To: Washington University IRB

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: December 2, 2020

RE: Clarification Memo #2

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

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The intent of this clarification memo is to provide clarification for the LB-102-002 Investigator's Brochure (17 November 2020, Edition 2). All items listed below have been incorporated into the IB and have been submitted to FDA.

Section 1 – Summary

Original Wording

LB Pharmaceuticals is proposing a Phase 1 study for LB-102. The first study will be a Phase 1, placebo-controlled, double-blind study to evaluate the safety, tolerability, and pharmacokinetics (PK) of single (SAD) and multiple (MAD) ascending oral doses of LB-102 in healthy adult subjects. For the SAD study, subjects (n=40) will be divided into 5 sequential groups of 8 healthy subjects for LB-102 (n=6) or placebo (n=2) treatment. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 (50 mg/day). Blood samples will be collected at various times on Days 1-3 for PK analysis. Safety assessments including 12-lead ECG, clinical labs (hematology, chemistry, urinalysis), and vital signs will be recorded at multiple timepoints throughout the trial. Subjects will remain in the clinic from Check-in to Discharge on Day 3 and then return for a Follow-up Visit on Day 8. Dose escalation to 100, 200, 400, and 800 mg/day LB-102 will occur after Safety Review Committee (SRC) approval. Subsequent groups will follow the same study procedures for each dose escalation.

For the MAD study, subjects (n=24) will be divided into 3 sequential groups of 8 healthy subjects for LB-102 (n=6) or placebo (n=2) treatment. Subjects will receive 2 oral doses of placebo or LB 102, 12 hours apart, on Days 1-6 and one dose on Day 7 for a total of 13 oral doses. The doses for this study are dependent on the results of the SAD study. Blood samples will be collected at various times on Days 1-9 for PK analysis. Safety assessments including 12-lead ECG, clinical labs, and vital signs will be recorded at multiple timepoints throughout the trial. Subjects will remain in the clinic from Check-in to Discharge on Day 9 and then return for a Follow-up Visit on Day 14. Subsequent groups will be administered increasing doses of LB-102 that are dependent on the results of the SAD study, following the same study procedures.

Revised Wording

A Phase 1 randomized, placebo-controlled, double-blinded study to evaluate the safety, tolerability, and pharmacokinetics (PK) of LB-102 in oral administration in healthy adults (LB 102 001) has been

completed. The investigation was conducted in two parts: Part A, a Single Ascending Dose (SAD) study and Part B, a Multiple Ascending Dose (MAD) study.

In Part A (SAD), 5 sequential cohorts (N = 8; 40 total subjects) received LB 102 (N = 6) or placebo (N = 2). In each cohort, single doses of LB 102 or placebo were administered (Day 1) after a 12-hour fast. Blood samples were collected on Days 1 3. Safety assessments were recorded at multiple timepoints and included, but were not limited to, 12 lead ECG, clinical labs (hematology, chemistry, urinalysis), and vital signs. Subjects remained in the clinic until Day 3 and Follow-up Visits were made on Day 8.

In Part B (MAD), 3 sequential cohorts (N = 8; 24 total subjects) received LB 102 (N = 6) or placebo (N = 2) treatment. Two (2) doses were administered 12 hours apart on Days 1 6 and one was administered on Day 7. Blood samples were collected on Days 1 9. Safety assessments followed similar procedures as in Part A. Subjects remained in the clinic from Check-in until Day 9 and Follow-up Visits were made on Day 14.

Plasma concentrations of LB-102 in Part A (SAD) showed the rapid absorption and biphasic disposition of the study drug. Exposure increased in a slightly greater than dose-proportional manner and clearance decreased as dose increased. The metabolite amisulpride was formed quickly after a single dose and its plasma concentration declined with a similar pattern to that of LB 102. Amisulpride was found at ~ 2.5% of LB 102 abundance and was not detected at the lowest dose of LB-102, 10 mg.

Analyses in Part B (MAD) demonstrated that trough concentrations of LB 102 and amisulpride plateaued before the Day 4 morning dose. LB 102 accumulated moderately after multiple doses, amisulpride accumulated more than LB 102, and exposure to LB 102 increased in a dose proportional manner. Apparent clearance of LB 102 at steady state was similar as dose increased.

LB-102 was well-tolerated; all Treatment-Emergent Adverse Events (TEAEs) were either mild (37) or moderate (6). All TEAEs were resolved with no further action or concomitant medications. The TEAEs included elevated serum prolactin, moderate dystonia, and mild ECG QT interval corrected for heart rate with Fridericia's formula (QTcF) prolongation. Twenty-nine (29) of the 43 adverse events were considered possibly, probably, or definitely related to the treatments.

Section 5 – Effects in Humans

Section 5.1 – **Introduction**

Original Wording

(No text)

Revised Wording

LB-102 is a novel benzamide under development for the treatment of schizophrenia. 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.

LB-102-001, a First-In-Human (FIH) Phase 1, randomized, double-blinded, placebo-controlled study (N = 64) of LB 102, designed to evaluate its safety, tolerability, and pharmacokinetics (PK) in oral administration, has been completed. Subjects in this study were healthy, consenting adults of both sexes. History of psychiatric/ neurological disease/ condition and/or a history or current evidence of suicidal behavior were causes for exclusion from the trial.

The investigation consisted of two parts: Part A, Single Ascending Dose (SAD), and Part B, Multiple Ascending Dose (MAD), studies. The objectives were evaluated in 5 cohorts of 8 healthy subjects (N = 6 assigned to LB-102 and N = 2 to placebo treatments) in Part A and 3 cohorts (N = 8 with the same assignments) in Part B. LB 102 administrations ranged from 10 mg to 200 mg QD in Part A and from 50 mg to 100 mg BID in Part B. The maximum total daily doses did not exceed 200 mg in either part of LB 102 001. For Part A (SAD), 1 dose of LB 102 or placebo was administered on Day 1 and was followed by discharge on Day 3. For Part B (MAD), 13 doses of LB 102 or placebo were administered on Days 1-7 (twice daily on Days 1-6 and once daily on Day 7). Subjects were discharged on Day 9 in Part B. Follow-up Visits were made on Day 8 (Part A) or Day 15 (Part B) for safety review. Subjects in Cohort 5 (SAD) returned for an additional Follow-up Visit.

For the assessment of PK parameters, individual plasma concentrations of LB 102 and its metabolite, amisulpride, were measured and non-compartmental and/or compartmental PK methods of analysis were utilized, as appropriate. PK parameters and results were summarized by cohort using descriptive statistics. Dose proportionality was assessed using a linear regression, or by other appropriate methods.

LB-102 was well-tolerated in this FIH study; all Treatment-Emergent Adverse Events (TEAEs) were rated as either mild or moderate. The most notable safety results were dystonia and elevated prolactin levels. QT interval corrected for heart rate with Fridericia's formula (QTcF) prolongation was recorded, but only at high doses.

Section 5.2 – Pharmacokinetics and Product Metabolism in Humans

<u>Original Wording</u>

Not studied.

<u>Revised Wording</u>

Preliminary studies in rodents showed that LB-102 is decomposed to a molecule with the same molecular weight as amisulpride. In mouse and rat studies, the total benzamide plasma concentrations (total concentration of LB 102 and amisulpride) were equivalent to the concentrations measured after dosing with amisulpride. These data, and the fact that amisulpride is not further

metabolized in rodents, support the in vivo metabolism of LB 102 to amisulpride in rodents. Accordingly, concentrations of LB 102 and amisulpride were measured to assess pharmacokinetics during this study.

For Part A of LB-102-001, the PK parameters assessed included AUC0-t, AUC0-24, AUC0-inf, AUC%/extrap, CL/F, Cmax, Tmax, λz, and t1/2. For Part B, the PK assessments included AUC0-12, D1, AUC0-24, D1, AUC0-inf, D1, AUC%/extrap, D1, Cmax, D1, Tmax, D1, λz, D1, t1/2, D1, AUC0-12, D7, AUC0-inf, D7, AUCextrap, D7, Cmax, D7, Tmax, D7, λz, D7, t½, D7, the accumulation ratio based on Cmax after the first dose and last dose (RCmax), accumulation ratio based on AUC after the first and last dose (RAUC), linearity index (LI), apparent clearance at steady state (CLss/F), and dosing interval (Tau). Dose proportionality of both LB 102 and the metabolite amisulpride were assessed for both Parts A and B, after a single dose.

PK analyses of Part A demonstrated that LB 102 is rapidly absorbed and declines in an approximately biphasic manner. Peak plasma concentrations were well maintained over 12 hours, the dosing interval tested in Part B. After multiple administrations of the test dug, slight to moderate accumulations of LB-102 were found. The trough concentrations of LB 102 and amisulpride were found to be stable with little relative change, or plateaued, in Part B (MAD) before the morning dose on Day 4, after 3 days of BID administrations.

Amisulpride, a minor metabolite of LB-102, was detectable in all subjects receiving at least 50 mg QD. Although the amisulpride cleared quickly after a single dose of LB 102, repeated doses resulted in its accumulation, and amisulpride had a higher accumulation (RCmax and RAUC) than LB 102 across dose levels. Apparent clearance at steady state to LB-102 appeared to be similar as dose increased.

In this study amisulpride was found to been present at ~ 2.5% of LB 102 concentration. Amisulpride thus represents a minor active metabolite (defined as either less than 10% parent concentration or less than 10% of total pharmacological activity).

Section 5.2.1 – Pharmacokinetics

<u>Original Wording</u>

Not studied.

<u>Revised Wording</u>

Analyses of the plasma concentrations of LB 102 in Part A (SAD) demonstrated that the drug was rapidly absorbed (Figure 12) and concentrations declined from peak in an approximately biphasic pattern. Mean peak plasma concentrations were obtained within 3.01 hours (median Tmax was 1.75 to 3.01 hours).

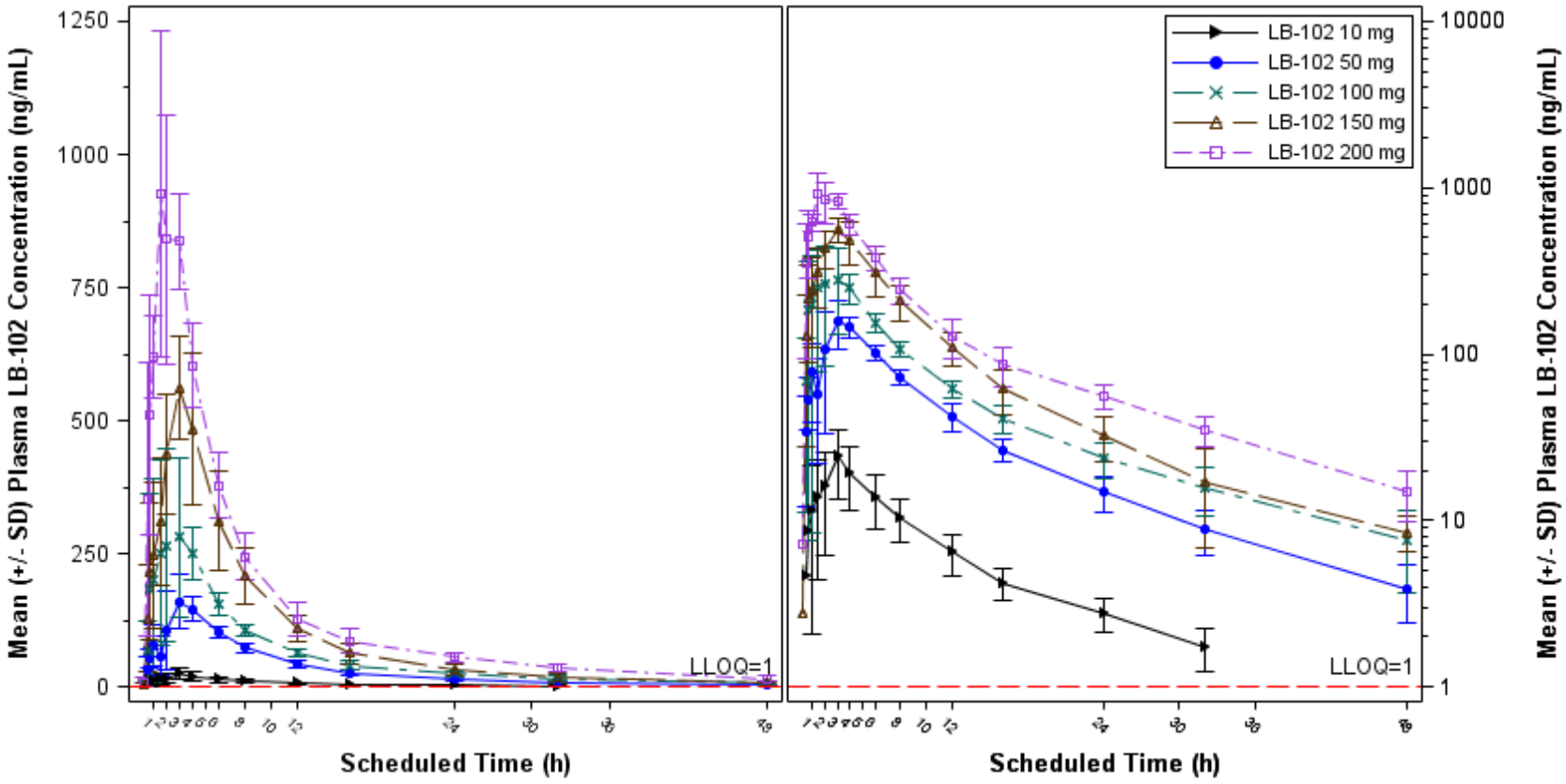
Mean t½ in Part A was 11.9 to 14.1 hours (measured by Cmax, AUC0-t, and AUC0-inf) and, at higher doses, mean t1/2 was found to increase in a slightly greater than dose-proportional manner. Dose

proportionality analyses for LB 102 plasma concentrations also suggested slightly greater than proportional increases at higher doses. Mean Cmax was 24.1 ng/mL at the lowest dose (10 mg) and 975.7 ng/mL at the highest dose (200 mg). Mean AUC0-t was 221.9 h•ng/mL at the lowest dose and 6709.8 h•ng/mL at the highest dose, while mean AUC0 inf was 252.6 h•ng/mL at the lowest dose and 7002.1 h•ng/mL at the highest dose. Apparent clearance (CL/F) results suggested that as dose increases, clearance decreases (42.4 L/h to 28.9 L/h). Some variability was found in the PK values, with geometric mean (GM) CV% ranging from 11.7% to 45.6% for Cmax and AUC values.

In Part A, the metabolite amisulpride was quickly formed after a dose of LB 102 (median Tmax = 2 to 3.5 hours). Plasma concentrations of amisulpride generally declined with an approximate biphasic disposition, consistent with LB-102, and with a mean t½ slightly shorter than LB-102, ranging from approximately 8.9 to 14.6 hours. Systemic exposures to amisulpride generally increased with increasing dose; but PK analyses of amisulpride were variable, with GM CV% ranging, for example, from 12.8% to 144.3% for Cmax and AUC0-t values, respectively. As a function of Cmax, the percentage of amisulpride, as compared to LB-102, was ~ 2.5% across the doses.

For Part B (MAD), deviations in planned sampling occurred in 2 of the cohorts. In Cohort 8 (LB 102 75 mg BID), all subjects except number 01S2092, who ended treatment on Day 3, had dosing terminated on Day 7. Extensive PK sampling was performed on Day 6 rather than Day 7 for this cohort to obtain sufficient data for the second dose of BID. In Cohort 7 (LB 102 100 mg BID), 5 of the 6 subjects had 5 total doses (ended treatment on Day 3). The remaining subject had 3 total doses (ended treatment on Day 2). There were no extensive post-treatment PK samples collected in Cohort 7.

Figure 12: Plot of Mean (±SD) Plasma LB-102 Concentrations versus Time by Treatment on Linear and Semi-Log Scale: Pharmacokinetic Population, Part A (SAD)



Note: Lower limit of quantitation for LB-102 = 1 ng/mL.
h = hours; SD = standard deviation.
Source: PK Report, Post-text Figure 14.2.1.1

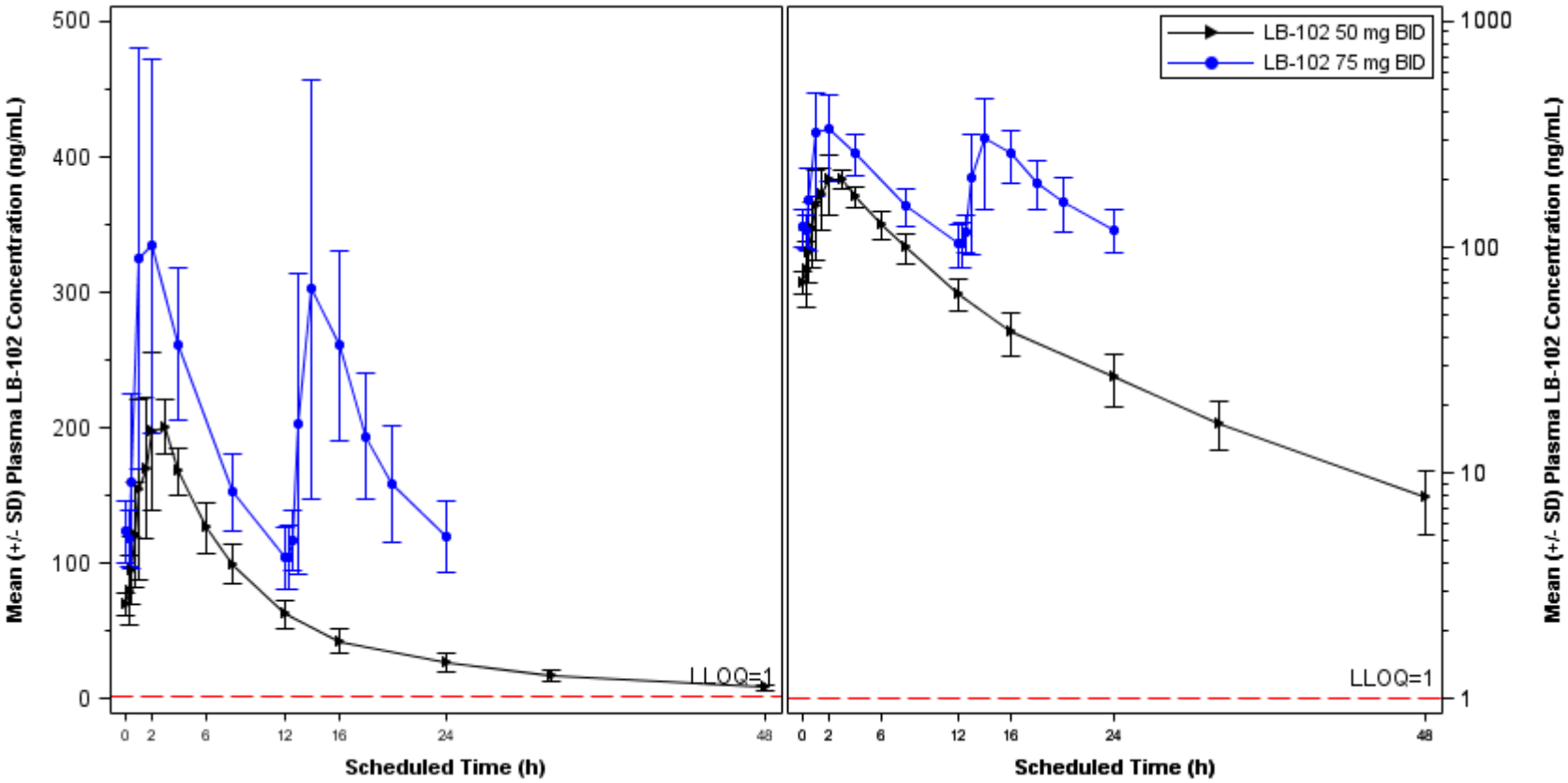
In Part B (MAD), peak plasma concentrations of LB 102 were attained rapidly (Figure 13 and Figure 14) following the first dose of the drug. Concentrations were maintained over the dosing interval.

Plasma trough concentrations of LB-102 (Figure 14) and amisulpride plateaued in Part B prior to the Day 4 morning dose (50 mg BID and 75 mg BID). After multiple doses, there was slight to moderate accumulation of LB-102 across dose levels. There was a transient decrease in concentrations of LB 102 and amisulpride before the Day 6 evening dose for subjects taking 75 mg BID.

In Part B dose-proportionality analyses, results obtained using Cmax, D1 (after a single dose) suggested that exposure to LB 102 increased in a slightly greater than proportional manner with increasing dosage. However, additional analyses suggested proportional increases based on AUC0 12, D1 and AUC0-inf, D1. Analyses based on Day 7 data after multiple doses of LB 102 also suggested proportional increases with increased dose. Apparent clearance of LB 102 at steady state in Part B appeared to be similar as dose increased.

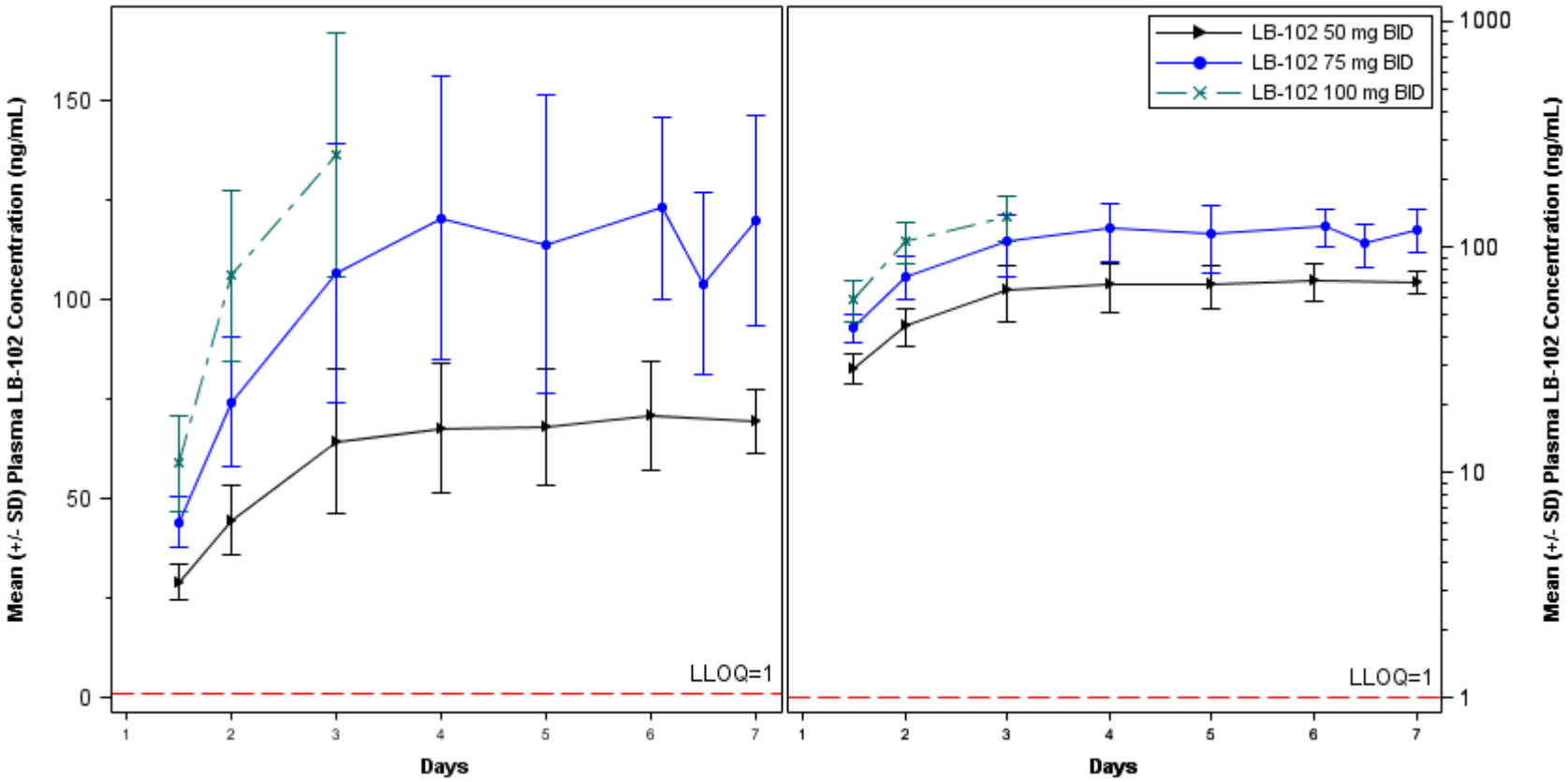
PK analyses in Part B showed that amisulpride concentration increased with increasing dose of LB 102. Mean RCmax values (accumulation ratio based on Cmax after the first dose and last dose) for amisulpride ranged from 1.3 to 2.0 compared to 1.1 to 1.8 for LB-102. In a similar pattern, RAUC values for amisulpride ranged from 1.8 to 2.2 as compared to RAUC values for LB-102 which ranged from 1.5 to 1.9.

Figure 13: Plot of Mean (±SD) Plasma LB-102 Concentrations versus Time after Multiple Dose by Treatment on Linear and Semi-Log Scale: Pharmacokinetic Population, Part B (MAD)



Note: Lower limit of quantitation for LB-102 = 1 ng/mL.
For Cohort 6 (LB-102 50 mg BID), the PK concentrations of the QD dosing on Day 7 were plotted. For Cohort 8 (LB-102 75 mg BID), the PK concentrations of both doses on Day 6 were plotted.
h = hours; SD = standard deviation.
Source: PK Report, Post-text Figure 14.2.1.4

Figure 14: Plot of Mean (±SD) Plasma Trough LB-102 Concentrations versus Visit Day by Treatment on Linear and Semi-log Scale: Pharmacokinetic Population, Part B (MAD)



Note: Lower limit of quantitation for LB-102 = 1 ng/mL.
All pre-dose concentrations except that for the first dose on Day 1 were plotted as trough concentration.
h = hours; SD = standard deviation.
Source: PK Report, Post-text Figure 14.2.1.7

Section 5.2.3 – Population Subgroup

Original Wording

Not studied.

Revised Wording

There were no population subgroups in LB-102-001. The populations studied in Parts A (SAD) and B (MAD) of LB 102 001 were healthy, consenting males and females with no significant concurrent medical findings. Subjects had no history/ presence of psychiatric or neurological disease/ condition, no history/ current evidence of suicidal behavior, and were willing to complete study assessments which included the Columbia Suicide Severity Rating Scale (C SSRS).

Section 5.3 – Safety and Efficacy

Original Wording

Not studied

Revised Wording

No analyses of the efficacy of LB-102 in the treatment of schizophrenia have been assessed clinically at this time.

Vital signs, PK evaluations, and safety assessments were analyzed for 48 healthy subjects receiving LB 102 and 16 receiving placebo as part of the LB-102-001 study.

No deaths or other Serious Adverse Events (SAEs) were reported in the LB-102-001 study. Forty three (43) Treatment-Emergent Adverse Events (TEAEs) were reported and were either mild (37) or moderate (6) in severity. Vital signs, physical examination, and chemistry laboratory results were largely unchanged during the study. C SSRS did not change during study treatments.

Section 5.3.2 – Safety Results in Clinical Studies

Original Wording

Not studied.

Revised Wording

LB-102 was generally well-tolerated in LB-102-001. Vital signs, physical examinations, and chemistry laboratory results deviated little from baseline, with the exception of elevations in serum prolactin

concentrations. Twenty-eight (28) of 64 subjects, experienced one, or more, TEAEs. All TEAEs were mild (37) or moderate (6) in severity and 67% were considered possibly, probably, or definitely related to treatment. No SAEs were recorded in LB-102-001.

All subjects receiving LB-102 experienced elevated prolactin levels. Prolactinemia is commonly associated with dopamine antagonists, such as LB 102, and is well documented in the literature (Rajkumar, 2014). Clinically significant levels of prolactin (≥100 µg/L) were recorded in 11 cases (50 mg QD, N = 3; 10 mg QD, N = 1; 100 mg QD, N = 1; 150 mg QD, N = 1; 50 mg BID, N = 2; 100 mg BID, N = 1; 75 mg BID, N = 2) and qualified as TEAEs.

Four (4) subjects reported treatment-related dystonia (200 mg QD, N = 1; 100 mg BID, N = 2; 75 mg BID, N = 1). Three (3) of the cases were moderate and resolved without action. One (1) case was acute (200 mg LB 102 QD) and was resolved with concomitant medication. Standard protocol stopping rules were reached. However, given that the dystonic events were associated with higher doses of LB 102, the dose for Cohort 8 was reduced to 75 mg LB 102 BID by the Safety Review Committee (SRC).

Five (5) subjects (200 mg QD, Cohort 4) displayed prolonged ECG QTcF intervals from pre dose values (20 46 msec). An additional subject in the same cohort, experienced a more notable, but mild, QTcF prolongation (>450 msec) at 2 hours post dose. None of these events qualified as criteria for stopping based on QT prolongation rules. However, an overall concern for QTcF prolongation led the SRC to reduce the Cohort 5 dose from 200 mg to 150 mg LB 102 QD.

Other TEAEs probably or possibly related to study drug included 4 cases of nausea and 1 case of vomiting. Additionally, urticaria, gastroesophageal disease, insomnia, dizziness, and somnolence were recorded.

Section 7 – Summary Of Data And Guidance For The Investigator

<u>Original Wording</u>

The following adverse effects have been commonly observed in ≥5% of patients treated with amisulpride in controlled clinical trials (n=921): EPS disorders, insomnia, anxiety, agitation, and weight increase (Amisulpride PI, 2019).

Amisulpride is contraindicated for hypersensitivity to the active substance or to any of its excipients (maize starch, lactose monohydrate, methylcellulose 400cP, colloidal silica anhydrous, magnesium stearate), concomitant prolactin-dependent tumors (e.g., pituitary gland prolactinomas or breast cancer), pheochromocytoma, children before the onset of puberty, lactation, combination with levodopa, and combination with the following medication which could induce torsades de pointes: class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide, Class III antiarrhythmic agents such as amiodarone, sotalol, and other medicines such as bepidril, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin. Precautions should be taken when combining amisulpride with medications that can enhance torsades de pointes or could prolong QT interval, CNS depressants, antihypertensive drugs, and dopamine agonists (Amisulpride PI, 2019).

Revised Wording

The following adverse effects have been commonly observed in ≥5% of patients treated with amisulpride in controlled clinical trials (n=921): EPS disorders, insomnia, anxiety, agitation, and weight increase (Amisulpride PI, 2019).

In LB-102-001, the FIH investigation of LB-102 in healthy adults (Phase 1), the study drug was generally well tolerated. Less than half (~ 44%) of the subjects (N = 64 total; N = 48 received LB 102 and 16 received placebo) experienced an AE. The AEs included elevated prolactin in serum of ≥100 µg/L (associated with all doses from 10 mg to 200 mg; 11% of all subjects), moderate dystonia (150 mg and 200 mg; 6% of all subjects), and mild ECG QTcF prolongation (200 mg; 9% of all subjects). While one dystonic reaction did require action in the form of concomitant medication, no other AE required action for resolution. Other events in this study that were probably or possibly related to treatment with LB-102 included nausea (6% of subjects) and vomiting (2% of subjects). Urticaria, gastroesophageal disease, insomnia, dizziness, and somnolence were also recorded.

Amisulpride is contraindicated for hypersensitivity to the active substance or to any of its excipients (maize starch, lactose monohydrate, methylcellulose 400cP, colloidal silica anhydrous, magnesium stearate), concomitant prolactin-dependent tumors (e.g., pituitary gland prolactinomas or breast cancer), pheochromocytoma, children before the onset of puberty, lactation, combination with levodopa, and combination with the following medication which could induce torsades de pointes: class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide, Class III antiarrhythmic agents such as amiodarone, sotalol, and other medicines such as bepidril, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin. Precautions should be taken when combining amisulpride with medications that can enhance torsades de pointes or could prolong QT interval, CNS depressants, antihypertensive drugs, and dopamine agonists (Amisulpride PI, 2019).

Section 8 – Reference Safety Information (RSI)

Original Wording

The RSI provides a list of ADRs considered expected for the purposes of expedited reporting to Regulatory Authorities, i.e., to determine whether certain events would be deemed a Suspected Unexpected Serious Adverse Reaction (SUSAR) should a Serious Adverse Reaction (SAR) occur.

For the purposes of regulatory reporting, there are no events expected, any SAR would therefore be considered as SUSARs.

Revised Wording

The RSI provides a list of ADRs considered expected for the purposes of expedited reporting to Regulatory Authorities, i.e., to determine whether certain events would be deemed a Suspected Unexpected Serious Adverse Reaction (SUSAR) should a Serious Adverse Reaction (SAR) occur.

For the purposes of regulatory reporting, there are no events expected, any SAR would therefore be considered as SUSARs.

In the FIH Phase 1 (LB-102-001) investigation of LB-102 in healthy adults no Serious Adverse Events (SAEs) were recorded, and the study drug was well-tolerated. However, the following AEs should be considered for inclusion in the RSI for LB-102 as expected adverse drug reactions (ADRs): elevated serum prolactin (≥100 µg/L), prolonged QT interval (>450 msec), and dystonic reaction. Given that none of the AEs in LB-102-001 were serious, these events are not classified as SARs or SUSARs and did not require expedited reporting. Escalation in seriousness in these ADRs would still be considered SUSARs.

pharmaceuticals

Zachary Prensky, CEO	Signature	Date
ZACHARY PRENSKY		12/2/20