To: Washington University IRB

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: December 8, 2020

RE: Clarification Memo #4

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 November 2020, Version 1). All items listed below have been incorporated into the protocol and will be submitted to FDA.

Section - Procedures in Case of Emergency

Original Wording

Procedures in Case of Emergency
Sponsor/CRO Contact Information

Role in Study	*Name*	*Address and Telephone Number*
Chief Medical Officer/Medical Monitor	*Anna Eramo, MD*	*LB Pharmaceuticals, Inc.* *575 Madison Ave., 10th Floor* *New York, NY 10022* *Email: anna@lbpharma.us* *(312)661.2021*
Clinical Project Manager	*Miguel Cabrera, PhD*	*Target Health LLC.* *261 Madison Ave, 24th Floor* *New York, NY 10016* *Email: mcabrera@targethealth.com* *Phone: 908-418-8121*
Clinical Project Manager/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*

Revised Wording

Procedures in Case of Emergency
Sponsor/CRO Contact Information

Role in Study	Name	Address and Telephone Number
Chief Medical Officer/Medical Monitor	*Anna Eramo, MD*	*LB Pharmaceuticals, Inc.* *575 Madison Ave., 10th Floor* *New York, NY 10022* *Email: anna@lbpharma.us* *(312)661.2021*
Medical Monitor	***Bruce Reidenberg, MD, FAAP, FCP***	***Target Health LLC.*** ***261 Madison Ave, 24th Floor*** ***New York, NY 10016*** ***Email: breidenberg@gmail.com*** ***Phone: 914-707-4195***
Clinical Project Manager	*Miguel Cabrera, PhD*	*Target Health LLC.* *261 Madison Ave, 24th Floor* *New York, NY 10016* *Email: mcabrera@targethealth.com* *Phone: 908-418-8121*
Clinical Project Manager/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 1 – Summary

Original Wording

Study Design: This is a Phase 1B, 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 9 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 the evening of discharge and 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 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)*

Revised Wording

*Study Design: This is a Phase 1B, 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**s 1-3** 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 9 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 the evening of discharge and the next day to check on subjects.* ***There will be a Pregnancy Follow-Up telephone call to determine whether female subjects of childbearing or the female partners of a male subjects (that are not surgically sterile) are pregnant 30 days after the final LB-102 dose.*** *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*
***2** (n=4)*	*LB-102 XX mg, single dose*
***3** (n=4)*	*LB-102 XX mg, single dose*
***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 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 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, 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 Screening (**baseline**~~, Cohorts 1-4~~), **and at** ~~baseline,~~ 2.5, 7.5, and 23.5 hours post oral dose of LB-102 **~~post-Day 1 dose~~** for Cohorts 1-3.* ***For Cohort 4, one PET scan will be done***

at Screening (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* ~~*for Cohort 4*~~ ***on Day 6****) 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 0-2*
    b. *Cohort 4: Days 0-6*

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 1-3: Days 0-****3***
    b. *Cohort 4: Days 0-****7***

Original 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*	
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[8]		*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; 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 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 (±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.*

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

Revised 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**		
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, ±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 (±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.*

Original 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	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	
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	
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; 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.*

Revised Wording

Table 1: 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*		
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, ±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* ***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.*

Section 6.9 – Concomitant Medications

<u>Original Wording</u>

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 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. All concomitant medication use will be documented from screening through study exit/early termination.

<u>Revised Wording</u>

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*** ***~~study exit~~****/early termination.*

Section 7 – Study Procedures

<u>Original Wording</u>

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of any prohibited concomitant therapy.

The schedule of events to be performed during the study are provided in Table 1.

<u>Revised Wording</u>

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of any prohibited concomitant therapy.

The schedule of events to be performed during the study are provided in Table 1 ***and Table 2****.*

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

<u>Original Wording</u>

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

<u>Revised Wording</u>

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

New Section Added

Section 7.1.6 – Pregnancy Follow-Up Visit (Visit 6, 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 7.2.4 – Discharge (Visit 4, Day 6)

Original Wording

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.*

Revised Wording

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;* ***23.5 h (±30 min) post LB-102 dose ~~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 5, Day 7)

Original Wording

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

Revised Wording

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

New Section Added

Section 7.2.6 – Pregnancy Follow-Up Visit (Visit 6, Day 35)

- ***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 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 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, 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.

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

***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 occupancy measurement (D2occ) 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 4 doses x 4 subjects/dose x 4 regions = 64 different occupancies in Cohorts 1, 2, 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 ensure consistency and reliability of the occupancy calculations.

Thus, the BPND 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 D2occ for each of the target brain regions above.

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 ***Screening (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 Screening (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])*** *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.

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

***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 occupancy measurement (D2occ) 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 4 doses x 4 subjects/dose x 4 regions = 64 different occupancies in Cohorts 1, 2, 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 ensure consistency and reliability of the occupancy calculations.*

Thus, the BPND 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 D2occ for each of the target brain regions above.

Section 8.6.2.3 – Reporting Adverse Events

Original Wording

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*

Revised Wording

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*
Medical Monitor	***Bruce Reidenberg, MD, FAAP, FCP***	***Target Health LLC.*** ***261 Madison Ave, 24th Floor*** ***New York, NY 10016*** ***Email: breidenberg@gmail.com*** ***Phone: 914-707-4195***
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 8.6.9 –

Original Wording

Concomitant medications will be reviewed and documented each day during the study.

Revised Wording

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

pharmaceuticals

Zachary Prensky, CEO	Signature	Date
ZACHARY PRENSKY		12/8/20