To:

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: November 11, 2020

RE: Clarification Memo #1

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 protocol clarification memo is to provide clarification for the LB-102-002 protocol (11 Nov 2020, v 1.1). All items listed below have been incorporated into the protocol and will be submitted to FDA.

Section 1 – Study Design

Original Wording

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

Cohort	*Treatment*
1 (n=4)	*LB-102 50 mg, single dose*
1 (n=4)	*LB-102 TBD, single dose*
1 (n=4)	*LB-102 TBD, single dose*
1 (n=4)	*LB-102 TBD, single or multiple dose*

Revised Wording

*This is a Phase 1**B**, open label study designed to evaluate the dopamine receptor occupancy in healthy subjects. There will be 4 cohorts consisting of 4 subjects each. Eligible subjects **from Cohort 1** will receive **1 dose** of LB-102 on Day 1. Subjects in the final cohort will be dosed for **4** days BID **(Days 1-4) and 1 day QD (Day 5 AM; i.e. a total of 10 doses)** on an inpatient basis. This will be an open label study. Blood samples for PK and safety assessments will be collected at screening, immediately pre-dose, and during/before/after PET scan. Subjects enrolled in the inpatient cohort will be monitored daily. Follow-up after discharge will consist of a phone call **after subject returns home (Discharge Visit) and during the***

Follow-Up Visit. *This will be an adaptive study and doses in Cohorts 2-4 will be determined after PET data from Cohort 1 are obtained.*

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

Section 1 – Duration of Treatment

Original Wording

1 day.

Revised Wording

1 ***or 5 days.***

Section 1 – Endpoint

Original Wording

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

Revised Wording

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

Section 1 – Safety

<u>Original Wording</u>

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

1. *AEs*
2. *Hematology, chemistry, urinalysis at:*
    a. *At screening, pre-dose, and at scan.*
3. *Prolactin at:*
    a. *screening, pre-dose, and at scan*
4. *ECG*
    a. *screening and at scan 4 (24 h post-dose)*
5. *Physical examination*
    a. *screening, pre-dose, and at scan*
6. *Vital signs (heart rate, respiratory rate, temperature, and blood pressure)*
    a. *screening, pre=dose, and at scan*

<u>Revised Wording</u>

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

1. *AEs*
    a. ***Cohorts 1-3: Days 0-2***
    b. ***Cohort 4: Days 0-6***
2. *Hematology, chemistry, urinalysis at:*
    a. ***Cohorts 1-3: Screening, Day 0, and Day 2****
    b. ***Cohort 4: Screening, Day 2, and Day 6****
        i. **** - Only blood will be collected for laboratory tests.***
3. *Prolactin at:*
    a. ***Cohorts 1-3: Screening and Day 2***
    b. ***Cohort 4: Screening and Day 6***
4. *ECG at*
    a. ***Cohorts 1-3: Screening, Day 0 (prior to PET scan, ±15 min), and Day 2 (24 h post-dose, ±15 min)***
    b. ***Cohort 4: Screening, Day 0 (prior to PET scan, ±15 min), and Day 6 (24 h post-dose, ±15 min)***
5. *Physical examination:*
    a. ***Cohorts 1-3: Screening and Day 0****

   b. ***Cohort 4: Screening and Days 0****
      i. **** - If physical examination was not performed at Screening then physical examination completed at Day 0***
6. *Vital signs (heart rate, respiratory rate, temperature, and blood pressure):*
   a. ***Cohorts 1-3: Screening, Day 0 (at the time of the PET scan, ±15 min), Days 1-2 (Day 1 at pre-dose, and at the time of each PET scan [±15 min, Visits 3 and 4])***
   b. ***Cohort 4: Screening, Day 0 (at the time of the PET scan, ±15 min), and Days 1-6 (Day 1 at pre-dose, and at the time of each PET scan [±15 min, Visits 3 and 4])***
7. ***C-SSRS:***
   a. ***Cohorts 1-3: Screening and Day 2***
   b. ***Cohort 4: Screening and Day 6***

Original Wording

Table 1: Schedule of Events, Single Dose Cohorts

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

Notes to the Schedule of Events:
BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-Up, height, and BMI will not.
[2] Vital Signs will be measured at Screening, Day 1 at pre-dose, and at time of scan.
[3] ECG will be measured at Screening and after scan 4 (24 h post-dose).
[4] MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.
[5] Serum pregnancy test at Screening and Urine pregnancy test at Day 0 for all females of childbearing potential.

[6] *Plasma PK samples will be collected at Day 1 at pre-dose, and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2).*

[7] *Subjects are required to fast for approximately 12 hours prior to Day 1 dosing.*

[8] *Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.*

[9] *For Cohort 1 PET scans will be done starting at 2.5, 7.5, and 23.5 hours post oral dose of LB-102. Timing of PET scans for subsequent doses will be determined based on data in Cohort 1.*

[10] *Day 2 follow-up call will be done in the evening when the subject returns to their home. Day 3 follow-up call will be done in the morning.*

Revised Wording

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

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

Notes to the Schedule of Events:
BMI = Body Mass Index; ECG = Electrocardiogram; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; ***MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography;*** *PK = Pharmacokinetic*

~~[1] Only Weight will be recorded at Follow-Up, height, and BMI will not.~~

[1]If physical examination was not performed at Screening then physical examination completed at Day 0.

[2] Vital Signs will be measured at Screening, ***Day 0 (at the time of the PET scan, ±15 min),*** *Day 1 at pre-dose, and at* ***the*** *time of* ***each PET*** *scan* ***(±15 min, Visits 3 and 4)****.*

[3] ***MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.***

[4] ***ECG will be measured at Screening , Day 0 (prior to PET scan, ±15 min), and Day 2 (24 h post-dose, ±15 min).***

[5] *Serum pregnancy test at Screening and Urine pregnancy test on* ***Days 0-2*** *for all females of childbearing potential.*

[6] *Plasma PK samples will be collected at Day 1 at pre-dose, and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2).*

[7] *Subjects are required to fast for approximately 12 hours prior to Day 1 dosing.*

[8] *Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.*

[9] *For Cohort 1****-3*** *PET scans will be done on* ***Day 0 and*** *2.5, 7.5, and 23.5 hours* ***(±30 min)*** *post oral dose of LB-102.* ~~***Timing of PET scans for subsequent doses will be determined based on data in Cohort 1.***~~

[10] *Day 2 follow-up call will be done in the evening when the subject returns to their home. Day 3 follow-up call will be done in the morning.*

**** On Day 6, only blood will be collected for laboratory tests.***

Original Wording

Table 2: Schedule of Events, Single Dose Cohorts

Table 1: Schedule of Events, Multiple Dose Cohort

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

Notes to the Schedule of Events:
BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic
[1] Only Weight will be recorded at Follow-Up, height, and BMI will not.
[2] Vital Signs will be measured at Screening, Day 1 at pre-dose, and at time of scan.
[3] ECG will be measured at Screening and after scan 4 (24 h post-dose).
[4] MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.
[5] Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 6 for all females of childbearing potential.
[6] Plasma PK samples will be collected on Day 1 at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2). Plasma PK samples will also be collected on Day 5 immediately pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 6)
[7] Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-X, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 5, subjects will receive 1 dose (8 AM ±1 hour).
[8] Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.

[9]Three PET scans will be done on days 5 and 6, two on Day 5 post LB-102 dose (at times TBD based on first 3 cohorts) and one on Day 6 24 h after last LB-102 dose

Revised Wording

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

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

Notes to the Schedule of Events:
*BMI = Body Mass Index; ECG = Electrocardiogram; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus****; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography;*** *PK = Pharmacokinetic*

[1]If physical examination was not performed at screening then physical examination completed at Day 0.

[2] Vital Signs will be measured at Screening, ***Day 0 (at the time of the PET scan, ±15 min),*** *Day 1 at pre-dose, and at* ***the*** *time of* ***each PET*** *scan* ***(±15 min, Visits 3 and 4).***

[3] MRI can be done any time before Day 0. An MRI obtained in the prior 6 months for research purposes can substitute for this screening scan.

[4] ECG will be measured at Screening, ***Day 0 (prior to PET scan, ±15 min),*** *and after scan 4 (24 h post-dose, ±15 min).*

[5] Serum pregnancy test at Screening and Urine pregnancy test on ***Days 0, 5, and 6*** *for all females of childbearing potential.*

[6] Plasma PK samples will be collected on Day 1 at pre-dose and at the following times post dose (±15 min): 0.5, 1,

2, 4, 8, and 24 h (Day 2). Plasma PK samples will also be collected on Day 5 immediately pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 6)

*[7] Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-**4**, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 5, subjects will receive 1 dose (8 AM ±1 hour).*

[8] Concomitant Medication and Adverse Event Assessment will be recorded once per day on the days indicated.

*[9] **One PET scan will be done on Day 0**. Three PET scans will be done on Days 5 and 6, two on Day 5 post LB-102 dose (at times TBD based on first 3 cohorts) and one on Day 6 24 h after last LB-102 dose.*

[10] Day 6 follow-up call will be done in the evening when the subject returns to their home. Day 7 follow-up call will be done in the morning.

**** On Day 6, only blood will be collected for laboratory tests.***

Section 6.3 – Treatment Administration

Original Wording

Subjects will be dispensed LB-102 capsule (s) based on their assigned treatment at 7 AM (±1 hour). Subjects will take the capsule orally with 240 mL of water. Site personnel will confirm that the capsule has been taken by the study subject.

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

Cohort	*Treatment*
1 (n=4)	*LB-102 50 mg x 1 day*
2 (n=4)	*LB-102 XX x 1 day*
3 (n=4)	*LB-102 XX x 1 day*
4 (n=4)	*LB-102 XX mg , multiple dose*

Revised Wording

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

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

Cohort	*Treatment*
1 (n=4)	*LB-102 50 mg x 1 day*
2 (n=4)	*LB-102 XX x 1 day*
3 (n=4)	*LB-102 XX x 1 day*

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

Section 6.9.2 – Dietary and Lifestyle Restrictions

Original Wording

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 THC containing product 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*

Revised Wording

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

- *Use of alcohol from* ***24*** *hours prior to Check-In through the end of the study*
- *Use of any THC containing product from* ***24*** *hours prior to Check-In through the end of the study*
- ~~***Strenuous exercise 48 hours prior to Check-In through the end of the study***~~

Section 7.1 – Single Dose Cohorts (1-3)

Original Wording

Section 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).*
- *Urine pregnancy test for all females of childbearing potential.*

- *Record concomitant medication use.*
- *Assess and record AEs.*
- *Undergo pre-dose PET/CT scan (scan 1)*

Revised Wording

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

The following procedures will be performed:

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

Section - 7.1.3

Original Wording

Section 7.1.3 - Treatment Evaluation (Visit 3, Days 1 and 2), Cohorts 1-3

The following procedures will be performed on Day 1:

- *Administer dose of study drug.*
- *Vital Signs (at pre-dose and at time of scans).*

- *12-lead ECG after Scan 4 (24 h post-dose).*
- *Undergo post-dose PET/CT scan (scan 2) starting at 2.5 hours post LB-102 dose*
- *Undergo post-dose PET/CT scan (scan 3) starting at 7.5 hours post LB-102 dose*
- *Undergo post-dose PET/CT scan (scan 4) starting at 23.5 hours post LB-102 dose (Day 2)*
- *Plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h*
- *Record concomitant medication use.*
- *Assess and record AEs if reported.*
- *Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day 2*
- *Follow up will be done telephonically the evening of scan 4 (Day 2) once the participant is home.*

Revised Wording

Section 7.1.3 – ***Check-In (Visit 3, Day 1)***

The following procedures will be performed on Day 1:

- *Administer dose of study drug.*
- *Vital Signs (at pre-dose and at* ***the*** *time of* ***each PET*** *scan* ***±15 min****).*
- ~~***12-lead ECG after Scan 4 (24 h post-dose).***~~
- *Undergo post-dose PET/CT scan (scan 2) starting at 2.5 hours post LB-102 dose* ***(±30 min).***
- *Undergo post-dose PET/CT scan (scan 3) starting at 7.5 hours post LB-102 dose* ***(±30 min).***
- ~~***Undergo post-dose PET/CT scan (scan 4) starting at 23.5 hours post LB-102 dose (Day 2)***~~
- *Plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4,* ***and*** *8* ***h*** ~~***, and 24 h***~~
- ***Urine pregnancy test for all females of childbearing potential.***
- *Record concomitant medication use.*

- *Assess and record AEs if reported.*
- *Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day 2*
- ~~*Follow up will be done telephonically the evening of scan 4 (Day 2) once the participant is home.*~~

Section 7.1.4

<u>Original Wording</u>

Section 7.1.4 - Dosing/Scans (Visit 3, Days 1-5), Cohort 4

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

- *Dosing at 8 AM and 8 PM (±1 hour) intervals on Days 1-5 (AM only on Day 5).*
- *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).*
- *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).*
- *Undergo post-dose PET/CT scan (scan 2) starting at 2.5 hours post LB-102 dose on Day 5*
- *Undergo post-dose PET/CT scan (scan 3) starting at 7.5 hours post LB-102 dose on Day 5*
- *Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day 6*
- *On Day 1 plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h*

<u>Revised Wording</u>

7.1.4 - Discharge (Visit 4, Day 2)

The following procedures will be performed on Day 2:

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

Section 7.1.5

Original Wording

Section 7.1.5 - Scan (Visit 4, Day 6), Cohort 4

The following procedures will be performed on Day 6:

- *Vital signs.*
- *Undergo post-dose PET/CT scan (scan 4) starting at 23.5 hours post LB-102 dose.*
- *12-lead ECG after Scan 4 (25 h post-dose).*
- *On Day 5 plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 6).*
- *Assess and record AEs.*
- *Follow up will be done telephonically the evening of scan 4 (Day 6) once the participant is home.*

Revised Wording

Section 7.1.5 – *Follow-Up (Visit 5, Day 3)*

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

Sections 7.1.6 and 7.1.7 Removed

New Sections Added

Section 7.2 - Multiple Dose Cohort (Cohort 4)

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

The following procedures will be performed:

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

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

The following procedures will be performed:

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

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

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

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

- ***On Day 1 plasma samples for PK analysis at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, 8, and 24 h (Day 2)***

- ***On Day 5 plasma samples for PK analysis at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 4, and 8 h.***

Section 7.2.4 - Discharge (Visit 4, Day 6)

The following procedures will be performed on Day 6:

- ***Vital signs (at the time of the PET scan ±15 min).***

- ***Undergo post-dose PET/CT scan (scan 4; TBD, dependent on data from Cohorts 1-3).***

- ***12-lead ECG after Scan 4 (24 h post-dose, ±15 min).***

- ***On Day 6 plasma samples for PK analysis at the following times post-dose (±15 min): 24 h.***

- ***Collect blood samples for clinical laboratory tests (hematology, clinical chemistry, and serum prolactin).***

- ***Urine pregnancy test for all females of childbearing potential.***

- ***C-SSRS***

- ***Record concomitant medication use.***

- ***Assess and record AEs.***

- ***Follow-up telephone call.***

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

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

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

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

- ***Physical exam and weight measurements.***

- ***Vital signs.***

- ***Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis).***

- ***Urine pregnancy test for all females of childbearing potential.***
- ***Record concomitant medication use.***
- ***Assess and record AEs.***

Section 8.2 Dopamine Receptor Occupancy

Original Wording

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

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

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

***post-drug BP_{ND} obtained at each of the 2.5, 7.5, and 23.5 hours scan start times*

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

Thus, the BP_{ND} from each region and each of the three post-scan doses will be dynamically calculated from the entire 90 minute PET scan to calculate the occupancies (D_{2occ}) for each of the target brain regions above at 2.5, 7.5, and 23.5 hours post drug administration.

Revised Wording

*LB-102 binding potential and dopamine receptor occupancy **will be** measured as **the** amount of 11C Raclopride displaced by LB-102 using PET at baseline, and starting at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 (only post final dose for Cohort 4) in the caudate, putamen, thalamus, cerebellum grey, and the temporal lobe. Timing of scans for Cohorts 2-4 may be altered based on observations in Cohort 1.*

*Dopamine D2 receptor occupancy (D2occ) after the 2nd 3rd and 4th scans will be expressed as percent change in the ratio of the **~~Binding potential~~** BP_{ND} at baseline (scan 1 with no drug) vs the BP_{ND} after scan 2 , scan 3, and scan 4.*

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

post-drug BPND obtained at **specified time points for each cohort

*Therefore, for each of the scan start times (2.5, 7.5, and 23.5 hours post administration of the oral dose) there will be an D2occ occupancy measurement ($D2_{occ}$) for each of the four brain regions in quadruplicate (i.e. N=4 subjects/dose). Therefore, for each modeling method (e.g. SRTM, etc.) there will be **~~three~~ 4** doses x 4 subjects/dose x 4 regions = 64 different occupancies in Cohorts 1, 2, and 3, **and 4**. The dose amount and the **PET scan** time in Cohort 4 will be established adaptively by the results from Cohorts 1, 2, and 3. The choice of kinetic model for the final results will be established by methods and criteria previously employed by Dr. Wong and his colleagues, including information content. Also, including more than one complete kinetic model will be used to ensure consistency and reliability of the occupancy calculations.*

*Thus, the BP_{ND} from each region and each of the three post-scan doses will be dynamically calculated from the entire 90 minute PET scan to calculate the **~~occupancies~~** $D2_{occ}$ for each of the target brain regions above **~~at 2.5, 7.5, and 23.5 hours post drug administration~~**.*

Section 8.4 - Blood Collection

Original Wording

For each subject in Cohorts 1-3, up to 7 blood samples will be collected during the study for clinical and PK analysis. For each subject in Cohort 4, up to 13 blood samples will be collected during the study for clinical and PK analysis.

Revised Wording

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

Section 8.6.2.1 – Adverse Event Definition

Original Wording

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.

Revised Wording

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

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

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

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

Section 8.6.2.2 – Eliciting and Documenting Adverse Events

Original Wording

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 3 (for Cohorts 1-3)/Day 7 (Cohort 4) or Early Discontinuation visit.

At each visit, subjects will be asked for any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented from any data collected in 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.

Revised Wording

*The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the **e**CRF **~~and reported to the Medical Monitor. Adverse events~~**. AEs will be collected from Check-in (Day 0) through the Day 3 (for Cohorts 1-3)/Day 7 (Cohort 4) or Early Discontinuation visit.*

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

Section 8.6.2.3 – Reporting Adverse Events

Original Wording

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dose, Investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. 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 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	*(1) Anna Eramo (LB); (2) Study site*	*LB Pharmaceuticals, Inc.* *575 Madison Ave., 10th flr* *New York, NY 10022* *(312)661.2021*
Safety Monitor	*(1) Anna Eramo (LB); (2) Study site*	*LB Pharmaceuticals, Inc.* *575 Madison Ave., 10th flr* *New York, NY 10022* *(312)661.2021*

Revised Wording

*All AEs reported or observed during the study will be recorded on the AE page of the **e**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. **AEs** resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the Med DRA will be used to code all AEs.*

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

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

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

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

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

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

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

Section 8.6.4 – Laboratory Safety Assessment

Original Wording

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

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.*

Revised Wording

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

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

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

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

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

Section 8.6.5 – Vital Signs

Original Wording

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).

Revised Wording

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).***

Section 8.6.5 – Electrocardiogram

Original Wording

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

Screening, Day 1 pre-dose, and at time of scan.

Revised Wording

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

~~***Screening, Day 1 pre-dose, and at time of scan.***~~

Section 8.6.6 – Physical Examination

Original Wording

A standard physical examination will be performed at Screening, Pre-dose on day 1 and at time of scan. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, neurological and musculoskeletal system/extremities. Interim physical examinations will be performed at the Investigator's discretion if necessary, to evaluate AEs or clinical laboratory abnormalities.

Revised Wording

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

New Section Added

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

The baseline C-SSRS will be completed at Screening. The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior during participation in a clinical trial of centrally acting drugs. The C-SSRS is composed of three questions addressing suicidal behavior and five questions addressing suicidal ideation, with sub-questions assessing the severity.

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

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

Screening positive and significant findings:

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

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

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

Section 9.3.4 – Pharmacokinetic Analyses

<u>Original Wording</u>

Plasma concentrations of LB-102 and amisulpride will be measured for each PK sample.

<u>Revised Wording</u>

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

Section 14 Removed.

pharmaceuticals

Zachary Prensky, CEO	Signature	Date
ZACHARY PRENSKY		11/17/20