To: Washington University IRB

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: March 18, 2021

RE: Clarification Memo #6

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 (22 February 2021, Version 2). All items listed below have been incorporated into the protocol and will be submitted to FDA as a protocol amendment.

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 Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 for Cohorts 1-3. For Cohort 4, one PET scan will be done at Day 0 (baseline) and 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 [23.5 h after last LB-102 dose]) 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 11C raclopride displaced by LB-102 using PET at Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 for Cohorts 1-~~3~~**2. For Cohort 3, PET scans will occur at Day 0 (baseline), 2.5, 23.5, and 47.5 hours post LB-102 dose.** For Cohort 4, one PET scan will be done at Day 0 (baseline) and 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 [23.5 h after last LB-102 dose]) 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.*

Section 1 – Safety

Original Wording

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 0-3*
   b. *Cohort 4: Days 0-7*
2. *Hematology, chemistry, urinalysis at:*
   a. *Cohorts 1-3: Screening, Day 0, and Day 2**
   b. *Cohort 4: Screening, Day 0, 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*
   a. *Cohorts 1-3: Screening, Day 0 (prior to PET scan, ±30 min), and Day 2 (24 h post-dose, ±30 min)*
   b. *Cohort 4: Screening, Day 0 (prior to PET scan, ±30 min), and Day 6 (24 h post dose, ±30 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, ±30 min), Days 1-2 (Day 1 at pre-dose, and at the time of each PET scan [±30 min, Visits 3 and 4])*
   b. *Cohort 4: Screening, Day 0 (at the time of the PET scan, ±30 min), Days 1-6 (Day 1 at pre-dose, and at the time of each PET scan [±30 min, Visits 3 and 4])*
7. *C-SSRS*
   a. *Cohorts 1-3: Screening and Day 2*
   b. *Cohort 4: Screening and Day 6*

Revised Wording

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-~~2~~**3**: Days 0-3*
   b. Cohort 3: Days 0-4
   c. *Cohort 4: Days 0-7*
2. *Hematology, chemistry, urinalysis at:*

a. *Cohorts 1-~~2~~**3**: Screening, Day 0, and Day 2**

b. Cohort 3: Screening, Day 0, Day 2*, and Day 3

c. *Cohort 4: Screening, Day 0, and Day 6**

i. *** - Only blood will be collected for laboratory tests.*

3. *Prolactin at:*

a. *Cohorts 1-~~2~~**3**: Screening and Day 2*

b. Cohort 3: Screening, Day 2, and Day 3

c. *Cohort 4: Screening and Day 6*

4. *ECG*

a. *Cohorts 1-~~2~~**3**: Screening, Day 0 (prior to PET scan, ±30 min), and Day 2 (24 h post-dose, ±30 min)*

b. Cohort 3: Screening, Day 0 (prior to PET scan, ±30 min), Day 1 (at pre-dose), Day 2 (24 h post-dose, ±30 min), and Day 3 (48 h post-dose, ±30 min)

b.c. *Cohort 4: Screening, Day 0 (prior to PET scan, ±30 min),* ***Day 1 (at pre-dose),*** *and Day 6 (24 h post dose, ±30 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-~~2~~**3**: Screening, Day 0 (at the time of the PET scan, ±30 min), Days 1-2 (Day 1 at pre-dose, and at the time of each PET scan [±30 min, Visits 3 and 4])*

b. Cohort 3: Screening, Day 0 (at the time of the PET scan, ±30 min), Days 1-3 (Day 1 at pre-dose, and at the time of each PET scan [±30 min, Visits 3, 4, and 5])

c. *Cohort 4: Screening, Day 0 (at the time of the PET scan, ±30 min), Days 1-6 (Day 1 at pre-dose, and at the time of each PET scan [±30 min, Visits 3 and 4])*

7. *C-SSRS*

a. *Cohorts 1-3: Screening and Day 2*

b. *Cohort 4: Screening and Day 6*

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Original Wording

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

	Screening	*Pre-Dose Scan*	*Check-In*	*Discharge*	*Follow-Up*	*Pregnancy Follow-Up*
Visit	*1*	*2*	*3*	*4*	*5*	*6*
Days	*Days -14 to -1*	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 31*
Location	*Outpatient*	*Outpatient*	*Inpatient*	*Inpatient/ Outpatient*	*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**		
Urine Drug Screen[@]	*X*	*X*	*X*			
Alcohol Breathalyzer		*X*	*X*			
Serum HbA1c	*X*					
Serum Prolactin	*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*	*X*	
Adverse Event Assessment[8]		*X*	*X*	*X*	*X*	
PET Scan[9]		*X*	*X*	*X*		
Follow-Up by Telephone[10]				*X*	*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; 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, ±30 min), Day 1 at pre-dose, and at the time of each PET scan (±30 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, ±30 min), and Day 2 (24 h post-dose, ±30 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 (±30 min) hours post oral dose of LB-102.*

[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. The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.*

* *On Day 2, only blood will be collected for laboratory tests.*

[@] *Urine Drug Screens will occur at Screening and Days 0-1. On Days 0 and 1, the urine drug screen will be analyzed* by the Easy@Home 10 Panel Instant Drug Test Kit

Revised Wording

*Table 1: Schedule of Events, Single Dose Cohorts (Cohorts 1-**23**)*

	Screening	*Pre-Dose Scan*	*Check-In*	*Discharge*	*Follow-Up*	*Pregnancy Follow-Up*
Visit	*1*	*2*	*3*	*4*	*5*	*6*
Days	*Days -14 to -1*	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 31*
Location	*Outpatient*	*Outpatient*	*Inpatient*	*Inpatient/ Outpatient*	*Outpatient*	*Outpatient*
Informed Consent	*X*					
Inclusion/Exclusion Criteria	*X*	~~***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**		
Urine Drug Screen[@]	*X*	*X*	*X*			
Alcohol Breathalyzer		*X*	*X*			
Serum HbA1c	*X*					
Serum Prolactin	*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*	*X*	
Adverse Event Assessment[8]		*X*	*X*	*X*	*X*	
PET Scan[9]		*X*	*X*	*X*		

Follow-Up by Telephone[10]				*X*	*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; 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, ±30 min), Day 1 at pre-dose, and at the time of each PET scan (±30 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, ±30 min), and Day 2 (24 h post-dose, ±30 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**s** 1-**2~~3~~** PET scans will be done on Day 0 and 2.5, 7.5, and 23.5 (±30 min) hours post oral dose of LB-102.*

[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. The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.*

[*] *On Day 2, only blood will be collected for laboratory tests.*

[@] *Urine Drug Screens will occur at Screening and Days 0-1. On Days 0 and 1, the urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*

New Section Added

Table 2: Schedule of Events, Single Dose Cohort (Cohort 3)

	Screening	Pre-Dose Scan	Check-In	Treatment Evaluation	Discharge	Follow-Up	Pregnancy Follow-Up
Visit	1	2	3	4	5	6	7
Days	Days -14 to -1	Day 0	Day 1[a]	Day 2	Day 3	Day 4	Day 31
Location	Outpatient	Outpatient	Inpatient	Inpatient	Inpatient/ Outpatient	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	X		
Structural MRI[3]	X						
Laboratory Tests*	X	X		X*	X		
Urine Drug Screen[@]	X	X	X				
Alcohol Breathalyzer		X	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	X	X		
Pregnancy Test[5]	X	X	X	X			
Plasma PK[6]			X	X	X		
Dose Subjects[7]			X				
Concomitant Medication[8]	X	X	X	X	X	X	

Adverse Event Assessment[8]		X	X	X	X	X	
PET Scan[9]		X	X	X	X		
Follow-Up by Telephone[10]					X	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; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; PK = Pharmacokinetic

[a] The interval allowance between Visit 0 and Visit 1 is up to 14 days.

[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, ±30 min), Day 1 at pre-dose, and at the time of each PET scan (±30 min, Visits 3, 4, and 5).

[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, ±30 min), Day 1 (pre-dose, ±30 min), Day 2 (24 h post-dose, ±30 min), and Day 3 (48 h post-dose, ±30 min).

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

[6] For Cohort 3, PK samples will be collected on Day 1 at pre-dose, and at the following times post dose (±15 min): 0.5, 1, 2, 3, 4, 8, 24 (Day 2), 25, 48 (Day 3), and 49 h.

[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 3, PET scans will be done on Day 0 and 2.5, 23.5, and 47.5 (±30 min) hours post oral dose of LB-102.

[10] Day 3 follow-up call will be done in the evening when the subject returns to their home. Day 4 follow-up call will be done in the morning. The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.

**** On Day 2, only blood will be collected for laboratory tests.***

[@] Urine Drug Screens will occur at Screening and Days 0-1. On Days 0 and 1, the urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.

Original Wording

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

	Screening	Pre-Dose Scan	Treatment Evaluation	Discharge	Follow-Up	Pregnancy Follow-Up
Visit	1	2	3	4	5	6
Days	Days -14 to -1	Day 0	Days 1-5	Day 6	Day 7	Day 35
Location	Outpatient	Outpatient	Inpatient	Inpatient/ Outpatient	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[1]				
Vital Signs[2]	X	X	X	X		
Laboratory Tests*	X	X*		X*		
Urine Drug Screen[@]	X[@]	X[@]	X[@] (Day 1)			
Alcohol Breathalyzer		X	X (Day 1)			
Structural MRI[3]	X					
Serum HbA1c	X					
Serum Prolactin	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			
Concomitant Medication[8]	X	X	X	X	X	
Adverse Event Assessment		X	X	X	X	
PET scan[9]		X	X	X		
Follow up by telephone[10]				X	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; 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, ±30 min), Day 1 at pre-dose, and at the time of each PET scan (±30 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, ±30 min) and Day 6 (24 h post-dose, ±30 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 (9 AM and 9 PM ±1 hour) separated by approximately 12 hours. On Day 5, subjects will receive 1 dose (9 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 (23.5 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. The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.*

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

[@] *Urine Drug Screen will occur at Screening and on Days 0 and 1. On Days 0 and 1, the urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*

Revised Wording

Table ~~23~~: Schedule of Events, Multiple Dose Cohort (Cohort 4)

	Screening	*Pre-Dose Scan*	*Treatment Evaluation*	*Discharge*	*Follow-Up*	*Pregnancy Follow-Up*
Visit	*1*	*2*	*3*	*4*	*5*	*6*
Days	*Days -14 to -1*	*Day 0*	*Days 1[a]-5*	*Day 6*	*Day 7*	*Day 35*
Location	*Outpatient*	*Outpatient*	*Inpatient*	*Inpatient/ Outpatient*	*Outpatient*	*Outpatient*
Informed Consent	*X*					
Inclusion/Exclusion Criteria	*X*	***~~X~~***	***X (Day 1)***			
Medical History	*X*	*X*				
Demographics	*X*					
Height, Weight, BMI[1]	*X*					
Physical Examination	*X*	*X[1]*				
Vital Signs[2]	*X*	*X*	*X*	*X*		
*Laboratory Tests**	*X*	*X~~*~~*		*X**		
Urine Drug Screen[@]	*X~~@~~*	*X~~@~~*	*X~~@~~ (Day 1)*			
Alcohol Breathalyzer		*X*	*X (Day 1)*			
Structural MRI[3]	*X*					
Serum HbA1c	*X*					
Serum Prolactin	*X*			*X*		
HIV, HBsAg, and HCV Labs	*X*					
C-SSRS	*X*			*X*		
12-Lead ECG[4]	*X*	*X*	***X (Day 1)***	*X*		
Pregnancy Test[5]	*X*	*X*	*X (Day 5)*	*X*		
Plasma PK[6]			*X*	*X*		
Dose Subjects[7]			*X*			
Concomitant Medication[8]	*X*	*X*	*X*	*X*	*X*	
Adverse Event Assessment		*X*	*X*	*X*	*X*	
PET scan[9]		*X*	*X*	*X*		
Follow up by telephone[10]				*X*	*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; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; PK = Pharmacokinetic

[a] – The interval allowance between Visit 2 and Visit 3 is up to 14 days.

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, ±30 min), Day 1 at pre-dose, and at the time of each PET scan (±30 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, ±30 min),* ***Day 1 (pre-dose),*** *and Day 6 (24 h post-dose, ±30 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 (9 AM and 9 PM ±1 hour) separated by approximately 12 hours. On Day 5, subjects will receive 1 dose (9 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 (23.5 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. The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.*

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

[@] *Urine Drug Screen will occur at Screening and on Days 0 and 1. On Days 0 and 1, the urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*

Section 6.9 – Concomitant Medication

Original Wording

Prescription and over-the-counter medications will be prohibited throughout the study except hormonal contraception for females of childbearing potential. No concomitant drug therapy will be allowed during the study (Visits 1-5) except one(s) required for the medical management of an AE. Any concomitant medication use will be evaluated on a case-by-case basis by the Investigator or a Sub investigator. Any concomitant medications used will be recorded in the source document and on the appropriate CRF. The medication name, dose, frequency, date, and indication for use must be recorded on the CRF. For Cohorts 1-4, all concomitant medication use will be documented from screening through Visit 5/early termination.

Revised Wording

*Prescription and over-the-counter medications will be prohibited throughout the study except hormonal contraception for females of childbearing potential. No concomitant drug therapy will be allowed during the study (Visits 1-5) except one(s) required for the medical management of an AE. Any concomitant medication use will be evaluated on a case-by-case basis by the Investigator or a Sub investigator. Any concomitant medications used will be recorded in the source document and on the appropriate CRF. The medication name, dose, frequency, date, and indication for use must be recorded on the CRF. For Cohorts 1**, 2, and** 4, all concomitant medication use will be documented from screening through Visit 5/early termination.* ***For Cohort 3, all concomitant medication use will be documented from screening through Visit 6/early termination.***

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 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*

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*

Subjects must fast 12 hours prior to the Screening Visit and 12 hours prior to the Day 1 Visit.

Section 7 – Study Procedures

<u>Original Wording</u>

Section 7.1 - Single Dose Cohorts (Cohorts 1-3)

<u>Revised Wording</u>

*Section 7.1 - Single Dose Cohorts (Cohorts 1-**23**)*

New Section Added

7.2 - Single Dose Cohort (Cohort 3)

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

This is an open-label, single center design exploratory clinical trial examining the occupancy of LB-102 using 11C-Racrlopride PET imaging.

Sixteen healthy human subjects will receive LB-102.

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).***
- ***C-SSRS***
- ***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 PI to determine the subject's eligibility for participation in the study in light of these findings. 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).*

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

The following procedures will be performed:

- *Record medical history.*
- *Physical examination (If physical examination was not performed at Screening).*
- *Vital signs (at the time of the PET scan, ±30 min).*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and urine drug screen*).*
    - **The Pre-Dose Scan Visit urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*
- *12-lead ECG (prior to PET scan, ±30 min).*
- *Urine pregnancy test for all females of childbearing potential.*
- *Alcohol Breathalyzer*
- *Record concomitant medication use.*
- *Assess and record AEs.*
- *Undergo pre-dose PET/CT scan (scan 1)*

7.2.3 - Check-In (Visit 3, Day 1)

The interval allowance between Visit 2 and Visit 3 is 14 days.

The following procedures will be performed on Day 1:

- *Alcohol Breathalyzer*

- *Urine Drug Screen*
    - *The Day 1 urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*
- *Review inclusion and exclusion criteria.*
- *12-lead ECG (at pre-dose, ±30 min).*
- *Vital Signs (at pre-dose and at time of each PET scan, ±30 min).*
- *Plasma samples for PK analysis pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, 3, 4, and 8 h.*
- *Administer dose of study drug.*
- *Undergo post-dose PET/CT scan (scan 2) starting at 2.5 hours post LB-102 dose (±30 min).*
- *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 3.*

7.2.4 - Treatment Evaluation (Visit 4, Day 2)

The following procedures will be performed on Day 2:

- *Vital Signs (at the time of the PET scan ±30 min).*
- *12-lead ECG (24 h post-dose, ±30 min).*
- *Undergo post-dose PET/CT scan (scan 3) 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 and 25 h*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, and serum prolactin).*
- *Record concomitant medication use.*
- *Assess and record AEs if reported.*
- *Subjects will be monitored on an in-patient basis until completion of the final scan on Day 3.*

7.2.5 - Discharge (Visit 5, Day 3)

The following procedures will be performed on Day 3:

- ***Vital Signs (at the time of the PET scan ±30 min).***
- ***12-lead ECG (48 h post-dose, ±30 min).***
- ***Undergo post-dose PET/CT scan (scan 4) starting at 47.5 hours (±30 min) post LB-102 dose.***
- ***Plasma samples for PK analysis at the following time post dose (±15 min): 48 and 49 h***
- ***Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, and prolactin).***
- ***Record concomitant medication use.***
- ***Assess and record AEs if reported.***
- ***Follow-up telephone call.***

7.2.6 - Follow-Up (Visit 6, Day 4)

- ***Follow up will be done telephonically one day after completion of the study.***
- ***Record concomitant medication use.***
- ***Assess and record AEs if reported.***

7.2.7 - Pregnancy Follow-Up Visit (Visit 7, Day 31)

- ***The Pregnancy Follow-Up telephone call will only determine whether female subjects of childbearing or the female partner of a male subject (that is not surgically sterile) is pregnant.***

Section 7.3.3 – Treatment Evaluation (Visit 3, Days 1-5)

<u>Original Wording</u>

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

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

- *Alcohol Breathalyzer (Day 1).*
- *Urine Drug Screen (Day 1).*

- *The Day 1 urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*

- *Review inclusion and exclusion criteria (Day 1).*
- *Dosing at 9 AM and 9 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, ±30 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.*

Revised Wording

The interval allowance between Visit 2 and Visit 3 is 14 days.

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

- *Alcohol Breathalyzer (Day 1).*
- *Urine Drug Screen (Day 1).*
    - *The Day 1 urine drug screen will be analyzed by the Easy@Home 10 Panel Instant Drug Test Kit.*
- *Review inclusion and exclusion criteria (Day 1).*
- *Dosing at 9 AM and 9 PM (±1 hour) intervals on Days 1-5 (AM only on Day 5).*
- ***12-lead ECG (at pre-dose, ±30 min).***
- *Vital signs (at pre-dose and at time of each PET scan, ±30 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 7.3.5 – Follow-Up Visit (Visit 5, Day 7)

Original Wording

- *Follow up will be done telephonically one day after completion of the study*
- *Assess and record AEs.*
- *Follow-up telephone call.*

Revised Wording

- *Follow up will be done telephonically one day after completion of the study*
- *Assess and record AEs.*
- ***Record concomitant medication use.***
- ~~***Follow-up telephone call.***~~

Section 8.2 – Dopamine Occupancy

Original 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 Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 for Cohorts 1-3. For Cohort 4, one PET scan will be done at Day 0 (baseline) and 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 [23.5 h after last LB-102 dose]) in the caudate, putamen, thalamus, and temporal cortex. The cerebellum (devoid of Dopamine D2/D3 receptors) will be used as a reference region. 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 BPND at baseline (scan 1 with no drug) vs the BPND after scan 2 , scan 3, and scan 4.

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 Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours post oral dose of LB-102 for Cohorts 1-**23**. **For Cohort 3, PET scans will occur at Day 0 (baseline), 2.5, 23.5, and 47.5 hours post LB-102 dose.** For Cohort 4, one PET scan will be done at Day 0 (baseline) and 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 [23.5 h after last LB-102 dose]) in the caudate, putamen, thalamus, and temporal cortex. The cerebellum (devoid of Dopamine D2/D3 receptors) will be used as a reference region. 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 BPND at baseline (scan 1 with no drug) vs the BPND after scan 2 , scan 3, and scan 4.

Section 8.4 - Blood Collection

Original 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.

Revised Wording

*For each subject in Cohorts 1-3, up to **20~~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 8.6.2.2 - Eliciting and Documenting Adverse Events

Original Wording

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF. 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.

Revised Wording

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF. ***For Cohorts 1, 2, and 4****, AEs will be collected from* ~~***Check-in***~~***Visit 2*** *(Day 0) through* ***Visit 5***~~***the Day 3 (for Cohorts 1-3)/Day 7 (Cohort 4)***~~* *or Early Discontinuation visit.* ***For Cohort 3, AEs will be collected from Visit 2 (Day 0) through Visit 6 or Early Discontinuation.***

Section 8.6.9 – Concomitant Medication

Original Wording

Concomitant medications will be reviewed and documented each day during the study (Visits 1 5).

Revised Wording

Concomitant medications will be reviewed and documented ~~***each day during the study (***~~***from*** *Visits 1-5*~~***)***~~ ***for Cohorts 1, 2, and 4. For Cohort 3, Concomitant medications will be reviewed and documented from Visits 1-6.***

pharmaceuticals

Zachary Prensky, CEO	Signature	Date
Zachary Prensky		6/8/2021