# A Randomized, Double-Blinded, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects

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|---|---|
| PROTOCOL NUMBER: | LB-102-001 |
| STUDY PHASE: | Phase 1 |
| IND NUMBER: | 137581 |
| PROTOCOL VERSION: | Version 1, 21 October, 2019<br>Version 2, 17 December, 2019<br>Version 3, 06 February, 2020<br>Version 4, 08 April 2020<br>Version 5, 18 May 2020 |
| SPONSORED BY: | LB Pharmaceuticals, Inc.<br>575 Madison Avenue<br>New York, NY 10022<br>Phone: (646)-588-8175 |
| CONTRACT RESEARCH ORGANIZATION: | Target Health LLC<br>261 Madison Avenue, 24th Floor<br>New York, NY 10016<br>Phone (212) 681-2100 (Ext 0) |

## PROTOCOL APPROVAL

| | |
|---|---|
| PROTOCOL TITLE: | A Randomized, Double-Blinded, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects |
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| SPONSOR: | LB Pharmaceuticals, Inc.<br>575 Madison Avenue<br>New York, NY 10022<br>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 |
|---|---|---|
| Clinical Operations Leader | Lucy Wang, PharmD | Target Health LLC<br>261 Madison Avenue, 24th Floor<br>New York, NY 10016<br>(646) 218-2072 |

**Investigator Agreement**

PROTOCOL TITLE: A Randomized, Double-blinded, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects

PROTOCOL NUMBER: LB-102-001

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): Leela Vrishabhendra, MD

Institution Name: Medpace Clinical Pharmacology Unit

Institution Address: 5355 Medpace Way, Cincinnati, OH 45227

Institution Telephone Number: 513-366-3220

# 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-102-001

**Title of Study:** A Randomized, Double-Blinded, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects

**Estimated Number of Study Center(s):** Single Center

**Phase of Development:** 1

**Objectives:**

The Primary Objectives:

Part A (SAD)

- To evaluate the safety and the tolerability of a single oral dose of LB-102 compared to placebo

Part B (MAD)

- To evaluate the safety and the tolerability of multiple oral doses of LB-102 compared to placebo

The Secondary Objectives:

Part A (SAD)

- To evaluate the pharmacokinetics (PK) of a single dose of LB-102

Part B (MAD)

- To evaluate the PK of multiple oral doses of LB-102

**Study Design:** This is a Phase 1, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and PK of LB-102 in healthy subjects. The study will consist of two parts: Part A – Single Ascending Dose and Part B – Multiple Ascending Doses. There will be 5 cohorts in Part A and 3 Cohorts in Part B of this study. Each cohort consists of 8 subjects, with 6 subjects assigned to LB-102 treatment and 2 subjects assigned to placebo treatment.

In Parts A and B, eligible subjects will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment. Eligible subjects will receive 1 dose on Day 1 (Part A) or 13 doses on Days 1-7 (Part B) of placebo or LB-102. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects. Blood samples for PK and safety assessments will be collected at nominal timepoints described below. Subjects will be discharged on Day 3 (Part A) or Day 9 (Part B)

and return for a Follow-up Visit (Day 8 or Day 15, respectively) for safety review. For Cohort 5 (Part A), subjects will return for an additional Follow-Up Visit.

A Safety Review Committee (SRC) will be assembled to review the blinded available study results for a cohort and agree whether the safety profile is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. The SRC will be comprised of the Investigator, Medical Monitor, and a Sponsor Representative (voting members). Other non-voting consultants, including to but not limited to, PK or medical expert, statistician, etc. may support the SRC on an as needed basis. Blinded data to be reviewed at the end of each cohort includes, but is not limited to adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory safety tests, and concomitant medications/procedures. Blinded PK analysis will occur at the end of each Cohort (Cohorts 1-5) for the SAD study and after the 1st cohort for the MAD study.

| **Part A** | |
|---|---|
| **Cohort** | **Treatment** |
| 1 (n=8)[a] | LB-102 50 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 2 (n=8)[b] | LB-102 10 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 3 (n=8)[b] | LB-102 100 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 4 (n=8)[b] | LB-102 200 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 5 (n=8)[b] | LB-102 150 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| **Part B** | |
| 6 (n=8) | LB-102 (n=6) 50 mg BID (100 mg/day) x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |
| 7 (n=8) | LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |
| 8 (n=8) | LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |

a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).
Y* - Dose will be determined by the SRC depending on the safety profile and clinical observations of the previous Cohort.
QD = Once daily; BID = Twice daily

**Number of Subjects (Planned):** A total of 64 subjects will be enrolled with 8 subjects being randomized for each of 8 cohorts (exclusive of possible replacements). Subjects will be considered enrolled at the point they are randomized to treatment.

**Diagnosis and 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 male and female 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.
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, 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.
4. History or presence of psychiatric or neurological disease or condition.
5. History of seizures.
6. Subject with any history or current evidence of suicidal behavior.
7. Unwilling to complete any planned study assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS).
8. Recent history of alcohol or drug abuse (within the last two years).
9. Any use of tobacco or tobacco-containing products (cigarettes, pipes, etc.) within one month prior to Screening.
10. Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.

11. Have received treatment with an investigational drug or device within 60 days prior to Screening.
12. Use of any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration.
13. Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.
14. Any subject who is known to be allergic to the study drug or any components of the study drug.
15. The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.
16. The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.
17. Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening (ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate in Part A for Cohort 5 and Part B, mean values will be used for the following criteria):
    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) Powder in Capsule in dosage strengths of 25 mg, 50 mg, 75 mg, and 100 mg, Oral administration

**Reference Therapy, Dosage and Mode of Administration:** Matching placebo capsules to be taken orally as described above.

**Duration of Treatment:** Part A: 1 day; Part B: 7 days.

**Endpoints:**
**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:

- AEs
- Hematology, chemistry, urinalysis at:
    - Part A: Screening, Check-in (Day 0), Day 2, and at Follow-up (Day 8).

- Part B: Screening, Check-in (Day 0), Day 4 prior to first dose, Day 8, and at Follow-up (Day 15).
- Prolactin at:
  - Part A: Screening, Day 3, Day 8, and Day 15 (For Cohort 5, Part A only).
  - Part B: Screening, Day 4, Day 9, and Day 15.
- ECG
  - Part A: Screening, Check-in, Day 1 at pre-dose and at 1, 2, 3, 4, 5, 6, 8 and 24 (Day 2) hours (±30 min) post-dose on Day 1. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5.
  - Part B: Screening, Check-in, Day 1 prior to the first dose and at 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose on Day 1 prior to first dose on Days 2-7, and Day 8 (24 hours post-dose Day 7; ±30 min). ECG will be measured in triplicate at each time point.
- Physical examination
  - Part A: Screening, Check-in, Day 2, and Follow-up (Day 8).
  - Part B: Screening, Check-in, Days 2, 4, and 8, and Follow-up (Day 15).
- Vital signs (heart rate, respiratory rate, temperature, and blood pressure)
  - Part A: Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 (Day 2), and 48 hours (Day 3) post-dose (±30 min), and at Follow-up (Day 8).
  - Part B: Screening, Check-in, Day 1 prior to first dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, prior to first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose (Day 8 and 9), and at Follow-up.
- C-SSRS
  - Part A: Screening, Day 3
  - Part B: Screening, Day 4, and Day 8.

**Pharmacokinetics:**

Plasma PK samples will be obtained at the following nominal time points:

- Part A
  - Day 1: pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post-dose.
  - Days 2-3: 24, 32, and 48 hours (±15 min) post Day 1 dose.
  - Days 8 and 15 (For Cohort 5, Part A only).
- Part B
  - Day 1: prior to the first dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose.
  - Days 2-6: prior to first dose.
  - Day 7: pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post dose.
  - Days 8-9: 24, 32, and 48 hours (±15 min) post Day 7 dose.

**Statistical Analysis**

**Safety:** Statistical methods will be primarily descriptive in nature. No formal statistical comparisons of dose levels will be made. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (N), mean, standard deviation, median, minimum, and maximum. Each cohort will be evaluated separately

for safety. All placebo subjects from the different cohorts will be combined into a single group for summary purposes.

A formal statistical analysis plan (SAP) will be developed and finalized prior to unblinding the data. This plan will define populations for analysis, outline all data handling conventions, and specify all statistical methods to be used for analysis of the data. A separate PK analysis plan will be created.

Safety data, including vital signs, ECGs, laboratory test results, physical examinations, and AEs, will be summarized by dose and assessment time points, as appropriate. Change from baseline will be included in summary tables for laboratory, ECG and vital sign parameters.

**Pharmacokinetics:** Plasma concentrations of LB-102 and amisulpride will be measured during the study and PK parameters derived using non-compartmental and/or compartmental methods as appropriate. The following PK parameters (as appropriate) will be calculated: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/F, $C_{max}$, $T_{max}$, $\lambda_z$, and $t_{1/2}$.

No value for $\lambda_z$, $AUC_{0\text{-}inf}$, CL/F, or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

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

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

PK parameters of LB-102 and amisulpride will be summarized by cohort using descriptive statistics (sample size, arithmetic means, geometric means, standard deviation, % coefficient of variation, minimum, median, and maximum). Figures will be created to display mean and individual subject LB-102 and amisulpride concentration time curves in plasma on both a linear and logarithmic scale. Dose proportionality will be assessed using a linear regression, or other acceptable approach.

**Sample Size Determination:**

The sample size for the study is based on clinical rather than statistical rationale. No formal sample size calculations were made. Cohorts of 8 subjects (6 active, 2 placebo) are sufficient to characterize the safety, tolerability, and PK profile of LB-102.

**Table 1: Schedule of Events for Part A**

| | Screening | Check-In | Treatment Evaluation | | | Follow-Up Visits |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | | | **4 and 5** |
| **Days** | **Days -28 to -1** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Days 8 and 15[9]** |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Medical History | X | X | | | | |
| Demographics | X | | | | | |
| Randomization | | | X | | | |
| Height, Weight, BMI[1] | X | | | | | X (Day 8 Only) |
| Physical Examination | X | X | | X | | X (Day 8 Only) |
| Vital Signs[2] | X | X | X | X | X | X (Day 8 Only) |
| Laboratory Tests | X | X | | X | | X (Day 8 Only) |
| Serum HbA1c | X | | | | | |
| Serum Prolactin | X | | | | X | X |
| HIV, HBsAg, and HCV Labs | X | | | | | |
| 12-Lead ECG[3] | X | X | X | X | | |
| C-SSRS | X | | | | X | |
| Urine Drug Screening | X | X | | | | |
| Alcohol Breathalyzer | X | X | | | | |
| Pregnancy Test[4] | X | X | | | | X (Day 8 Only) |
| FSH[5] | X | | | | | |
| Plasma PK[6] | | | X | X | X | X |
| Dose Subjects[7] | | | X | | | |
| Concomitant Medication[8] | X | X | X | X | X | X |
| Adverse Event Assessment[8] | | X | X | X | X | X |

**Notes to the Schedule of Events for Part A:**
BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-Up, height and BMI will not.
[2] Vital Signs will be measured at Screening, Check-in, Day 1 at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 (±30 min) hours post-dose, and at Follow-up (Day 8).
[3] ECG will be measured at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, 8, and 24 (±30 min) hours post-dose. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate (approximately 1 min apart) for Cohort 5.
[4] Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 8 for all females of childbearing potential.
[5] FSH test for postmenopausal women.
[6] Plasma PK samples will be collected on Day 1 at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose, and Days 8 and 15.
[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] Day 15 Follow-Up Visit is scheduled for Cohort 5, Part A only.

**Table 2: Schedule of Events for Part B**

| | Screening | Check-In | Treatment Evaluation | | | Follow-Up Visit |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | | | **4** |
| **Days** | **Days -28 to -1** | **Day 0** | **Day 1** | **Days 2-7** | **Days 8-9** | **Day 15** |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Medical History | X | X | | | | |
| Demographics | X | | | | | |
| Randomization | | | X | | | |
| Height, Weight, BMI[1] | X | | | | | X |
| Physical Examination | X | X | | X (Days 2, 4 only) | X (Day 8 only) | X |
| Vital Signs[2] | X | X | X | X | X | X |
| Laboratory Tests | X | X | | X (Day 4 only) | X (Day 8 only) | X |
| Serum HbA1c | X | | | | | |
| Serum Prolactin | X | | | X (Day 4 only) | X (Day 9 only) | X |
| HIV, HBsAg, and HCV Labs | X | | | | | |
| 12-Lead ECG[3] | X | X | X | X | X (Day 8 only) | |
| C-SSRS | X | | | X (Day 4 only) | X (Day 8 only) | |
| Urine Drug Screening | X | X | | | | |
| Alcohol Breathalyzer | X | X | | | | |
| Pregnancy[4] | X | X | | | | X |
| FSH[5] | X | | | | | |
| Plasma PK[6] | | | X | X | X | |
| Dose Subjects[7] | | | X | X | | |
| Concomitant Medication[8] | X | X | X | X | X | X |
| Adverse Event Assessment[8] | | X | X | X | X | X |

**Notes to the Schedule of Events for Part B:**
BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-up, height and BMI will not.
[2] Vital Signs will be measured at Screening, Check-in, Day 1 prior to the first dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up.
[3] ECG will be measured in triplicate at Screening, Check-in, Day 1 prior to the first dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).
[4] Serum pregnancy test at screening and Urine pregnancy test at Day 0 and Day 15 for all females of childbearing potential.
[5] FSH test for postmenopausal women.
[6] Plasma PK samples will be collected on Day 1 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours (±15 min) post first dose, Days 2-6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose.
[7]Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-6, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 7, 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.

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# 2. LIST OF ABBREVIATIONS AND DEFINITIONS 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 |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| $D_2$ | 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 |

| Abbreviation | Definition |
|---|---|
| HCV | Hepatitis C Virus |
| 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 |
| 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.

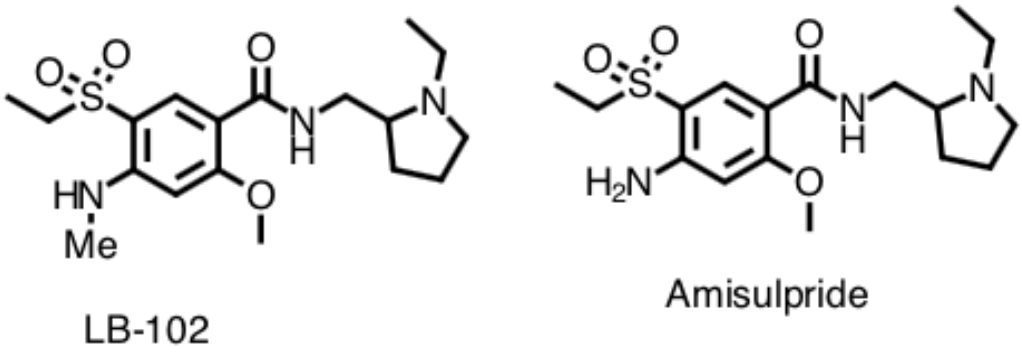


**Figure 1: Structure of LB-102**

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 suggest they will be similar.

## 3.4 Clinical Experience and Pharmacokinetics

LB Pharmaceuticals has not conducted any studies of LB-102 in humans, however pharmacokinetic data from prior studies in mice, rats, and dogs have provided initial feedback on how the pharmacokinetic (PK) profile LB-102 compares to amisulpride.

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).

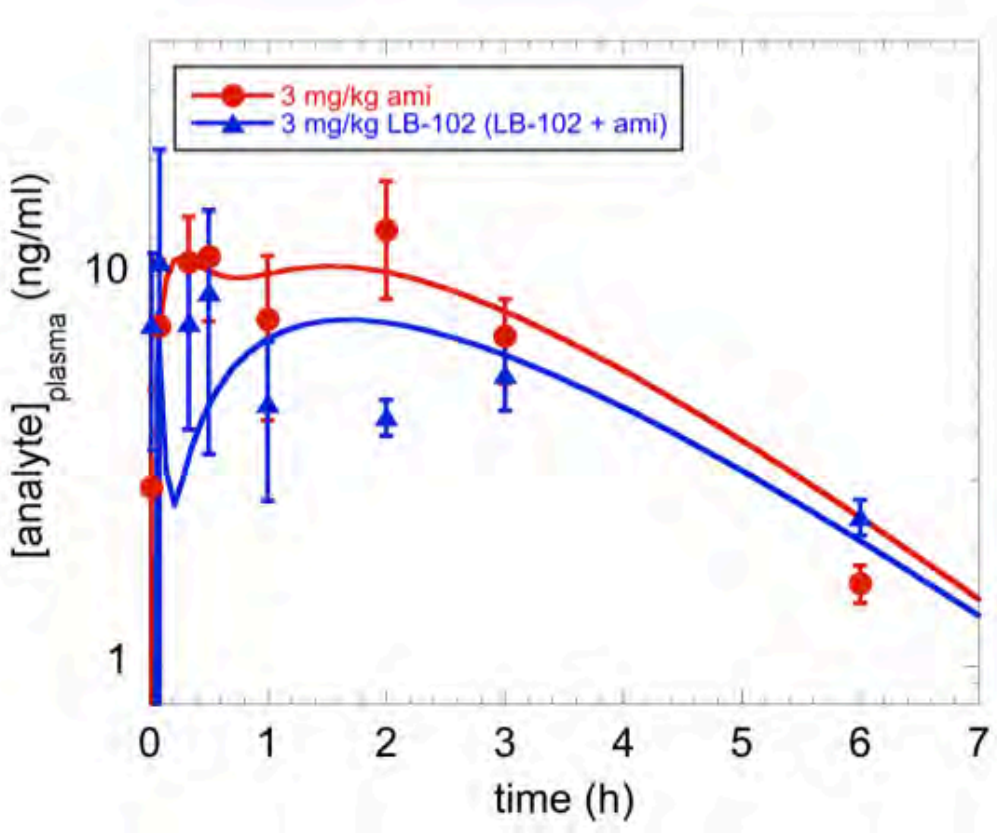


**Figure 2: Plasma Concentration Vs. Time Curves Following Single Oral Dose at 3 mg/kg of LB-102 (Exposures To Amisulpride Plus LB-102) or Amisulpride (Exposures to Amisulpride) in Rats**

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.

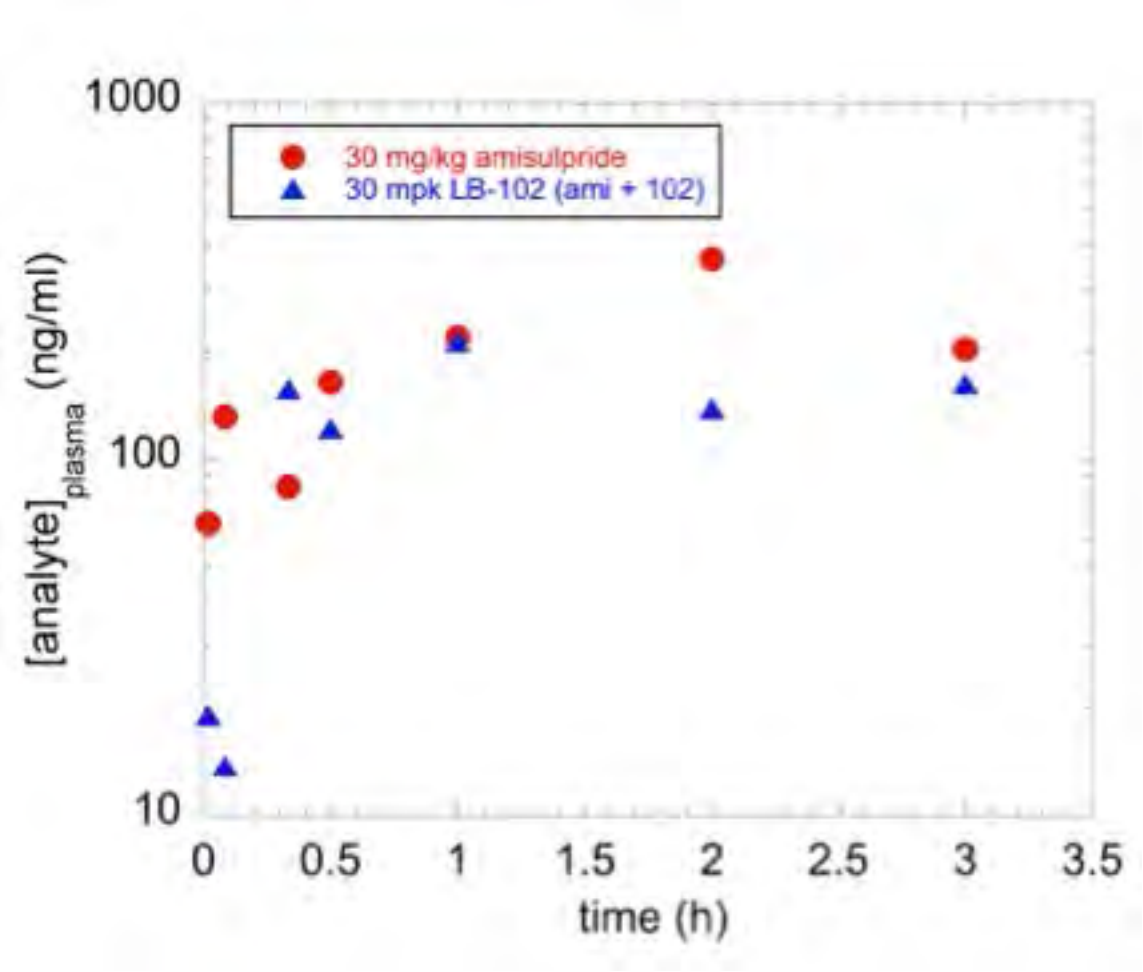


**Figure 3: Pharmacokinetic Profile of 30 mg/kg Dose PO to Mice (n = 3/group)**

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

## 4. OBJECTIVES

The Primary Objectives:

Part A (SAD)

- To evaluate the safety and the tolerability of a single oral dose of LB-102 compared to placebo

Part B (MAD)

- To evaluate the safety and the tolerability of multiple oral doses of LB-102 compared to placebo

The Secondary Objectives:

Part A (SAD)

- To evaluate the PK of a single dose of LB-102

Part B (MAD)

- To evaluate the PK of multiple oral doses of LB-102

# 5. STUDY DESIGN

## 5.1 Overall Study Design and Plan

This is a Phase 1, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and PK of LB-102 in healthy subjects. The study will consist of two parts: Part A – Single Ascending Dose and Part B – Multiple Ascending Dose. There will be 5 cohorts in Part A and 3 Cohorts in Part B of this study. 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.

In Part A, eligible subjects, in 5 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 40 subjects. Four (4) visits will occur as follows: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-3), and Follow-up (Visit 4, Day 8 and Visit 5, Day 15 [for Cohort 5, Part A only]). The study procedures for these visits are presented in detail in Table 1. Dosage of LB-102 will begin at 50 mg/day and subsequent groups will administered 10, 100, 200, and 150 mg/day, respectively. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 at 8 AM (±1 hour). For each cohort, blood samples for PK will be collected on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose, and Day 8 and Day 15. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours (±30 min) post-dose, and at the Follow-up visit (Day 8). 12-lead ECG will be done on at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, 8 and 24 hours (±30 min) post-dose. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5. Clinical labs (hematology, chemistry, urinalysis) will be assessed at Screening, Check-in, Day 2, and Follow-Up. Hemoglobin A1c (HbA1c) will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 3, Day 8, and Day 15. C-SSRS will be assessed at Screening and Day 3. Subjects will remain in the clinic from Check-in to Discharge on Day 3 for additional safety assessment and then return for a Follow-up Visit on Day 8. Subsequent groups will follow the same study procedures.

In Part B, eligible subjects, in 3 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 24 subjects. Four (4) visits will be scheduled for this study: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-9), and Follow-up (Visit 4, Day 15). The study procedures for these visits are presented in

detail in Table 2. Dosage of LB-102 will be based on the PK observed in a minimum of two Part A cohorts. Subjects will receive 2 doses of placebo or LB-102, first dose at 8:00 AM (±1 hour) and second dose approximately 12 hours later, on Days 1-6 and one dose at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. The first dose on Day 1 will occur following a 12 hour, overnight fast. For each cohort, blood samples for PK will be collected at multiple timepoints starting on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose. On Days 2-6, blood samples for PK will be collected prior to the first dose. On Day 7 blood samples for PK will be collected pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, at pre-dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up. 12-lead ECG will be done in triplicate at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and on Day 8 (24 hours (±30 min) post-dose Day 7). Clinical labs will be assessed at Screening, Check-in, prior to first dose on Day 4, Day 8, and at Follow-up. HbA1c will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 4, Day 9, and Day 15. C-SSRS will be assessed at Screening, Day 4, and Day 8. Subjects will remain in the clinic from Check-in to Discharge on Day 9 for additional safety assessment and then return for a Follow-up Visit on Day 15. Subsequent groups will follow the same study procedures.

When there are two or more procedure (ECG, Vital Signs, and PK) scheduled for the same timepoint, the procedures will be as close to the time point as possible and in the following order: ECG, Vital Signs, and then PK blood collection.

The PK profile will include $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/F, $C_{max}$, $T_{max}$, $\lambda_z$, and $t_{1/2}$.PK samples will be analyzed for all subjects in each cohort prior to dose escalation. These data will be used as adjunct information for a safety review, which will include a review of adverse events, changes in vital signs, physical examination and clinical laboratory test results.

If the starting dose (50 mg/day) for Cohort 1 (Part A) results in a total benzamide (LB-101 and LB-102) geometric mean $C_{max}$ greater than 175 ng/mL or a geometric mean of total benzamide exposure ($AUC_{inf}$) greater than 3,270 ng/mL*h, the dose for Cohort 2 will be adjusted downward, to the nearest 10 mg, by the equations below (equations are based on the observed PK and assume dose linearity). The equation producing the lower dose will be selected. If the terminal phase PK is not captured adequately by the last time point collection, time will be extended to capture at least 2 time points of the terminal phase. Upon collection of the PK from Cohort 2, the human PK model will incorporate the human PK data and any elements of non-dose-linear PK. Dosing of the 3rd cohort will resume at 100 mg unless there is a clinical concern with safety in Cohort 2. If there is a clinical concern in Cohort 2, the SRC will convene and determine an appropriate dose for Cohort 3. Dose escalation is designed to at least capture the exposure range listed in Table 3 with the intent to exceed a $C_{max}$ of 1,200 ng/mL and or an $AUC_{inf}$ of 16,000 ng/mL*h (Refer to Section 6.8) unless there are clinical findings limiting further escalation. Dose escalation to 200 mg in Cohort 4 and 400 mg in Cohort 5 will be dependent on clinical observations.

Dose 2 = 50 mg * $C_{max}$ 35 ng/mL / Observed $C_{max}$ (ng/mL)
or
Dose 2 = 50 mg * $AUC_{inf}$ 655 ng/mL*h / Observed $AUC_{inf}$ (ng/mL*h)

**Table 3: Target $C_{max}$ and $AUC_{inf}$ for Total Benzaminde Plasma Concentration Resulting from Dosing LB-102**

| Dose (mg) | $C_{max}$ (ng/ml) | $AUC_{inf}$ (ng/ml*h) |
|---|---|---|
| 10 | 35 | 330 |
| 50 | 173 | 1648 |
| 100 | 346 | 3297 |
| 200 | 692 | 6593 |
| 400 | 1384 | 13186 |

A Safety Review Committee (SRC) will be assembled to review the blinded available study results for a cohort and agree whether the safety profile is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. The SRC will be comprised of the Investigator, Medical Monitor, and a Sponsor Representative (voting members). Other non-voting consultants, including to but not limited to, PK or medical expert, statistician, etc. may support the SRC on an as needed basis. Blinded data to be reviewed after each cohort includes, but is not limited to adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory safety tests, and concomitant medications/procedures. Blinded PK analysis will occur at the end of each Cohort (Cohorts 1-5) for the SAD study and after the 1st cohort for the MAD study.

### 5.2 Discussion of Study Design

The randomization of subjects to active treatment or placebo in small cohorts along with the review of data between each cohort ensures that dose escalation can occur safely and efficiently.

### 5.3 Study Sites

The study will be conducted at a single site.

### 5.4 Selection of Study Population

#### 5.4.1 Inclusion Criteria

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

- Competent to provide informed consent.
- 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.

- Healthy adult male and female subjects between 18 to 55 years of age inclusive at the screening visit.

- Body Mass Index (BMI) $\geq$ 18 and $\leq$ 30 kg/m$^2$ at screening visit.

- 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.

- Have normal clinical laboratory test results and ECG, which are not considered to be clinically significant by the Investigator.

- 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:

     - condom plus spermicide
     - condom plus diaphragm
     - condom plus cervical cap or female condom
     - hormonal contraceptives
     - intrauterine device
     - partner vasectomy and a use of barrier contraception methods

- 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.

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

### 5.4.2 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.

4. History or presence of psychiatric or neurological disease or condition.

5. History of seizures.

6. Subject with any history or current evidence of suicidal behavior.

7. Unwilling to complete any planned study assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS).

8. Recent history of alcohol or drug abuse (within the last two years).

9. Any use of tobacco or tobacco-containing products (cigarettes, pipes, etc.) within one month prior to Screening.

10. Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.

11. Have received treatment with an investigational drug or device within 60 days prior to Screening.

12. Use of any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration.

13. Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.

14. Any subject who is known to be allergic to the study drug or any components of the study drug.

15. The subject has a fasting blood glucose ≥126 mg/dL or hemoglobin A1C ≥6.5% at Screening.

16. The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.

17. Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening (ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate in Part A for Cohort 5 and Part B, mean values will be used for the following criteria):

    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

### 5.5 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.

Additional subjects will be screened as reserve subjects for each cohort. Reserve subjects who are eligible for enrollment will also be admitted to the clinical unit to ensure enough eligible subjects are available to fill the cohort. Subjects who fulfill the eligibility criteria but are not randomized may either remain at the clinical unit for participation on a subsequent dosing date or they may be discharged and return for a future dosing date. Check-In (Day 0) procedures do not need to be repeated if the subject remains confined to the clinical unit and protocol restrictions are monitored and followed. If the subject is discharged and returns, Check-In procedures will be repeated. Subjects fulfilling the entry criteria and not randomized may be admitted to the Phase 1 Unit for

participation in a subsequent cohort so long as they remain within the 28-day screening period. Subjects who fall outside the 28-day Screening period will be allowed to rescreen.

# 6. STUDY TREATMENTS

## 6.1 Method of Assigning Subjects to Treatment Groups

Upon confirmation of eligibility, subjects will be randomized to LB-102 or placebo.

**Part A**: In each cohort, eight (8) new participants will be enrolled, randomized to 3:1 LB-102 capsule: placebo capsules, i.e., 6 receiving LB-102 capsules and 2 receiving placebo capsules. Five (5) cohorts will be enrolled for a total of 40 subjects receiving a single dose.

**Part B**: In each cohort, eight (8) new participants will be enrolled, randomized to 3:1 LB-102 capsule: placebo capsules, i.e., 6 receiving LB-102 capsules and 2 receiving placebo capsules. Three (3) cohorts will be enrolled for a total of 24 subjects receiving multiple doses.

Study randomization will be computer generated.

## 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.

LB-102 capsules at each dose level will have matching placebo capsules. All study personnel, sponsor personnel, and vendors will be blinded. Only the unblinded pharmacist will know which study participants are randomized to LB-102 or placebo.

## 6.3 Treatment Administration

For Part A of the protocol, subjects will be dispensed either an LB-102 capsule or matching placebo based on their assigned treatment at 8 AM (±1 hour) after fasting for approximately 12 hours. 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. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects.

For Part B of the protocol, subjects will be dosed both at 8 AM (±1 hour) and approximately 12 hours later on Days 1-6, and once at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. Subjects are required to fast approximately 12 hours before prior to the first Day 1 dose.

Each cohort will be dosed as follows:

| Part A | |
|---|---|
| **Cohort** | **Treatment** |
| 1 (n=8)[a] | LB-102 50 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 2 (n=8)[b] | LB-102 10 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 3 (n=8)[b] | LB-102 100 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 4 (n=8)[b] | LB-102 200 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| 5 (n=8)[b] | LB-102 150 mg (n=6) or Matching Placebo (n=2) QD x 1 day |
| **Part B** | |
| 6 (n=8) | LB-102 (n=6) 50 mg BID (100 mg/day) x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |
| 7 (n=8) | LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |
| 8 (n=8) | LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7) |

a – For Cohort 1, the first 2 subjects will be randomized to receive LB-102 (n=1) or placebo (n=1) at least 24 hours prior to the remaining 6 subjects.
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).
Y* - Dose will be determined by the SRC depending on the safety profile and clinical observations of the previous Cohort.
QD = Once daily; BID = Twice daily

### 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 unblinded 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 Blinding and Unblinding Treatment Assignment

This study will be conducted under double-blind conditions so that neither the subject nor the Investigator or study staff members will know the identity of each subject's treatment. LB-102 will be dispensed by an unblinded pharmacist to study staff for administration to the patient.

Treatment assignment for an individual subject should be unblinded only in an emergency, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The Investigator should contact the Medical Monitor or project manager before unblinding, when possible, but priority should be given to treatment of the subject. If unblinding occurs without prior approval, the Investigator should promptly communicate the circumstances leading to the unblinding by telephone and in writing to the Medical Monitor.

Breaking of the blind, other than as described above, will be considered a protocol violation. Any subject whose study drug treatment is unblinded will be discontinued and the date, time, and reason for the unblinding must be documented.

### 6.8 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).

### 6.9 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.

### 6.10 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.

#### 6.10.1 Smoking

Smoking is not allowed during the study.

#### 6.10.2 Dietary and Lifestyle Restrictions

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

- Use of alcohol from 48 hours prior to Check-In through the end of the study
- Use of any product containing caffeine or xanthine from 48 hours prior to Check-In through the end of the study
- Any foods or beverages containing grapefruit or its juice, Seville oranges or star fruit from 48 hours prior to Check-In through the end of the study
- Strenuous exercise 48 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 (Part A and Part B) are provided in Table 1 and Table 2, respectively.

## 7.1 Part A

### 7.1.1 Screening (Visit 1, Days -28 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. In Part A, ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5.
- Alcohol Breathalyzer.
- Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).
- C-SSRS

### 7.1.2 Check-In (Visit 2, Day 0)

The following procedures will be performed:

- Record medical history.

- Review inclusion and exclusion criteria.
- Physical examination.
- Vital signs.
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen).
- 12-lead ECG.
- Alcohol Breathalyzer.
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs.
- Begin 12 hour fast.
- Admit to Clinical Research Unit (for subjects not currently admitted).

### 7.1.3 Treatment Evaluation (Visit 3, Day 1)

Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:

- Administer dose of study drug.
- Vital Signs (at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post-dose).
- 12-lead ECG (at pre-dose and at 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post-dose).
- Plasma sample for PK analysis (at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post-dose).
- Record concomitant medication use.
- Assess and record AEs.

### 7.1.4 Treatment Evaluation (Visit 3, Day 2)

The following procedures will be performed on Day 2:

- Physical exam.
- Vital signs (24 hours (±30 min) post Day 1 dose).

- 12-lead ECG (24 hours (±30 min) post Day 1 dose).
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis).
- Plasma sample for PK analysis (24 and 32 hours (±15 min) post Day 1 dose).
- Record concomitant medication use.
- Assess and record AEs.

### 7.1.5 Treatment Evaluation (Visit 3, Day 3; Discharge)

The following procedures will be performed on Day 3, Discharge:

- Vital signs (48 hours (±30 min) post Day 1 dose).
- Plasma sample for PK analysis (48 hours (±15 min) post Day 1 dose).
- Serum Prolactin.
- C-SSRS
- Record concomitant medication use.
- Assess and record AEs.

### 7.1.6 Follow-Up (Visit 4, Day 8 and Visit 5, Day 15 [For Cohort 5, Part A Only])

The following procedures will be performed:

- Physical exam and weight measurements (Day 8 only).
- Vital signs (Day 8 only).
- Plasma sample for PK analysis on Day 8 and Day 15.
- Collect blood and urine samples for clinical laboratory tests on Day 8 (hematology, clinical chemistry, urinalysis, and prolactin [Days 8 and 15]).
- Urine pregnancy test for all females of childbearing potential (Day 8 only).
- Record concomitant medication use (Days 8 and 15).
- Assess and record AEs (Days 8 and 15).

## 7.2 Part B

### 7.2.1 Screening (Visit 1, Days -28 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. In Part B, ECG will be measured in triplicate at each time point.
- C-SSRS.
- Alcohol Breathalyzer.
- Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).

### 7.2.2 Check-In (Visit 2, Day 0)

The following procedures will be performed:

- Record medical history.
- Review inclusion and exclusion criteria.
- Physical examination.
- Vital signs.
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen).

- 12-lead ECG.
- Alcohol Breathalyzer.
- Urine pregnancy test for all females of childbearing potential.
- Record concomitant medication use.
- Assess and record AEs.
- Begin 12 hour fast.
- Admit to Clinical Research Unit.

### 7.2.3 Treatment Evaluation (Visit 3, Day 1)

Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:

- Administer study drug.
- Vital Signs (prior to the first dose and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post first dose).
- 12-lead ECG (prior to the first dose and at 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose).
- Plasma sample for PK analysis (prior to the first dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose).
- Record concomitant medication use.
- Assess and record AEs.

### 7.2.4 Treatment Evaluation (Visit 3, Days 2 – 7)

The following procedures will be performed on Days 2-7:

- Dosing at 8 AM and 8 PM (±1 hour) intervals on Days 2-6 (AM only on Day 7).
- Physical exam (prior to first dose on Days 2 and 4 only).
- Vital signs (prior to first dose and 2 hours (±30 min) post first dose on All Days).
- Plasma sample for PK analysis (Refer to Table 2).
- 12-lead ECG (prior to first dose on All Days).

- Blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and prolactin) prior to first dose on Day 4 only.
- C-SSRS (Day 4 only).
- Record concomitant medication use (prior to first dose on All Days).
- Assess and record AEs (prior to first dose on All Days).

### 7.2.5 Treatment Evaluation (Visit 3, Day 8)

The following procedures will be performed on Day 8:

- Plasma sample for PK analysis (24 and 32 hours (±15 min) post Day 7 dose).
- Physical examination.
- Vital signs (24 hours (±30 min) post Day 7 dose).
- 12-lead ECG (24 hours (±30 min) post Day 7 dose).
- Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis).
- C-SSRS.
- Record concomitant medication use.
- Assess and record AEs.

### 7.2.6 Treatment Evaluation (Visit 3, Day 9; Discharge)

The following procedures will be performed on Day 9 prior to discharge:

- Plasma sample for PK analysis (48 hours (±15 min) post Day 7 dose).
- Vital signs (48 hours (±30 min) post Day 7 dose).
- Serum Prolactin
- Record concomitant medication use.
- Assess and record AEs.

### 7.2.7 Follow-Up (Visit 4, Day 15)

The following procedures will be performed on Day 15:

- Physical exam and weight measurements.

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

### 7.2.8 Early Termination Visit and Withdrawal Procedures

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.
- C-SSRS (MAD only)

# 8. STUDY ASSESSMENTS

## 8.1 Efficacy

No efficacy measures will be performed in this protocol.

## 8.2 Pharmacokinetics

PK samples will be collected according to the lab manual.

## 8.3 Blood Collection

For each subject in Part A, up to 16 and 18 blood samples will be collected during the study for PK analysis for Cohorts 1-4 and Cohort 5, respectively. For each subject in Part B, up to 34 blood samples will be collected during the study for PK analysis. In addition, blood will be collected at Screening and Check-in (Day 0), blood will be collected at Day 2 (Part A) or Days 4 and 8 (Part B), blood will be collected at Day 8 and Follow-Up (Part A) for clinical laboratory testing. A separate blood sample will be collected strictly for serum prolactin at Day 4 for Part B, Discharge (On Day 3 for Part A or Day 9 for Part B) and Follow-Up (Day 8 for Part A and Day 15 for Cohort 5, Part A only or Day 15 for Part B).

## 8.4 Analytical Procedures

### 8.4.1 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.

### 8.4.2 Bioanalytical Methodology

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.

## 8.5 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.

### 8.5.1 Safety Review Committee (SRC)

The SRC will be assembled to review the blinded available study results for a cohort and agree the safety profile is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. The SRC will be comprised of the Investigator, Medical Monitor, and a Sponsor Representative (voting members). Other non-voting consultants, including to but not limited to, PK or medical expert, statistician, etc. may support the SRC on an as needed basis. Blinded data to be reviewed after each cohort includes, but is not limited to adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory safety tests, and concomitant medications/procedures. Blinded PK analysis will occur at the end of each Cohort (Cohorts 1-5) for the SAD study and after the 1$^{st}$ cohort for the MAD study.

### 8.5.2 Dose Escalation

#### 8.5.2.1 Part A

The study will begin at the lowest planned dose level (50 mg/day). Data from at least 6 evaluable subjects through 48 hours within the cohort are required for safety review by the SRC before dose escalation in the subsequent cohort, provided any discontinuations are not suspected of being related to LB-102. For purposes of dose escalation, an evaluable subject is defined as a subject who received a dose of LB-102 or placebo and has completed through 48-hour study procedures.

If the starting dose (50 mg/day) for Cohort 1 (Part A) results in a total benzamide (LB-101 and LB-102) geometric mean $C_{max}$ greater than 175 ng/mL or a geometric mean of total benzamide exposure ($AUC_{inf}$) greater than 3,270 ng/mL*h, the dose for Cohort 2 will be adjusted downward, to the nearest 10 mg, by the equations below (equations are based on the observed PK and assume dose linearity). The equation producing the lower dose will be selected. If the terminal phase PK is not captured adequately by the last time point collection, time will be extended to capture at least 2 time points of the terminal phase. Upon collection of the PK from Cohort 2, the human PK model will incorporate the human PK data and any elements of non-dose-linear PK. Dosing of the 3rd cohort will resume at 100 mg unless there is a clinical concern with safety in Cohort 2. If there is a clinical concern in Cohort 2, the SRC will convene and determine an appropriate dose for Cohort 3. Dose escalation is designed to at least capture the exposure range listed in Table 3 with the intent to exceed a $C_{max}$ of 1,200 ng/mL and or an $AUC_{inf}$ of 16,000 ng/mL*h (Refer to Section 6.8) unless there are clinical findings limiting further escalation. Dose escalation to 200 mg in Cohort 4 and 400 mg in Cohort 5 will be dependent on clinical observations.

$$\text{Dose 2} = 50 \text{ mg} * C_{max}\ 35 \text{ ng/mL} / \text{Observed } C_{max} \text{ (ng/mL)}$$

or

$$\text{Dose 2} = 50 \text{ mg} * AUC_{inf}\ 655 \text{ ng/mL*h} / \text{Observed } AUC_{inf} \text{ (ng/mL*h)}$$

#### 8.5.2.2 Part B

Multiple day continuous dosing for 7 days will begin at the lowest planned Part B exposure level, based on the PK observed in a minimum of two Part A cohorts. Dose escalation may occur when the SRC has reviewed the available study results for a cohort and agrees that the safety profile through Study Day 9 is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. Data from at least 6 evaluable subjects within the cohort are required for safety review before dose escalation, provided any discontinuations are not suspected of being related to LB-102. For purposes of dose escalation, an evaluable subject is defined as a subject who received 13 doses of LB-102 or placebo.

### 8.5.3 Dose Escalation/Stopping Criteria

After each cohort, blinded data for all patients will be reviewed by the SRC, containing a minimum of 48 hours safety data for Part A and through Study Day 9 for Part B. The SRC will determine grade, seriousness, and relatedness in a blinded fashion.

Escalation to the next dose level may not continue as planned if any of the following conditions from the preceding cohort are met:

- A SAE occurs in 1 or more LB-102 or placebo-treated subjects that is not clearly unrelated to LB-102 or placebo.

- One or more LB-102 or placebo-treated subjects experience a ≥ Grade 3 AE that is not clearly unrelated to LB-102 or placebo.

- Two or more LB-102 or placebo-treated subjects experience a ≥ Grade 2 AE in the same system organ class (SOC) that is not clearly unrelated to LB-102 or placebo.

- Any other event that is deemed by the Investigator or Sponsor to pose an unacceptable risk to subjects as a result of dose escalation.

Thereafter, the following may occur:

- Dose escalation may be stopped.

- Dose escalation may continue as originally planned. This is only permissible if the AE(s) that met stopping criteria is judged, after unblinded review, as not being related to LB-102;

- The planned dose escalation may be modified to include repetition of the dose level at which the AE(s) that met stopping criteria had occurred (in a new cohort of up to 8 Part subjects or 8 Part B subjects randomized in the same ratio as other cohorts), based on the results of the safety and tolerability review or if further characterization of a safety signal is appropriate. This is only permissible if the AE(s) that met stopping criteria is judged, after unblinded review, as not being related to LB-102;

- An intermediate dose (lower than the dose that met stopping criteria) cohort may be added

If the SRC decides on any action other than continuing dose escalation as planned, they will communicate to the Unblinded Statistician the subject numbers who they believe meet stopping criteria. The Unblinded Statistician will check the treatment assignment of that subject; if the subject received placebo then the stopping criteria are not triggered for that subject, otherwise the stopping criteria will be triggered. The Unblinded Statistician will communicate to the SRC their agreement that the stopping criteria are met after review of the treatment assignments, if applicable. If stopping criteria are not met due to events of concern occurring in placebo subjects, the Unblinded Statistician will communicate that the stopping criteria were not met and communicate the subject numbers who do not qualify based on receiving placebo. This unblinding will only occur in cases where the SRC has identified events potentially meeting stopping criteria and will be limited only to subject numbers experiencing the events in question. The whole cohort will not be unblinded to the SRC.

### 8.5.4 Individual Subject Stopping Criteria

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

- Any SAE regardless of association to LB-102 or placebo.
- Any ≥ Grade 3 AE according to the appropriate toxicity grading scale. If a subject experiences an AE assessed as ≥ Grade 3, that subject should not receive any additional doses and the subject should be followed until the AE resolves or stabilizes.
- Any other event that is deemed by the Investigator or Sponsor to pose an unacceptable risk to the subject.

### 8.5.5 Intra-Cohort Stopping Criteria

Dosing of all subjects within any dose level cohort will cease if any of the following criteria are met:

- An SAE for which the event cannot be clearly determined to be unrelated to LB-102 administration in 1 subject.
- The occurrence of a ≥ Grade 3, non-serious AE, for which the event cannot be clearly determined to be unrelated to LB-102 administration in 2 subjects at the same dose level (Part A or Part B cohorts).
- Any other event that is deemed by the Investigator or Sponsor to pose an unacceptable risk to the subjects in the cohort.
- If 2 or more subjects experience QTcF as described in Section 8.5.6.

If any of the above are met, the SRC will perform a blinded review of available safety data. Once an evaluation of the data has occurred, and following review and approval by the IRB (if required by local regulations), the following may occur:

- Further evaluation of the dose level may be stopped, and the dose that met stopping criteria (or higher doses) will not be administered in the study.
- The dose level may be repeated (in a new cohort of up to 8-12 subjects). This is only permissible if the AE(s) that met stopping criteria is judged, after review, as not

### 8.5.6 QT Prolongation Stopping Criteria

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

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

OR

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

ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate in Part A for Cohort 5 and Part B, mean values will be used for Stopping Criteria. A confirmation of an abnormal finding meeting the stopping criteria will be required within 15 minutes of the initial QTcF reading.

### 8.5.7 Adverse Events

#### 8.5.7.1 Adverse Event Definitions

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

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. For a marketed drug, the known information is in the current package insert.

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

#### 8.5.7.2 Eliciting and Documenting Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the CRF and reported to the Medical Monitor. Adverse events will be collected from Check-in (Day 0) through the Day 8 (Cohorts 1-4, Part A; End of Study), or 15 (Cohort 5, Part A or Cohorts 6-8, Part B, respectively; End of Study), 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 data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

#### 8.5.7.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. 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. Adverse events 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 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 e-mail a written SAE report form to the Medical Monitor/Safety team. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. 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 | Thomas Thompson, MD | Medpace<br>5375 Medpace Way<br>Cincinnati, OH 45227<br>Phone: (513) 579-9911 ext. 11869<br>Mobile: (919) 602-5726 |
| Safety Monitor | Lucy Wang, PharmD | Target Health LLC<br>261 Madison Avenue, 24th floor<br>New York, NY 10016<br>(646) 218-.2072 |

#### 8.5.7.4 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. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

#### 8.5.7.5 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.

#### 8.5.7.6 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.

#### 8.5.7.7 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 CRF.

### 8.5.8 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.

### 8.5.9 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). The blood samples for serum chemistry tests will be collected following a minimum 8-hour fast.

Given that it may be possible for individuals who have access to prolactin data to presume which subjects received LB-102 and which subjects received placebo, prolactin data will be de-identified prior to Investigator review during the Treatment Period. Likewise, de-identified prolactin data will be provided to the SRC members for review prior to each dose escalation meeting. Subject IDs will be disclosed for clinical evaluation for prolactin levels that are ≥ 100 ng/mL.

| | |
|---|---|
| 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.

### 8.5.10 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.

### 8.5.11 Electrocardiogram

A 12-lead ECG will be performed after the subject has been in supine resting for at least 10 minutes, and at the following times:

Part A: Screening, Check-in, Day at pre-dose and 1, 2, 3, 4, 5, 6, 8, and 24 hours (±30 min) post-dose. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5.

Part B: Screening, Check-in, Day 1 Pre-dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post-dose, prior to the first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose). ECG will be measured in triplicate at each time point.

### 8.5.12 Physical Examination

A standard physical examination will be performed at Screening, Check-in, Day 2, and Follow-up in Part A and at Screening, Check-in, Days 2, 4, and 8, and Follow-up in Part B. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, neurological (with a particular focus on monitoring for manifestations of Extrapyramidal Symptoms), and musculoskeletal system/extremities. Interim physical examinations will be performed at the Investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at Screening and only weight will be measured again at Follow-up for Part A and B.

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

The baseline C-SSRS will be completed at Screening (both SAD and MAD) and at Day 3 (SAD), Day 4 and Day 8 or early termination (MAD only). 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 or Day 3 (SAD only) Day 4 or Day 8 (MAD only) the following will occur, at the discretion of the Principal Investigator and Medical Monitor:

Screening positive and significant findings (SAD and MAD):

- For positive and significant findings at Screening the subject will be considered a screen fail according to exclusion criterion 6 (Section 5.4.2). Proper follow up will be based on the severity of the symptoms.

Day 3 (SAD) or Day 4 or Day 8 positive and significant findings (MAD only)

- 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 based on the severity of symptoms and at the discretion of the Principal Investigator

### 8.5.14 Concomitant Medications

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

### 8.5.15 Sample Collection and Processing

Details of sample process will be provided in the lab manual

### 8.5.16 Sample Storage

Plasma samples will be stored according to the lab manual.

### 8.5.17 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

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

A separate SAP for the PK analyses will be prepared for the study and will be finalized prior to database lock. Data from subjects who participated in the study will be included in the PK analysis. Subjects with missing sample concentrations will be included in the PK analyses provided their PK parameters can be adequately characterized based upon the remaining data.

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

All PK parameters will be calculated using non-compartmental analysis using WinNonlin Version 5.2 or higher. Actual sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean plasma concentrations for graphical displays.

Other PK analyses may be performed as appropriate.

### 9.4 Sample Size Determination

The sample size for the study is based on clinical rather than statistical rationale. No formal sample size calculations were made. Cohorts of 8 subjects (6 active, 2 placebo) are sufficient to characterize the safety, tolerability, 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).

#### 10.2.2 Target e*CTR® Viewer (Target e*Clinical Trial Record Viewer)

Clinical trial data entered into the Target e*CRF® (EDC) system are stored in PDF format in the Target e*CTR Viewer, an independent repository controlled by the clinical Investigator. Target e*CTR® Viewer is a validated 21 CFR Part 11 compliant Internet-based software system. The

subject data PDF files are read-only. Users' access to the Target e*CTR® Viewer is granted by the Investigator, or a designee. The Investigator can download a bookmarked PDF copy of records of individual subjects or all subjects, including an audit trail of changes and electronic signatures.

### 10.3 Data Management

A Data Management Plan (DMP) is created by a Target Health Data Manager (DM) to specifically identify how data management will be performed for the study. The following summarizes the DMP:

The clinical database is held and managed by Target Health during the lifetime of the study. In order to build the EDC application, an Application Setup Instructions (ASI) document is created. The ASI document contains the specific instructions to both the EDC and DM programmers.

Data validation is performed according to the specifications in the Data Validation Plan (DVP). Target e*CRF® will be used for online edit checks, batch edit checks and query management. Within the DVP, there are 3 possible types of validation checks:

- Online checks performed by the EDC system during data entry and could include data outside established ranges or missing data. Target Health is responsible for programming these checks.

- Batch edit checks are run periodically to check for consistency across data forms. Target Health is responsible for programming these checks.

- Manual checks performed by the monitor and DM to identify data entry errors that cannot be identified by online or batch edit checks. The DM is responsible for providing listings to monitors to be used for manual checks.

Data queries are handled within the Target e*CRF® application. The monitors and DMs are the only persons who can generate a query. Under direction of the Investigator, the site addresses the query. If the query is due to a data entry error, the site can immediately make the corrections in the applicable eCRF pages. If the query needs clarification, the Investigator is responsible for resolution. The site then enters the correct value or submits an answer to the query without modifying the data. The monitor or DM then reviews the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, the monitor or DM closes the query. If the answer is not acceptable, the monitor submits an additional query for clarification. All changes to the database require a "Reason for Change" and are subject to an audit trail. The audit trails identify the changed data, reason(s) for change, who changed the data and the time and date of the change (based on the Target e*CRF® server's time).

### 10.4 Good Clinical Practice Monitoring Plan

A Good Clinical Practice (GCP) Monitoring Plan is prepared by the Medpace Lead Clinical Research Associate (LCRA) 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 y 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.<br><br>All Initiation, Monitoring and Close-out Visit Reports are reviewed by the Lead CRA.<br><br>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 the 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.

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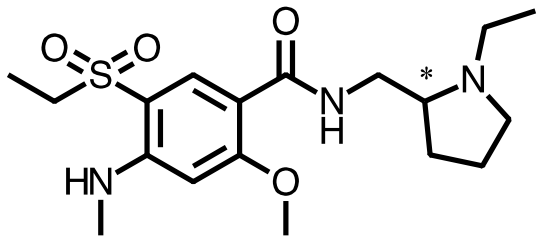
# 14. APPENDICES

## 14.1 Appendix 1: Clinical Pharmacology Summary Table

**Table 1: Clinical Pharmacology Summary Table**

**General Information**

**Chemical Structure and Major Physical and Chemical Properties**



**Molecular Weight**: 383.51

| | |
|---|---|
| **Description** | White to off-white powder |
| **pKa** | 9.36 |
| **Partition Coefficient (LogP)** | 1.72 (pH 7) |

**Aqueous Solubility**

| Vehicle | HPLC Area of Sample (225 nm) | Sample Concentration (mg/mL) | Calculated Solution Concentration (mg/mL) | Comment |
|---|---|---|---|---|
| 30% DMF 70% pH 4.7 MES | 2769 | 0.44 | 44.0 | 100:1 dilution, pH of buffer is unchanged |
| pH 4.7 MES Buffer | 3770 | 0.614 | 61.4 | 100:1 dilution, pH of buffer is unchanged |
| pH 5 HCl | 4990 | 0.839 | 83.9 | 100:1 dilution, pH of buffer is unchanged |
| pH 6 phosphate buffer | 3827 | 0.625 | 625 | 1000:1 dilution, pH of buffer is unchanged |
| pH 5 acetate buffer | Not Determined | >800 | >800 | pH of solution becomes 6.5 |

| | |
|---|---|
| Indication (for this IND) | For the Treatment of Schizophrenia. |
| Route and Formulation Type (for this IND) | Oral Capsule. |
| Planned Strengths (for this IND) | LB-102 consists of API in a Size 2 white opaque/white opaque hard gelatin capsule in dosage strengths of 25 mg, 50 mg, 75 mg, and 100 mg. |
| Planned Dose Levels (for this IND) | For Part A (Single Ascending Dose Study) there were 5 dose levels: 50, 10, 100, 200, and 150 mg QD.<br>For Part B (Multiple Ascending Doses Study) there will be 3 dose levels (BID), starting with 50 mg (100 mg/day). The remaining doses will be determined by the |

<table>
<tr><td></td><td>SRC depending on the safety profile and clinical observations of the previous Cohort.</td></tr>
<tr><td>Mechanism of Action (for this Indication)</td><td>The proposed mechanism of action for LB-102 is through dopamine D2/D3 receptor antagonism.</td></tr>
<tr><td colspan="2">Dose and AEs</td></tr>
<tr><td>Therapeutic Dose and Exposure (for this IND)</td><td>
<table>
<tr><td colspan="2">Part A</td></tr>
<tr><td>Cohort</td><td>Treatment</td></tr>
<tr><td>1 (n=8)[a]</td><td>LB-102 50 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>2 (n=8)[b]</td><td>LB-102 10 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>3 (n=8)[b]</td><td>LB-102 100 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>4 (n=8)[b]</td><td>LB-102 200 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>5 (n=8)[b]</td><td>LB-102 150 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td colspan="2">Part B</td></tr>
<tr><td>6 (n=8)</td><td>LB-102 (n=6) 50 mg BID (100 mg/day) x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
<tr><td>7 (n=8)</td><td>LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>Or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
<tr><td>8 (n=8)</td><td>LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>Or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
</table>
a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.<br>
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).<br>
Y* - Dose will be determined by the SRC depending on the safety profile and clinical observations of the previous Cohort.<br>
QD = Once daily; BID = Twice daily<br>
<u>Treatment Exposure:</u><br>
Part A: 1 day<br>
Part B: 7 days</td></tr>
<tr><td>Maximum Tolerated Dose</td><td><u>Rats</u><br>• In the 14-day repeat dose phase study, the maximum tolerated dose was determined to be 200 mg/kg/day<br><u>Dogs</u><br>• In the single-dose phase of the dog range-finding study, the maximum tolerated dose was determined to be 25 mg/kg/day<br>• In the 14-day repeat-dose phase study, the maximum tolerated dose was determined to be 5 mg/kg/day</td></tr>
</table>

| | | |
|---|---|---|
| Principal Adverse Events | Prolactin elevation (≥ 100 ng/mL) | |
| **PK Features** | | |
| Dose/Exposure Range Tested in Clinic (Data from this IND and/or Elsewhere) | Single Dose | 50 mg, 10 mg, 100 mg, 200 mg, 150 mg |
| | Multiple Dose | N/A |
| Range of Linear PK | At least to 200 mg (highest dose examined to date) | |
| Accumulation at Steady State | Repeat dose PK model suggests 40% of Cmax with b.i.d. dosing | |
| Metabolites | LB-101 approximately 2.5% | |
| Absorption | Absolute/Relative Bioavailability | N/A |
| | Mean Tmax | 50 mg – 3.000 h<br>10 mg – 3.000 h<br>100 mg – 2.833 h<br>200 mg – 2.083 h<br>150 mg – 3.167 h |
| Distribution | Vd/F or Vd | N/A |
| | % bound in plasma | N/A |
| | Blood / plasma partition ratio | N/A |
| Elimination | Route | Oral (PO) |
| | Mean Terminal t½ | 50 mg – 12.311 h<br>10 mg – 13.675 h<br>100 mg – 14.656 h<br>200 mg – 12.835 h<br>150 mg – 12.620 h |
| | Mean CL/F or CL | 50 mg – 31.624 L/h<br>10 mg – 42.323 L/h<br>100 mg – 36.346 L/h<br>200 mg – 28.901 L/h<br>150 mg – 32.964 L/h |
| Metabolism | • by CYP450 ☐ Yes ☐ No ☒ NA, if yes, specify<br>• by Phase 2 enzymes ☐ Yes ☐ No ☒ NA<br>• by other enzyme systems ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits CYP450 ☒ Yes ☐ No ☐ NA, if yes, specify and provide $K_i$ and/or$IC_{50}$. A Cytochrome P450 Inhibition Assay demonstrated that LB-102 slightly inhibits CYP2C8 ($IC_{50}$ = 75.5 μM).<br>• inhibits Phase II enzymes ☐ Yes ☐ No ☒ NA, if yes specify and provide $K_i$ and/or $IC_{50}$.<br>• induces CYP450 ☐ Yes ☐ No ☒ NA, if yes specify | |

| | | |
|---|---|---|
| Transporters | by major transporters ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits major transporters ☐ Yes ☐ No ☒ NA, if yes, specify and provide Ki and/or IC50.<br>• induces major transporters ☐ Yes ☐ No ☒ NA, if yes specify | |
| Intrinsic Factors | Age | N/A |
| | | N/A |
| | Sex | N/A |
| | Race | N/A |
| | Hepatic Impairment | N/A |
| | Renal Impairment | N/A |
| | Poor Metabolizers | N/A |
| Extrinsic Factors | Drug interactions | N/A |
| | Food Effects | N/A |
| | Alcohol Effects (Oral MR formulation only) | N/A |
| **PD Features** | | |
| PD Studies: e.g.,<br>QT Effect<br>Driving Test<br>Receptor Occupancy<br>Sleeping Test<br>Other Safety Evaluation | Part A (Single Ascending Dose)<br>Cohort 1 - 50 mg LB-102:<br>• Three (3) mild, Grade 1 AEs (elevated prolactin, ≥100 ng/mL) that were experienced by 3 subjects. All 3 prolactin elevations were asymptomatic. The 3 AEs were considered definitely related to LB-102 in Cohort 1. All 3 AEs resolved by Day 8 (Follow-Up Visit).<br>Cohort 2 – 10 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experience by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 2. The AE resolved by Day 8.<br>Cohort 3 – 100 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experienced by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 3. The AE resolved by Day 8.<br>Cohort 4 – 200 mg:<br>• One (1) mild, Grade 1 AE (QTcF prolongation of > 450 ms was noted, 2 hours post-dose on Day 1) was experienced by 1 subject. The AE was considered definitely related to LB-102 in Cohort 4. The AE resolved by 3 hours post-dose on Day 1. The overall maximum QTcF prolongation for the subject was 43 msec from baseline.<br>• One (1) moderate, Grade 2 AE (acute dystonic reaction). The acute dystonic reaction was definitely related to the study drug in Cohort 4. The AE resolved on the same day it was experienced (Day 1) with no recurrence. Subject was treated with concomitant medication for the symptoms. | |

| | |
|---|---|
| | Cohort 5 – 150 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experienced by 1 subject. The subject was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 5. The AE resolved by Day 15 Follow-Up Visit. |
| E-R Studies: e.g.: Important E-R Relationships | N/A |
| **Other Studies** | |
| e.g., Genotype | N/A |

# Summary of Changes

## A Randomized, Double-Blinded, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects

| | |
|---|---|
| PROTOCOL NUMBER: | LB-102-001 |
| STUDY PHASE: | Phase 1 |
| IND NUMBER: | 137581 |
| PROTOCOL VERSION: | Version 1, 21 October, 2019<br>Version 2, 17 December, 2019<br>Version 3, 06 February, 2020<br>Version 4, 20 March 2020<br>Version 5, 18 May 2020 |
| SPONSORED BY: | LB Pharmaceuticals, Inc.<br>575 Madison Avenue<br>New York, NY 10022<br>Phone: (646)-588-8175 |
| CONTRACT RESEARCH ORGANIZATION: | Target Health LLC<br>261 Madison Avenue, 24th Floor<br>New York, NY 10016<br>Phone (212) 681-2100 (Ext 0) |

## Section 1 – Study Design

**Original Wording**

A Safety Review Committee (SRC) will be assembled to review the blinded available study results for a cohort and agree whether the safety profile is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. The SRC will be comprised of the Investigator, Medical Monitor, and a Sponsor Representative (voting members). Other non-voting consultants, including to but not limited to, PK or medical expert, statistician, etc. may support the SRC on an as needed basis. Blinded data to be reviewed at the end of each cohort includes, but is not limited to adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory safety tests, and concomitant medications/procedures. Blinded PK analysis will occur at the end of the 1st, 2nd, and 3rd cohorts for the SAD study and after the 1st cohort for the MAD study.

**Revised Wording**

A Safety Review Committee (SRC) will be assembled to review the blinded available study results for a cohort and agree whether the safety profile is sufficiently acceptable to support proceeding with the evaluation of the next higher dose level. The SRC will be comprised of the Investigator, Medical Monitor, and a Sponsor Representative (voting members). Other non-voting consultants, including to but not limited to, PK or medical expert, statistician, etc. may support the SRC on an as needed basis. Blinded data to be reviewed at the end of each cohort includes, but is not limited to adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory safety tests, and concomitant medications/procedures. Blinded PK analysis will occur at the end ***of each Cohort (Cohorts 1-5)*** for the SAD study and after the 1st cohort for the MAD study.

**Original Wording**

- Prolactin at:
    - Part A: Screening, Day 3, Day 8, and Day 15 (For Cohort 5, Part A only).
    - Part B: Screening, Day 9, and Day 15.

**Revised Wording**

- Prolactin at:
    - Part A: Screening, Day 3, Day 8, and Day 15 (For Cohort 5, Part A only).
    - Part B: Screening, ***Day 4,*** Day 9, and Day 15.

## Section 1 - Study Design - Test Product, Dose, and Mode of Administration

**Original Wording**

*N*-methyl amisulpride (LB-102) Powder in Capsule, Oral administration

**Revised Wording**

*N*-methyl amisulpride (LB-102) Powder in Capsule ***in dosage strengths of 25 mg, 50 mg, 75 mg, and 100 mg***, Oral administration

## Section 1 – Study Design and Section 6.3 – Treatment Administration

**Original Wording**

| **Part A** | |
|---|---|
| **Cohort** | **Treatment** |
| 1 (n=8)[a] | LB-102 50 mg (n=6) or Matching Placebo (n=2) x 1 day |
| 2 (n=8)[b] | LB-102 100 mg (n=6) or Matching Placebo (n=2) x 1 day |
| 3 (n=8)[b] | LB-102 200 mg (n=6) or Matching Placebo (n=2) x 1 day |
| 4 (n=8)[b] | LB-102 400 mg (n=6) or Matching Placebo (n=2) x 1 day |
| 5 (n=8)[b] | LB-102 800 mg (n=6) or Matching Placebo (n=2) x 1 day |
| **Part B** | |
| 6 (n=8) | LB-102 Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7) |
| 7 (n=8) | LB-102 2Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7) |
| 8 (n=8) | LB-102 3Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7) |

a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).
Y* - Dose will be based on the PK observed in a minimum of two Part A cohorts.
QD = Once daily; BID = Twice daily

**Revised Wording**

| Part A | |
|---|---|
| **Cohort** | **Treatment** |
| 1 (n=8)[a] | ***LB-102 50 mg (n=6) or Matching Placebo (n=2) QD x 1 day*** |
| 2 (n=8)[b] | ***LB-102 10 mg (n=6) or Matching Placebo (n=2) QD x 1 day*** |
| 3 (n=8)[b] | ***LB-102 100 mg (n=6) or Matching Placebo (n=2) QD x 1 day*** |
| 4 (n=8)[b] | ***LB-102 200 mg (n=6) or Matching Placebo (n=2) QD x 1 day*** |
| 5 (n=8)[b] | ***LB-102 150 mg (n=6) or Matching Placebo (n=2) QD x 1 day*** |
| **Part B** | |
| 6 (n=8) | ***LB-102 (n=6) 50 mg BID (100 mg/day) x 6 days (Days 1-6) and QD x 1 day (Day 7)***<br>***or***<br>***Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)*** |
| 7 (n=8) | ***LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)***<br>***or***<br>***Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)*** |
| 8 (n=8) | ***LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)***<br>***or***<br>***Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)*** |

a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).
***Y* - Dose will be determined by the SRC depending on the safety profile and clinical observations of the previous Cohort.***
QD = Once daily; BID = Twice daily.

## Table 1: Schedule of Events for Part B

**Original Wording**

**Table 1: Schedule of Events for Part B**

| | Screening | Check-In | Treatment Evaluation | | | Follow-Up Visit |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | | | **4** |
| **Days** | **Days -28 to -1** | **Day 0** | **Day 1** | **Days 2-7** | **Days 8-9** | **Day 15** |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Medical History | X | X | | | | |
| Demographics | X | | | | | |
| Randomization | | | X | | | |
| Height, Weight, BMI[1] | X | | | | | X |
| Physical Examination | X | X | | X (Days 2, 4 only) | X (Day 8 only) | X |
| Vital Signs[2] | X | X | X | X | X | X |
| Laboratory Tests | X | X | | X (Day 4 only) | X (Day 8 only) | X |
| Serum HbA1c | X | | | | | |
| Serum Prolactin | X | | | | X (Day 9 only) | X |
| HIV, HBsAg, and HCV Labs | X | | | | | |
| 12-Lead ECG[3] | X | X | X | X | X (Day 8 only) | |
| C-SSRS | X | | | X (Day 4 only) | X (Day 8 only) | |
| Urine Drug Screening | X | X | | | | |
| Alcohol Breathalyzer | X | X | | | | |
| Pregnancy[4] | X | X | | | | X |
| FSH[5] | X | | | | | |
| Plasma PK[6] | | | X | X | X | |
| Dose Subjects[7] | | | X | X | | |
| Concomitant Medication[8] | X | X | X | X | X | X |
| Adverse Event Assessment[8] | | X | X | X | X | X |

**Notes to the Schedule of Events for Part B:**
BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-up, height and BMI will not.
[2] Vital Signs will be measured at Screening, Check-in, Day 1 prior to the first dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up.
[3] ECG will be measured in triplicate at Screening, Check-in, Day 1 prior to the first dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).
[4] Serum pregnancy test at screening and Urine pregnancy test at Day 0 and Day 15 for all females of childbearing potential.
[5] FSH test for postmenopausal women.
[6] Plasma PK samples will be collected on Day 1 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours (±15 min) post first dose, Days 2-6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose.
[7]Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-6, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 7, 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.

**Revised Wording**

**Table 1: Schedule of Events for Part B**

| | Screening | Check-In | Treatment Evaluation | | | Follow-Up Visit |
|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | | | **4** |
| **Days** | **Days -28 to -1** | **Day 0** | **Day 1** | **Days 2-7** | **Days 8-9** | **Day 15** |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Medical History | X | X | | | | |
| Demographics | X | | | | | |
| Randomization | | | X | | | |
| Height, Weight, BMI[1] | X | | | | | X |
| Physical Examination | X | X | | X (Days 2, 4 only) | X (Day 8 only) | X |
| Vital Signs[2] | X | X | X | X | X | X |
| Laboratory Tests | X | X | | X (Day 4 only) | X (Day 8 only) | X |
| Serum HbA1c | X | | | | | |
| Serum Prolactin | X | | | ***X (Day 4 only)*** | X (Day 9 only) | X |
| HIV, HBsAg, and HCV Labs | X | | | | | |
| 12-Lead ECG[3] | X | X | X | X | X (Day 8 only) | |
| C-SSRS | X | | | X (Day 4 only) | X (Day 8 only) | |
| Urine Drug Screening | X | X | | | | |
| Alcohol Breathalyzer | X | X | | | | |
| Pregnancy[4] | X | X | | | | X |
| FSH[5] | X | | | | | |
| Plasma PK[6] | | | X | X | X | |
| Dose Subjects[7] | | | X | X | | |
| Concomitant Medication[8] | X | X | X | X | X | X |
| Adverse Event Assessment[8] | | X | X | X | X | X |

**Notes to the Schedule of Events for Part B:**
BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-up, height and BMI will not.
[2] Vital Signs will be measured at Screening, Check-in, Day 1 prior to the first dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up.
[3] ECG will be measured in triplicate at Screening, Check-in, Day 1 prior to the first dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).
[4] Serum pregnancy test at screening and Urine pregnancy test at Day 0 and Day 15 for all females of childbearing potential.
[5] FSH test for postmenopausal women.
[6] Plasma PK samples will be collected on Day 1 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours (±15 min) post first dose, Days 2-6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose.
[7]Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-6, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 7, 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.

## Section 5.1 - Overall Study Design and Plan

**Original Wording**

In Part A, eligible subjects, in 5 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 40 subjects. Four (4) visits will occur as follows: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-3), and Follow-up (Visit 4, Day 8 and Visit 5, Day 15 [for Cohort 5, Part A only]). The study procedures for these visits are presented in detail in Table 1. Dosage of LB-102 will begin at 50 mg/day and subsequent groups will administered 100, 200, 400, and 800 mg/day, respectively. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 at 8 AM (±1 hour). For each cohort, blood samples for PK will be collected on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose, and Day 8 and Day 15. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours (±30 min) post-dose, and at the Follow-up visit (Day 8). 12-lead ECG will be done on at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, 8 and 24 hours (±30 min) post-dose. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5. Clinical labs (hematology, chemistry, urinalysis) will be assessed at Screening, Check-in, Day 2, and Follow-Up. Hemoglobin A1c (HbA1c) will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 3, Day 8, and Day 15. C SSRS will be assessed at Screening and Day 3. Subjects will remain in the clinic from Check-in to Discharge on Day 3 for additional safety assessment and then return for a Follow-up Visit on Day 8. Subsequent groups will follow the same study procedures.

In Part B, eligible subjects, in 3 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 24 subjects. Four (4) visits will be scheduled for this study: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-9), and Follow-up (Visit 4, Day 15). The study procedures for these visits are presented in detail in Table 2. Dosage of LB-102 will be based on the PK observed in a minimum of two Part A cohorts. Subjects will receive 2 doses of placebo or LB-102, first dose at 8:00 AM (±1 hour) and second dose approximately 12 hours later, on Days 1-6 and one dose at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. The first dose on Day 1 will occur following a 12 hour, overnight fast. For each cohort, blood samples for PK will be collected at multiple timepoints starting on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose. On Days 2-6, blood samples for PK will be collected prior to the first dose. On Day 7 blood samples for PK will be collected pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, at pre-dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up. 12-lead ECG will be done in triplicate at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and on Day 8 (24 hours (±30 min) post-dose Day 7). Clinical labs will be assessed at Screening, Check-in, prior to first dose on Day 4,

Day 8, and at Follow up. HbA1c will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 9, and Day 15. C-SSRS will be assessed at Screening, Day 4, and Day 8. Subjects will remain in the clinic from Check-in to Discharge on Day 9 for additional safety assessment and then return for a Follow-up Visit on Day 15. Subsequent groups will follow the same study procedures.

**Revised Wording**

In Part A, eligible subjects, in 5 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 40 subjects. Four (4) visits will occur as follows: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-3), and Follow-up (Visit 4, Day 8 and Visit 5, Day 15 [for Cohort 5, Part A only]). The study procedures for these visits are presented in detail in Table 1. Dosage of LB-102 will begin at 50 mg/day and subsequent groups will administered ***10, 100, 200, and 150*** mg/day, respectively. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 at 8 AM (±1 hour). For each cohort, blood samples for PK will be collected on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose, and Day 8 and Day 15. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours (±30 min) post-dose, and at the Follow-up visit (Day 8). 12-lead ECG will be done on at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, 8 and 24 hours (±30 min) post-dose. ECG will be measured once at each time point for Cohorts 1-4 and in triplicate for Cohort 5. Clinical labs (hematology, chemistry, urinalysis) will be assessed at Screening, Check-in, Day 2, and Follow-Up. Hemoglobin A1c (HbA1c) will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 3, Day 8, and Day 15. C SSRS will be assessed at Screening and Day 3. Subjects will remain in the clinic from Check-in to Discharge on Day 3 for additional safety assessment and then return for a Follow-up Visit on Day 8. Subsequent groups will follow the same study procedures.

In Part B, eligible subjects, in 3 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 24 subjects. Four (4) visits will be scheduled for this study: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-9), and Follow-up (Visit 4, Day 15). The study procedures for these visits are presented in detail in Table 2. Dosage of LB-102 will be based on the PK observed in a minimum of two Part A cohorts. Subjects will receive 2 doses of placebo or LB-102, first dose at 8:00 AM (±1 hour) and second dose approximately 12 hours later, on Days 1-6 and one dose at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. The first dose on Day 1 will occur following a 12 hour, overnight fast. For each cohort, blood samples for PK will be collected at multiple timepoints starting on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose. On Days 2-6, blood samples for PK will be collected prior to the first dose. On Day 7 blood samples for PK will be collected pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, at pre-dose and 2 hours (±30 min) post first

dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up. 12-lead ECG will be done in triplicate at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, and 8 hours (±30 min) post first dose, prior to first dose on Days 2-7, and on Day 8 (24 hours (±30 min) post-dose Day 7). Clinical labs will be assessed at Screening, Check-in, prior to first dose on Day 4, Day 8, and at Follow up. HbA1c will be measured in serum at Screening. Prolactin will be measured in serum at Screening, ***Day 4,*** Day 9, and Day 15. C-SSRS will be assessed at Screening, Day 4, and Day 8. Subjects will remain in the clinic from Check-in to Discharge on Day 9 for additional safety assessment and then return for a Follow-up Visit on Day 15. Subsequent groups will follow the same study procedures.

## Section 7.2.4 - Treatment Evaluation (Visit 3, Days 2 – 7)

**Original Wording**

The following procedures will be performed on Days 2-7:

- Dosing at 8 AM and 8 PM (±1 hour) intervals on Days 2-6 (AM only on Day 7).
- Physical exam (prior to first dose on Days 2 and 4 only).
- Vital signs (prior to first dose and 2 hours (±30 min) post first dose on All Days).
- Plasma sample for PK analysis (Refer to Table 2).
- 12-lead ECG (prior to first dose on All Days).
- Blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis) prior to first dose on Day 4 only.
- C-SSRS (Day 4 only).
- Record concomitant medication use (prior to first dose on All Days).
- Assess and record AEs (prior to first dose on All Days).

**Revised Wording**

The following procedures will be performed on Days 2-7:

- Dosing at 8 AM and 8 PM (±1 hour) intervals on Days 2-6 (AM only on Day 7).
- Physical exam (prior to first dose on Days 2 and 4 only).
- Vital signs (prior to first dose and 2 hours (±30 min) post first dose on All Days).
- Plasma sample for PK analysis (Refer to Table 2).
- 12-lead ECG (prior to first dose on All Days).

- Blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, ***and prolactin***) prior to first dose on Day 4 only.
- C-SSRS (Day 4 only).
- Record concomitant medication use (prior to first dose on All Days).
- Assess and record AEs (prior to first dose on All Days).

## Section 8.3 – Blood Collection

**Original Wording**

For each subject in Part A, up to 16 and 18 blood samples will be collected during the study for PK analysis for Cohorts 1-4 and Cohort 5, respectively. For each subject in Part B, up to 34 blood samples will be collected during the study for PK analysis. In addition, blood will be collected at Screening and Check-in (Day 0), blood will be collected at Day 2 (Part A) or Days 4 and 8 (Part B), blood will be collected at Day 8 and Follow-Up (Part A) for clinical laboratory testing. A separate blood sample will be collected strictly for serum prolactin at Discharge (On Day 3 for Part A or Day 9 for Part B) and Follow-Up (Day 8 for Part A and Day 15 for Cohort 5, Part A only or Day 15 for Part B).

**Revised Wording**

For each subject in Part A, up to 16 and 18 blood samples will be collected during the study for PK analysis for Cohorts 1-4 and Cohort 5, respectively. For each subject in Part B, up to 34 blood samples will be collected during the study for PK analysis. In addition, blood will be collected at Screening and Check-in (Day 0), blood will be collected at Day 2 (Part A) or Days 4 and 8 (Part B), blood will be collected at Day 8 and Follow-Up (Part A) for clinical laboratory testing. A separate blood sample will be collected strictly for serum prolactin at ***Day 4 for Part B,*** Discharge (On Day 3 for Part A or Day 9 for Part B) and Follow-Up (Day 8 for Part A and Day 15 for Cohort 5, Part A only or Day 15 for Part B).

## Section 8.5.12 – Physical Examination

**Original Wording**

A standard physical examination will be performed at Screening, Check-in, Day 2, and Follow-up in Part A and at Screening, Check-in, Days 4 and Day 8, and Follow-up in Part B. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, neurological (with a particular focus on monitoring for manifestations of Extrapyramidal Symptoms), and musculoskeletal system/extremities. Interim physical examinations will be performed at the Investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at Screening and only weight will be measured again at Follow-up for Part A and B.

**Revised Wording**

A standard physical examination will be performed at Screening, Check-in, Day 2, and Follow-up in Part A and at Screening, Check-In, ***Days 2, 4, and 8,*** and Follow-Up in Part B. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, neurological (with a particular focus on monitoring for manifestations of Extrapyramidal Symptoms), and musculoskeletal system/extremities. Interim physical examinations will be performed at the Investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Height and weight will be measured at Screening and only weight will be measured again at Follow-up for Part A and B.

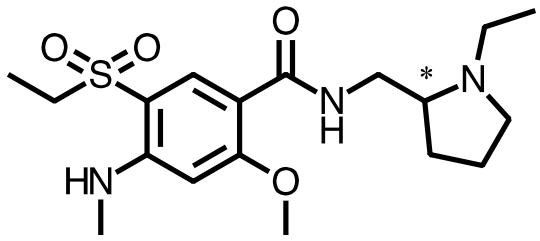
## Section 14 – Appendices
## Section 14.1 – Appendix 1 Clinical Pharmacology Summary Table

**Original Wording**

### Table 1: Clinical Pharmacology Summary Table

**General Information**

**Chemical Structure and Major Physical and Chemical Properties**



**Molecular Weight**: 383.51

| | |
|---|---|
| **Description** | White to off-white powder |
| **pKa** | 9.36 |
| **Partition Coefficient (LogP)** | 1.72 (pH 7) |

**Aqueous Solubility**

| Vehicle | HPLC Area of Sample (225 nm) | Sample Concentration (mg/mL) | Calculated Solution Concentration (mg/mL) | Comment |
|---|---|---|---|---|
| 30% DMF 70% pH 4.7 MES | 2769 | 0.44 | 44.0 | 100:1 dilution, pH of buffer is unchanged |
| pH 4.7 MES Buffer | 3770 | 0.614 | 61.4 | 100:1 dilution, pH of buffer is unchanged |
| pH 5 HCl | 4990 | 0.839 | 83.9 | 100:1 dilution, pH of buffer is unchanged |
| pH 6 phosphate buffer | 3827 | 0.625 | 625 | 1000:1 dilution, pH of buffer is unchanged |
| pH 5 acetate buffer | Not Determined | >800 | >800 | pH of solution becomes 6.5 |

| | |
|---|---|
| Indication (for this IND) | For the Treatment of Schizophrenia. |
| Route and Formulation Type (for this IND) | Oral Capsule. |
| Planned Strengths (for this IND) | LB-102 consists of API in a Size 2 white opaque/white opaque hard gelatin capsule in dosage strengths of 25 mg, 50 mg, 75 mg, and 100 mg. |
| Planned Dose Levels (for this IND) | For Part A (Single Ascending Dose Study) there will be 5 dose levels: 50, 100, 200, 400, 800 mg QD. |

<table>
<tr><td></td><td>For Part B (Multiple Ascending Doses Study) there will be 3 dose levels (BID). These doses will be based on the PK observed in a minimum of two Part A cohorts</td></tr>
<tr><td>Mechanism of Action (for this Indication)</td><td>The proposed mechanism of action for LB-102 is through dopamine D2/D3 receptor antagonism.</td></tr>
<tr><td colspan="2">Dose and AEs</td></tr>
<tr><td>Therapeutic Dose and Exposure (for this IND)</td><td>
<table>
<tr><td colspan="2">Part A</td></tr>
<tr><td>Cohort</td><td>Treatment</td></tr>
<tr><td>1 (n=8)[a]</td><td>LB-102 50 mg (n=6) or Matching Placebo (n=2) x 1 day</td></tr>
<tr><td>2 (n=8)[b]</td><td>LB-102 100 mg (n=6) or Matching Placebo (n=2) x 1 day</td></tr>
<tr><td>3 (n=8)[b]</td><td>LB-102 200 mg (n=6) or Matching Placebo (n=2) x 1 day</td></tr>
<tr><td>4 (n=8)[b]</td><td>LB-102 400 mg (n=6) or Matching Placebo (n=2) x 1 day</td></tr>
<tr><td>5 (n=8)[b]</td><td>LB-102 800 mg (n=6) or Matching Placebo (n=2) x 1 day</td></tr>
<tr><td colspan="2">Part B</td></tr>
<tr><td>6 (n=8)</td><td>LB-102 Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7)</td></tr>
<tr><td>7 (n=8)</td><td>LB-102 2Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7)</td></tr>
<tr><td>8 (n=8)</td><td>LB-102 3Y* mg (n=6) or Matching Placebo (n=2) BID x 6 days and QD x 1 day (Day 7)</td></tr>
</table>
a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.<br>
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).<br>
Y* - Dose will be based on the PK observed in a minimum of two Part A cohorts.<br>
QD = Once daily; BID = Twice daily<br>
<u>Treatment Exposure:</u><br>
Part A: 1 day<br>
Part B: 7 days</td></tr>
<tr><td>Maximum Tolerated Dose</td><td><u>Rats</u><br>• In the 14-day repeat dose phase study, the maximum tolerated dose was determined to be 200 mg/kg/day<br><u>Dogs</u><br>• In the single-dose phase of the dog range-finding study, the maximum tolerated dose was determined to be 25 mg/kg/day<br>• In the 14-day repeat-dose phase study, the maximum tolerated dose was determined to be 5 mg/kg/day</td></tr>
<tr><td>Principal Adverse Events</td><td>Prolactin elevation (≥ 100 ng/mL)</td></tr>
<tr><td colspan="2">PK Features</td></tr>
<tr><td rowspan="2">Dose/Exposure Range Tested in Clinic (Data from this IND and/or Elsewhere)</td><td>Single Dose</td><td>50 mg, 10 mg, 100 mg, 200 mg</td></tr>
<tr><td>Multiple Dose</td><td>N/A</td></tr>
</table>

| | | |
|---|---|---|
| Range of Linear PK | At least to 200 mg (highest dose examined to date) | |
| Accumulation at Steady State | Repeat dose PK model suggests 40% of Cmax with b.i.d. dosing | |
| Metabolites | LB-101 approximately 2.5% | |
| Absorption | Absolute/Relative Bioavailability | N/A |
| | Mean Tmax | 50 mg – 3.000 h<br>10 mg – 3.000 h<br>100 mg – 2.833 h<br>200 mg – 2.083 h |
| Distribution | Vd/F or Vd | N/A |
| | % bound in plasma | N/A |
| | Blood / plasma partition ratio | N/A |
| Elimination | Route | Oral (PO) |
| | Mean Terminal t½ | 50 mg – 12.311 h<br>10 mg – 13.675 h<br>100 mg – 14.656 h<br>200 mg – 12.835 h |
| | Mean CL/F or CL | 50 mg – 31.624 L/h<br>10 mg – 42.323 L/h<br>100 mg – 36.346 L/h<br>200 mg – 28.901 L/h |
| Metabolism | • by CYP450 ☐ Yes ☐ No ☒ NA, if yes, specify<br>• by Phase 2 enzymes ☐ Yes ☐ No ☒ NA<br>• by other enzyme systems ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits CYP450 ☒ Yes ☐ No ☐ NA, if yes, specify and provide $K_i$ and/or$IC_{50}$. A Cytochrome P450 Inhibition Assay demonstrated that LB-102 slightly inhibits CYP2C8 ($IC_{50}$ = 75.5 μM).<br>• inhibits Phase II enzymes ☐ Yes ☐ No ☒ NA, if yes specify and provide $K_i$ and/or $IC_{50}$.<br>• induces CYP450 ☐ Yes ☐ No ☒ NA, if yes specify | |
| Transporters | by major transporters ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits major transporters ☐ Yes ☐ No ☒ NA, if yes, specify and provide Ki and/or IC50.<br>• induces major transporters ☐ Yes ☐ No ☒ NA, if yes specify | |
| Intrinsic Factors | Age | N/A |
| | | N/A |
| | Sex | N/A |
| | Race | N/A |
| | Hepatic Impairment | N/A |
| | Renal Impairment | N/A |

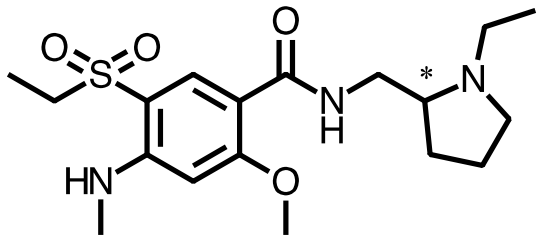
| | | |
|---|---|---|
| | Poor Metabolizers | N/A |
| Extrinsic Factors | Drug interactions | N/A |
| | Food Effects | N/A |
| | Alcohol Effects<br>(Oral MR formulation only) | N/A |
| **PD Features** | | |
| PD Studies: e.g.,<br>QT Effect<br>Driving Test<br>Receptor Occupancy<br>Sleeping Test<br>Other Safety Evaluation | Part A (Single Ascending Dose)<br>Cohort 1 - 50 mg LB-102:<br>• Three (3) mild, Grade 1 AEs (elevated prolactin, ≥100 ng/mL) that were experienced by 3 subjects. All 3 prolactin elevations were asymptomatic. The 3 AEs were considered definitely related to LB-102 in Cohort 1. All 3 AEs resolved by Day 8 (Follow-Up Visit).<br>Cohort 2 – 10 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experience by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 2. The AE resolved by Day 8.<br>Cohort 3 – 100 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experienced by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 3. The AE resolved by Day 8.<br>Cohort 4 – 200 mg:<br>• One (1) mild, Grade 1 AE (QTcF prolongation, 2 hours post-dose on Day 1) was experienced by 1 subject. The AE was considered definitely related to LB-102 in Cohort 4. The AE resolved by 3 hours post-dose on Day 1.<br>• One (1) moderate, Grade 2 AE (acute dystonic reaction). The acute dystonic reaction was definitely related to the study drug in Cohort 4. The AE resolved on the same day it was experienced (Day 1). | |
| E-R Studies: e.g.:<br>Important E-R Relationships | N/A | |
| **Other Studies** | | |
| e.g., Genotype | N/A | |

**Revised Wording**

## Table 1: Clinical Pharmacology Summary Table

**General Information**

**Chemical Structure and Major Physical and Chemical Properties**



**Molecular Weight**: 383.51

| | |
|---|---|
| **Description** | White to off-white powder |
| **pKa** | 9.36 |
| **Partition Coefficient (LogP)** | 1.72 (pH 7) |

**Aqueous Solubility**

| Vehicle | HPLC Area of Sample (225 nm) | Sample Concentration (mg/mL) | Calculated Solution Concentration (mg/mL) | Comment |
|---|---|---|---|---|
| 30% DMF 70% pH 4.7 MES | 2769 | 0.44 | 44.0 | 100:1 dilution, pH of buffer is unchanged |
| pH 4.7 MES Buffer | 3770 | 0.614 | 61.4 | 100:1 dilution, pH of buffer is unchanged |
| pH 5 HCl | 4990 | 0.839 | 83.9 | 100:1 dilution, pH of buffer is unchanged |
| pH 6 phosphate buffer | 3827 | 0.625 | 625 | 1000:1 dilution, pH of buffer is unchanged |
| pH 5 acetate buffer | Not Determined | >800 | >800 | pH of solution becomes 6.5 |

| | |
|---|---|
| Indication (for this IND) | For the Treatment of Schizophrenia. |
| Route and Formulation Type (for this IND) | Oral Capsule. |
| Planned Strengths (for this IND) | LB-102 consists of API in a Size 2 white opaque/white opaque hard gelatin capsule in dosage strengths of 25 mg***, 50 mg, 75 mg,*** and 100 mg. |
| Planned Dose Levels (for this IND) | ***For Part A (Single Ascending Dose Study) there were 5 dose levels: 50, 10, 100, 200, and 150 mg QD.***<br>***For Part B (Multiple Ascending Doses Study) there will be 3 dose levels (BID), starting with 50 mg (100 mg/day). The remaining doses will be determined by the*** |

<table>
<tr><td></td><td>SRC depending on the safety profile and clinical observations of the previous Cohort.</td></tr>
<tr><td>Mechanism of Action (for this Indication)</td><td>The proposed mechanism of action for LB-102 is through dopamine D2/D3 receptor antagonism.</td></tr>
<tr><td colspan="2">Dose and AEs</td></tr>
<tr><td>Therapeutic Dose and Exposure (for this IND)</td><td>
<table>
<tr><td colspan="2">Part A</td></tr>
<tr><td>Cohort</td><td>Treatment</td></tr>
<tr><td>1 (n=8)[a]</td><td>LB-102 50 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>2 (n=8)[b]</td><td>LB-102 10 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>3 (n=8)[b]</td><td>LB-102 100 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>4 (n=8)[b]</td><td>LB-102 200 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td>5 (n=8)[b]</td><td>LB-102 150 mg (n=6) or Matching Placebo (n=2) QD x 1 day</td></tr>
<tr><td colspan="2">Part B</td></tr>
<tr><td>6 (n=8)</td><td>LB-102 (n=6) 50 mg BID (100 mg/day) x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
<tr><td>7 (n=8)</td><td>LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>Or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
<tr><td>8 (n=8)</td><td>LB-102 (n=6) Y* mg BID x 6 days (Days 1-6) and QD x 1 day (Day 7)<br>Or<br>Matching Placebo (n=2) BID x 6 days (Days 1-6) and QD x 1 day (Day 7)</td></tr>
</table>
a – In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects.<br>
b – For Cohorts 2-5, the doses may be reduced based on the PK results of Cohort 1 (Refer to Section 5.1).<br>
Y* - Dose will be determined by the SRC depending on the safety profile and clinical observations of the previous Cohort.<br>
QD = Once daily; BID = Twice daily<br>
<u>Treatment Exposure:</u><br>
Part A: 1 day<br>
Part B: 7 days</td></tr>
<tr><td>Maximum Tolerated Dose</td><td><u>Rats</u><br>
• In the 14-day repeat dose phase study, the maximum tolerated dose was determined to be 200 mg/kg/day<br>
<u>Dogs</u><br>
• In the single-dose phase of the dog range-finding study, the maximum tolerated dose was determined to be 25 mg/kg/day<br>
• In the 14-day repeat-dose phase study, the maximum tolerated dose was determined to be 5 mg/kg/day</td></tr>
</table>

| | | |
|---|---|---|
| Principal Adverse Events | Prolactin elevation (≥ 100 ng/mL) | |
| **PK Features** | | |
| Dose/Exposure Range Tested in Clinic (Data from this IND and/or Elsewhere) | Single Dose | 50 mg, 10 mg, 100 mg, 200 mg, ***150 mg*** |
| | Multiple Dose | N/A |
| Range of Linear PK | At least to 200 mg (highest dose examined to date) | |
| Accumulation at Steady State | Repeat dose PK model suggests 40% of Cmax with b.i.d. dosing | |
| Metabolites | LB-101 approximately 2.5% | |
| Absorption | Absolute/Relative Bioavailability | N/A |
| | Mean Tmax | 50 mg – 3.000 h<br>10 mg – 3.000 h<br>100 mg – 2.833 h<br>200 mg – 2.083 h<br>***150 mg – 3.167 h*** |
| Distribution | Vd/F or Vd | N/A |
| | % bound in plasma | N/A |
| | Blood / plasma partition ratio | N/A |
| Elimination | Route | Oral (PO) |
| | Mean Terminal t½ | 50 mg – 12.311 h<br>10 mg – 13.675 h<br>100 mg – 14.656 h<br>200 mg – 12.835 h<br>***150 mg – 12.620 h*** |
| | Mean CL/F or CL | 50 mg – 31.624 L/h<br>10 mg – 42.323 L/h<br>100 mg – 36.346 L/h<br>200 mg – 28.901 L/h<br>***150 mg – 32.964 L/h*** |
| Metabolism | • by CYP450 ☐ Yes ☐ No ☒ NA, if yes, specify<br>• by Phase 2 enzymes ☐ Yes ☐ No ☒ NA<br>• by other enzyme systems ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits CYP450 ☒ Yes ☐ No ☐ NA, if yes, specify and provide $K_i$ and/or$IC_{50}$. A Cytochrome P450 Inhibition Assay demonstrated that LB-102 slightly inhibits CYP2C8 ($IC_{50}$ = 75.5 μM).<br>• inhibits Phase II enzymes ☐ Yes ☐ No ☒ NA, if yes specify and provide $K_i$ and/or $IC_{50}$.<br>• induces CYP450 ☐ Yes ☐ No ☒ NA, if yes specify | |

| | | |
|---|---|---|
| Transporters | by major transporters ☐ Yes ☐ No ☒ NA, if yes, specify<br>• inhibits major transporters ☐ Yes ☐ No ☒ NA, if yes, specify and provide Ki and/or IC50.<br>• induces major transporters ☐ Yes ☐ No ☒ NA, if yes specify | |
| Intrinsic Factors | Age | N/A |
| | | N/A |
| | Sex | N/A |
| | Race | N/A |
| | Hepatic Impairment | N/A |
| | Renal Impairment | N/A |
| | Poor Metabolizers | N/A |
| Extrinsic Factors | Drug interactions | N/A |
| | Food Effects | N/A |
| | Alcohol Effects (Oral MR formulation only) | N/A |
| **PD Features** | | |
| PD Studies: e.g.,<br>QT Effect<br>Driving Test<br>Receptor Occupancy<br>Sleeping Test<br>Other Safety Evaluation | Part A (Single Ascending Dose)<br>Cohort 1 - 50 mg LB-102:<br>• Three (3) mild, Grade 1 AEs (elevated prolactin, ≥100 ng/mL) that were experienced by 3 subjects. All 3 prolactin elevations were asymptomatic. The 3 AEs were considered definitely related to LB-102 in Cohort 1. All 3 AEs resolved by Day 8 (Follow-Up Visit).<br>Cohort 2 – 10 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experience by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 2. The AE resolved by Day 8.<br>Cohort 3 – 100 mg:<br>• One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experienced by 1 subject. The prolactin elevation was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 3. The AE resolved by Day 8.<br>Cohort 4 – 200 mg:<br>• One (1) mild, Grade 1 AE (QTcF prolongation ***of > 450 msec was noted***, 2 hours post-dose on Day 1) was experienced by 1 subject. The AE was considered definitely related to LB-102 in Cohort 4. The AE resolved by 3 hours post-dose on Day 1. ***The overall maximum QTcF prolongation for the subject was 43 msec from baseline.***<br>• One (1) moderate, Grade 2 AE (acute dystonic reaction). The acute dystonic reaction was definitely related to the study drug in Cohort 4. The AE resolved on the same day it was experienced (Day 1) ***with no recurrence. Subject was treated with concomitant medication for the symptoms.*** | |

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| | ***Cohort 5 – 150 mg:***<br>• ***One (1) mild, Grade 1 AE (elevated prolactin, > 100 ng/mL) was experienced by 1 subject. The subject was asymptomatic. The AE was considered definitely related to LB-102 in Cohort 5. The AE resolved by Day 15 Follow-Up Visit.*** |
| E-R Studies: e.g.: Important E-R Relationships | N/A |
| **Other Studies** | |
| e.g., Genotype | N/A |