the pregnancy, whenever possible. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Target Health LLC. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6.4 Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Table 1 and Table 2).

Hematology:	Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count)
Serum chemistry:	Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose, HbA1c*, albumin, prolactin, and total protein

Urinalysis:	Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive
Serum* and Urine pregnancy test:	Conducted for females of childbearing potential only
FSH	Postmenopausal females (at screening only)
Urine Drug Screen:	Cocaine, amphetamine, phencyclidine, benzodiazepines, opiates, and marijuana.

*Serum for pregnancy test and HbA1c assessment are only required at Screening.

Serum prolactin values ≥ 100 ng/mL will be considered clinically significant and recorded as an AE. Serum prolactin values greater than the normal reference range value but < 100 ng/mL will not be considered clinically significant.

8.6.5 Vital Signs

Resting vital signs, including blood pressure, heart rate, respiratory rate and temperature will be measured after the subject has been in a seated position for at least 5 minutes at the time points specified in the schedule of events (Table 1 and Table 2).

Blood pressure or heart rate outside of the recommended ranges will be rechecked if considered clinically significant by the Investigator.

8.6.6 Electrocardiogram

A 12-lead ECG will be performed after the subject has been in supine resting for at least 10 minutes, and at the time points specified in the schedule of events (Table 1 and Table 2).

8.6.7 Physical Examination

A standard physical examination will be performed at the time points specified in the schedule of events (Table 1 and Table 2). The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, neurological and musculoskeletal system/extremities. Interim physical examinations will be performed at the Investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

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

The baseline C-SSRS will be completed at Screening. 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 three questions addressing suicidal behavior and five questions addressing suicidal ideation, with sub-questions assessing the severity.

The tool is administered via interview with the subject (by a trained operator/interviewer). All attempts will be made to use the same interviewer for the same subject throughout the study.

In the event the subject has a positive and significant finding for depression and/or suicidal ideation upon assessment at screening (Cohorts 1-4) or Days 4 and 6 (Cohort 4) the following will occur at the discretion of the Principal Investigator and Medical Monitor:

Screening positive and significant findings:

- For positive and significant findings at Screening the subject will be considered a screen fail according to Exclusion Criterion 7 (Section 5.2.2). Proper follow up will be based on the severity of the symptoms.

Days 2 (Cohorts 1-3) or 6 (Cohort 4) positive and significant findings:

- The subject will be continuously monitored at the site by qualified personnel, including one-on-one observation, as needed
- The subject will be re-evaluated on an as-needed basis by the Investigator
- Dosing will be interrupted or discontinued
- Psychiatric consultation may be pursued

8.6.9 Concomitant Medications

Concomitant medications will be reviewed and documented each day during the study.

8.6.10 Sample Collection and Processing

Details of sample process will be provided in the lab manual

8.6.11 Sample Storage

Plasma samples will be stored according to the lab manual.

8.6.12 Sample Shipment

- Prior to shipment, the samples will be appropriately packed into a styrofoam cooler containing dry ice.
- Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 72 hours for remote shipments.
- Samples will be shipped in two aliquots. The second set will be shipped once the status of the first set has been verified.
- The site staff will maintain an inventory of the samples that are to be shipped to the bioanalytical laboratory, including the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. A copy of the inventory will accompany the frozen PK samples.
- The samples will be tracked to ensure arrival in a safe and timely manner.

9. STATISTICAL METHODS

9.1 General Considerations

A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be finalized before database lock.

9.2 Analysis Populations

The following analysis populations are planned:

- Safety Population: All subjects who receive study drug.

9.3 Statistical Analyses

Regional radioactivity in the target regions (caudate, putamen, thalamus, and temporal lobe) and the reference region (cerebellum) will be measured for each PET scan, corrected for ^{11}C-decay and plotted versus time. Specific binding (B) in the target regions will be calculated as the binding potential ($BP_{ND)}$ using the kinetic modelling methods given above. The estimate of the reference tissue will be obtained from the radioactivity in the cerebellum of each patient and target regions and reference region used for estimating the BP_{ND} as determined in section 8.2. The occupancy will expressed as percent reduction of the BP_{ND} when compared to the BP_{ND} obtained before treatment with LB-102.

Occupancy will be plotted vs various plasma concentration analyses of LB-102 during the PET scan sessions (e.g. Area under the curve, average concentration during the PET scan, Cmax) and also as a function of the time of administration of the oral drug vs the PET scans for Cohorts 1-3 and for trough vs peak concentration of the steady state of LB-102 for Cohort 4.

Finally curves will be fit to the occupancies (ordinate) vs plasma concentrations of LB-102 and confidence and prediction limits generated as well as standard deviations and error around the points where appropriate (eg where the timing of the drug vs the PET scan start was the same).

Continuous variables will be summarized by treatment using descriptive statistics (n, mean, median, standard deviation, 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 Statistical Analysis Plan which will be finalized prior to database lock.

9.3.1 Subject Disposition and Demographic Characteristics

Subject disposition will include the number of subjects who enroll in the study and the number and percentage of subjects included in each analysis population by treatment. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will be summarized by treatment.

Demographics and baseline characteristics, including age, sex, race, weight, height and BMI, will be summarized by treatment for the Safety Population.

9.3.2 Efficacy Analyses

Since no efficacy data will be collected in this protocol, no efficacy analyses are planned.

9.3.3 Safety Analyses

All safety analyses will be performed using the Safety Population. All subjects who received at least one dose of study drug will be included in the population for safety analysis.

Adverse events (AEs) will be characterized by type, severity, seriousness, and relationship to treatment. Adverse events will be coded by preferred term and system organ class using MedDRA version 20.0. Incidence of AEs will be summarized by treatment overall, by severity, and by relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented.

Vital sign, ECG, and clinical laboratory results will be summarized by treatment. Physical examination findings will be listed.

9.3.4 Pharmacokinetic Analyses

Plasma concentrations of LB-102 and amisulpride will be measured for each PK sample. A PK analysis plan that describes the details of the analyses to be conducted will be finalized before database lock.

9.4 Sample Size Determination

The sample size for the study is based on clinical dose guidance and is exploratory rather than a statistical rationale. No formal sample size calculations were made. Cohorts of 4 subjects are sufficient to characterize the safety, tolerability, dopamine receptor occupancy, and PK profile of LB-102.

10. DATA QUALITY

10.1 Source Data and Records

Source data/records contain all the information that is necessary for the reconstruction and evaluation of the study. Source data/records are 1) original records, 2) certified copies of original records, 3) observations, 4) laboratory reports, 5) paper Case Report Forms (CRFs) and/or data sheets, 6) data entered directly into the eCRF. Source data/records are to be kept within the control of the Investigator until the end of the regulatory retention period. The Investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

10.2 Target e*CRF® (Electronic Data Capture)

Clinical trial data will be entered by the Investigator or a designee into Target e*CRF®, a validated 21 CFR Part 11 compliant Internet-based EDC system. Changes to the clinical trial data can only be performed by the Investigator or designee through the change management methodology that is subject to a full audit trail.

The Investigator and staff will be trained on Target e*CRF® prior to enrollment of the first subject. A list of the status of each user, including an audit trail of status changes will be maintained. In addition, the user module of Target e*CRF® maintains the original status and an audit trail of any changes.

At the end of the study, the completed online eCRF must be reviewed and signed electronically by the Principal Investigator for the site who signed Form FDA 1572) or by a designated sub Investigator authorized to sign. A certification must be obtained from all authorized persons to sign electronically indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with their username and password and reenter their password on the page(s) requiring a signature(s).

10.2.1 Original Data

This study will not use *direct data entry* of clinical trial data into the Target e*CRF® (EDC) system. Clinical trial data will be transcribed into the Target e*CRF® (EDC) system from the original data source (i.e. paper or equivalent).

10.3 Data Management and Quality Assurance

The research team, under the supervision of the Principal Investigator, will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the research records. Data reported to regulatory bodies that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Any change or correction to a research

records should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The Investigator should retain records of the changes and corrections, both written and electronic.

Data handling procedures for this trial have been designed to permit data changes so that they are documented. No entered data may be deleted without appropriate documentation. Data changes may only be made by individuals so authorized.

10.4 Good Clinical Practice Monitoring Plan

A Good Clinical Practice (GCP) Monitoring Plan is prepared by the Target Health to assure that the study is conducted according to international ethical and scientific quality standards. The Monitoring Plan identifies the monitoring methodologies to be used during the study, including the rationale for the frequency of site monitoring visits and monitoring activities. Results from the monitoring visits are discussed in meetings with the Sponsor and Target Health.

EDC management reports are also available to monitor data. Examples of basic reports are:

- Overall Data Entry Status (By Site/Subject)
- Investigator signature status (By Site/Subject)
- Query Age Report (by Site)
- Query Report (by Site/Subject)
- Query Frequency (by Site)
- Query Frequency (by Edit Check)
- Query Frequency (by Form)
- Subject Visit Status Report (by Site / Subject)
- AE Report (By Site/Subject)
- Concomitant Medication Report (By Site/Subject)
- Serious AE Report (by Site/Subject)
- Subject Status Report (by Site)
- Treated (by Site / Subject)
- Subject Tracking Report (Individual)

Additional management reports can be specified and programmed during the course of the study.

The following table summarizes the general activities of the monitor that will be specified in more detail in the Monitoring Plan.

Communication	Timeframe
Site qualification visit (SQV)	All sites will be qualified.
Site initiation visit (SIV)	All sites will have a SIV. The SIV will occur after the site has received Institutional Review Board (IRB) approval for their site and the IMP has been received.
First on-site monitoring visit	The Monitoring Plan will define the criteria for the first on-site visit.
Interim monitoring visits (IMV) (as needed)	The Monitoring Plan will define the criteria for determining the need for IMVs.
Close-out visit (COV)	All sites must have a COV. Non-enrolling sites may have a COV over the telephone as permitted by the Sponsor.
Site Update and Monitoring Calls	The site may be contacted as needed via email or telephone depending on site activity and the quality of data entry.
Teleconference Calls between the sites and CRO	As appropriate, teleconferences are scheduled to discuss the overall study status and to discuss study wide related issues.
Initiation, Monitoring and Close-out Visit Reports	Monitoring visits (interim and close-out), are performed on-site. Visits are preceded by a confirmation letter sent to the site when applicable. The confirmation letter must outline the date, time and purpose of the visit. All Initiation, Monitoring and Close-out Visit Reports are reviewed by the Lead CRA. Following the completion of a monitoring visit report, the monitor sends a follow-up letter to the site identifying any outstanding issues from the visit.
Adverse Events (AE) and Serious Adverse Events (SAE)	The monitor performs AE and SAE reconciliation in Target e*CRF®.

10.5 Audits

The Investigator will make all trial-related source data and records available at any time to a quality assurance auditor mandated by the Sponsor or to domestic/foreign regulatory inspectors or representatives from IRBs, who will audit/inspect the trial.

10.6 Essential Documents

The electronic Trial Master File (eTMF) for both the Investigator and the Sponsor will be maintained within Target Document®. Target Document is a 21 CFR Part 11 compliant software. The partial list below identifies the documents that must be filed in the Site Master File (as applicable) and will be maintained in the Sponsor TMF (as applicable). Additional documents will be added based on the template provided in Target Document, which hosts the TMF.

Correspondence	CV's, FDA 1572, and current medical licenses	Informed Consent
Informed Consent Updates	Financial Agreements Signed	Financial Disclosure Forms Signed and Dated
Investigator's Brochure or IB	IB - Updates	IRB Approval – Initial
IRB Updates/Amendments	IRB Roster – Initial	Laboratory - Ranges (Local and Central), Current Licensure and Accreditation (if applicable)
Laboratory – Updated Ranges (Local and Central), Updated Licensure and Accreditation (if applicable)	Monitoring – Signed Personnel Logs	Monitoring Log – Signed by all Monitors each day
Target e*CRF® Training Log	SAE Reports (if applicable)	Protocol and Protocol Amendments

10.7 Investigational Medicinal Product

Monitors will verify that the Investigator maintains accurate and adequate records including dates of treatment, duration of treatment, and appropriate follow-up, and that the source documents are being maintained. Monitors will perform Investigational Medicinal Product (IMP) accountability and verify storage conditions of the IMP (secure location, temperature logs, etc.) in accordance with manufacturers' instructions after unblinding is authorized by the Sponsor.

At the end of the study, the monitor is responsible for the accountability and reconciliation of the IMP. To assist with this, the following documents will need to be reviewed by the monitor, as appropriate:

- IMP Shipment Request Form
- IMP Receipt

10.8 Record Retention

All study records will be retained for a period of time as defined by the regulatory authority for the country in which the investigation is conducted. Generally, this means at least 2 years following the date on which the drug is approved by the regulatory authority for marketing for the purposes that were the subject of the investigation. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical program is completed, terminated or discontinued, or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor. The Investigator must contact the Sponsor prior to disposal of any records related to this study.

10.9 Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. In the CRF or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by an identification system, which consists of their initials and number in the study. The Investigator will maintain documents not meant for submission to the Sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence. All data is subject to monitoring, audits and inspection.

11. REPORTING AND PUBLICATION

11.1 Confidentiality of Study Data

Any information relating to the study product or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Sponsor.

11.2 Publication Policy

Sponsor agrees to make the report of the single center study results available to investigators for preparing a publication of the results in meeting abstract or medical journal form. Sponsor will have 30 days to review any proposed publication of the data for accuracy and proprietary information.

12. ETHICAL AND LEGAL CONSIDERATIONS

12.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP and the 1996 Version of the Declaration of Helsinki.

12.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent has been obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

12.3 Approval by Institutional Review Board

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the Sponsor monitor before shipment of investigational drug supplies and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Sponsor IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by the Sponsor before implementation. This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

13. REFERENCES

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