To: Medpace Clinical Pharmacology Unit

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: April 30, 2020

RE: Clarification Memo #6

LB-102-001: 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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The intent of this protocol clarification memo is to provide clarification for the LB-102-001 protocol (Protocol Version 4, 08 April 2020). All items listed below will be incorporated into the next amendment. The protocol amendment will be sent after it is filed with FDA.

Section 1 – Study Design

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.*

Table 1: Schedule of Events for Part B

<u>Original Wording</u>

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

<u>Original Wording</u>

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.

<u>Revised Wording</u>

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, ***Days 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.

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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.

Zachary Prensky		4/30/2020
Zachary Prensky, CEO	Signature	Date