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To: Medpace Clinical Pharmacology Unit

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: June 19, 2020

RE: Clarification Memo #9

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 5, 18 May 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 - Pharmacokinetics

Original Wording

- *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.*

Revised Wording

- *Part B*
  - ***For Cohorts 6-7***
    - *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.*
  - ***For Cohort 8 only:***
    - ***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 2-5: prior to first dose.***
    - ***Day 6: pre-dose, 15 and 30 minutes (±5 minutes), and 1, 2, 4, 8, 12, 12.25, 12.5, 13, 14, 16, 18, and 20 hours (±15 min) post dose.***
    - ***Day 7: prior to first dose.***

- ***Days 8-9: 24, 32, and 48 hours (±15 min) post Day 7 dose.***
- ***Day 15***

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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 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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Original Wording

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] ***For Cohorts 6-7,*** *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.*

For Cohort 8 only, 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 2-5: prior to first dose, Day 6 prior to the first dose, 15 and 30 minutes (±5 minutes), and 1, 2, 4, 8, 12, 12.25, 12.5, 13, 14, 16, 18, and 20 hours (±15 min) post dose. On Day 7, blood samples for PK will be collected prior to first dose, 24 (Day 8), 32 (Day 8), and 48 (Day 9) hours (±15 min) post Day 7 dose, and Day 15.

[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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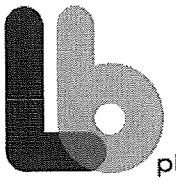
Section 5.1 – Overall Study Design and Plan

Original Wording

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.

Revised Wording

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 ***Cohorts 6-7****, 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.* ***For Cohort 8, 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 2-5, blood samples for PK will be collected prior to the first dose. On Day 6, blood samples for PK will be collected pre-dose, at***



15 and 30 minutes (±5 min), and 1, 2, 4, 8, 12, 12.25, 12.5, 13, 14, 16, 18, and 20 hours (±15 min) post dose. On Day 7, blood samples for PK will be collected prior to first dose, 24 (Day 8), 32 (Day 8), and 48 (Day 9) hours (±15 min) post Day 7 dose, 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 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 7.2.7 – Follow-Up (Visit 4, Day 15)

Original Wording

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.*

Revised Wording

The following procedures will be performed on Day 15:

- *Physical exam and weight measurements.*
- *Vital signs.*
- ***Plasma sample for PK analysis (Cohort 8 only)***
- *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.*

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 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).

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 ***and 37*** *blood samples will be collected during the study for PK analysis* ***for Cohorts 6-7 and 8, respectively****. 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).*

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Andrew Vaino		6/19/20
Andrew Vaino, CSO	Signature	Date