To: Washington University IRB

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: June 04, 2021

RE: Clarification Memo #7

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 (19 March 2021, Version 3). All items listed below have been incorporated into the protocol and will be submitted to FDA as a protocol amendment (Version 4, 01 June 2021).

Section 1 – Study Design

Original Wording

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 Cohorts 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)*

Revised Wording

*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 Cohorts 1-3 will receive 1 dose of LB-102 on Day 1. Subjects in the **~~final~~** Cohort 4 will be dosed for **34** days BID (Days 1-**34**) and 1 day QD (Day **~~45,~~** AM **dose**; i.e., a total of **~~79~~** 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~~ all previous cohort(s) (PET data from at least 3 subjects per cohort)*** *are obtained.*

Cohort	***Treatment***
1 (n=4)	*LB-102 50 mg, single dose*
2 (n=4)	*LB-102* ***~~XX~~100*** *mg, single dose*
3 (n=4)	*LB-102* ***~~XX~~75*** *mg, single dose*
4 (n=4)	*LB-102 XX mg,* ***34*** *x BID (Days 1-****34****) and 1 x QD (Day* ***~~45,~~*** *AM* ***dose****; i.e., a total of* ***~~79~~*** *doses)*

Section 1 – Main Criteria for Eligibility

Original Wording

Inclusion Criteria:

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. *Competent to provide informed consent.*
2. *Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.*
3. *Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.*
4. *Body Mass Index (BMI) ≥ 18 and ≤ 30 kg/m^2 at screening visit.*
5. *Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.*
6. *Have normal clinical laboratory test results and ECG, which are not considered to be clinically significant by the Investigator.*
7. *Females participating in the study:*

a. *Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's rang**es; OR***

b. ***Females of child-bearing potential mus**t have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:*

   i. *condom plus spermicide*

   ii. *condom plus diaphragm*

   iii. *condom plus cervical cap or female condom*

   iv. *hormonal contraceptives*

   v. *intrauterine device*

   vi. *partner vasectomy and a use of barrier contraception methods*

8. *If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:*

   c. *Have had a vasectomy (at least 6 months earlier);*

   d. *Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);*

   e. *Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;*

   f. *Partner use of an intrauterine device;*

   g. *Complete abstinence from sexual intercourse;*

   h. *Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.*

9. *If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.*

Exclusion Criteria:

A subject will be excluded from the study if he or she meets the following criteria:

1. *Are pregnant or lactating.*
2. *Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological or psychological/psychiatric disorders which, in the*

opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.

3. *Clinically significant abnormal findings on physical examination or vital signs as determined by PI.*
4. *Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.*
5. *History or presence of psychiatric or neurological disease or condition as determined by the PI.*
6. *History of seizures.*
7. *Subject with any history or current evidence of suicidal behavior.*
8. *Unwilling to complete any planned study assessments.*
9. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*
10. *Have received treatment with an investigational drug or device within 30 days prior to Screening.*
11. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
12. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
13. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*
14. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*
15. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:*
    a. *Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)*
    b. *QTcF interval > 450 msec for males and females*
    c. *PR interval ≥ 200 msec*
    d. *Intraventricular conduction delay with QRS duration > 120 msec*
    e. *Evidence of second- or third-degree atrioventricular block (AVB)*
    f. *Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB*
16. *Any subject who has a positive Urine Drug Screen test on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*
17. *Any subject who has an Alcohol Breathalyzer test result deemed positive by the Investigator (Principal Investigator or Sub-Investigator) on the Day 0 or Day 1 Visit, unless in the Investigator's*

(Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.

Revised Wording

Inclusion Criteria:

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. *Competent to provide informed consent.*
2. *Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.*
3. *Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.*
4. *Body Mass Index (BMI) ≥ 18**.0** and ≤ 30**.0** kg/m^2 at screening visit.*
5. *Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.*
6. *Have normal clinical laboratory test results and **electrocardiogram (**ECG**) at Screening**, which are not considered to be clinically significant by the Investigator.*
7. *Females participating in the study:*
    a. *Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's rang**es; OR***
    b. ***Females of child-bearing potential mus**t have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:*
        i. *condom plus spermicide*
        ii. *condom plus diaphragm*
        iii. *condom plus cervical cap or female condom*

iv. *hormonal contraceptives*

v. *intrauterine device*

vi. *partner vasectomy and a use of barrier contraception methods*

8. *If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:*

    c. *Have had a vasectomy (at least 6 months earlier);*

    d. *Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);*

    e. *Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;*

    f. *Partner use of an intrauterine device;*

    g. *Complete abstinence from sexual intercourse;*

    h. *Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.*

9. *If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.*

Exclusion Criteria:

A subject will be excluded from the study if he or she meets the following criteria:

1. *Are pregnant or lactating.*
2. *Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological or psychological/psychiatric disorders which, in the opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.*
3. *Clinically significant abnormal findings on physical examination or vital signs as determined by* ***the Principal Investigator (****PI****).***
4. *Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.*
5. *History or presence of psychiatric or neurological disease or condition as determined by the PI.*
6. *History of seizures.*
7. *Subject with any history or current evidence of suicidal behavior.*
8. *Unwilling to complete any planned study assessments.*
9. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*

10. *Have received treatment with an investigational drug or device within 30 days prior to Screening.*
11. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
12. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
13. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*
14. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*
15. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:*
    a. *Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)*
    b. *QTcF interval > 450 msec for males and females*
    c. *PR interval ≥ 200 msec*
    d. *Intraventricular conduction delay with QRS duration > 120 msec*
    e. *Evidence of second- or third-degree atrioventricular block (AVB)*
    f. *Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB*

    Note: If the PI determines that an abnormal ECG is borderline, the PI may conduct an additional ECG. Clinically significant abnormal findings and/or evidence of cardiac abnormalities (see 15 a-f) on the second ECG will be exclusionary.
16. *Any subject who has a positive Urine Drug Screen test on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*
17. *Any subject who has an Alcohol Breathalyzer test result deemed positive by the Investigator (Principal Investigator or Sub-Investigator) on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*

Section 1 – Duration of Treatment

<u>Original Wording</u>

1 day or 5 days.

Revised Wording

*1 day or **~~45~~** days.*

Section 1 – Endpoint

Original Wording

LB-102 binding potential and dopamine receptor occupancy measured as amount of ^{11}C 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 1-2. 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.

Revised Wording

*LB-102 binding potential and dopamine receptor occupancy measured as amount of ^{11}C--Raclopride displaced by LB-102 using PET at Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours **(±30 min)** post oral dose of LB-102 for Cohorts 1-2. For Cohort 3, PET scans will occur at Day 0 (baseline), 2.5, 23.5, and 47.5 hours **(±30 min)** 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 **~~45~~** and **~~56~~** (two on Day **~~45~~** post LB 102 dose [**~~at times determined following Cohorts 1-3~~2.5 and 7.5 h after last LB-102 dose, ±30 min]** and one on Day **~~56~~** [23.5 h after last LB-102 dose**, ±30 min**]) 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. **The timing above is subject to possible technical confounds such as cyclotron and radiochemistry synthesis failure or PET scanner failures. In the event that these unanticipated delays might exceed the windows of PET scan time post LB-102 dose, verbal scientific permission will be sought from the Sponsor if it does not involve a subject safety issue.***

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 1-2: Days 0-3*
    b. *Cohort 3: Days 0-4*
    c. *Cohort 4: Days 0-7*
2. *Hematology, chemistry, urinalysis at:*
    a. *Cohorts 1-2: 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: 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: 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)*
    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: 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*

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: Days 0-3*
    b. *Cohort 3: Days 0-4*
    c. *Cohort 4: Days 0-~~6~~**7***

2. *Hematology, chemistry, urinalysis at:*
    a. *Cohorts 1-2: 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 **~~5~~6****
        i. ** - Only blood will be collected for laboratory tests.*
3. *Prolactin at:*
    a. *Cohorts 1-2: Screening and Day 2*
    b. *Cohort 3: Screening, Day 2, and Day 3*
    c. *Cohort 4: Screening and Day **~~5~~6****
4. *ECG*
    a. *Cohorts 1-2: 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)*
    c. *Cohort 4: Screening, Day 0 (prior to PET scan, ±30 min), Day 1 (at pre-dose), and Day **~~5~~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: 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-**~~5~~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 **~~5~~6****

Original Wording

Table 3: 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 (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 (at 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.*

Revised Wording

Table 3: 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]-**45***	*Day **56***	*Day 6**~~7~~***	*Day 3**~~45~~***
Location	***Outpatient***	***Outpatient***	***Inpatient***	***Inpatient/ Outpatient***	***Outpatient***	***Outpatient***
Informed Consent	*X*					
Inclusion/Exclusion Criteria	*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 **45**)*	*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 (at pre-dose), and Day **56** (24 h post-dose, ±30 min).*

5 *Serum pregnancy test at Screening and Urine pregnancy test on Days 0, **45**, and **56** 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, **3,** 4, 8, **and** 24**, and 25** h (Day 2). Plasma PK samples will also be collected on Day 4 immediately pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, **3,** 4, 8, **and** 24**, and 25** h (Day **56**)*

[7] *Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-**34**, subjects will receive 2 doses per day (9 AM and 9 PM ±1 hour) separated by approximately 12 hours. On Day **45**, 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 **45** and **56**, two on Day **45** (**2.5 and 7.5 hours [±30 min] after last** LB-102 dose **at times TBD based on first 3 cohorts**) and one on Day **56** (23.5 h **[±30 min]** after last LB-102 dose).*

[10] *Day **56** follow-up call will be done in the evening when the subject returns to their home. Day **67** 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 **56**, 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 5.2.1 - Inclusion Criteria

<u>Original Wording</u>

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. *Competent to provide informed consent.*

2. *Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.*

3. *Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.*

4. *Body Mass Index (BMI) ≥ 18 and ≤ 30 kg/m2 at screening visit.*

5. *Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.*

6. *Have normal clinical laboratory test results and electrocardiogram (ECG), which are not considered to be clinically significant by the Investigator.*

7. *Females participating in the study:*

    a. *Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's rang**es; OR***

    b. ***Females of child-bearing potential mus**t have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:*

        i. *condom plus spermicide*

        ii. *condom plus diaphragm*

        iii. *condom plus cervical cap or female condom*

        iv. *hormonal contraceptives*

v. *intrauterine device*

vi. *partner vasectomy and a use of barrier contraception methods*

8. *If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:*

   a. *Have had a vasectomy (at least 6 months earlier);*

   b. *Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);*

   c. *Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;*

   d. *Partner use of an intrauterine device;*

   e. *Complete abstinence from sexual intercourse;*

   f. *Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.*

9. *If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.*

Revised Wording

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1. *Competent to provide informed consent.*

2. *Voluntarily provide informed consent and Health Insurance Portability and Accounting Act (HIPAA) Authorization in accordance with local regulations and governing Institutional Review Board (IRB) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.*

3. *Healthy adult female and male subjects between 18 to 55 years of age inclusive at the screening visit.*

4. *Body Mass Index (BMI) ≥ 18**.0** and ≤ 30**.0** kg/m2 at screening visit.*

5. *Subjects must be in good general health as determined by medical history and physical examination with no clinically significant medical findings and no history of significant medical*

disease (e.g., cardiovascular, pulmonary, renal, etc.) or acute condition with the past 30 days, as determined by the study investigators.

6. *Have normal clinical laboratory test results and* ***electrocardiogram (****ECG****) at Screening,*** *which are not considered to be clinically significant by the Investigator.*

7. *Females participating in the study:*

    a. *Either must be of non-childbearing potential [surgically sterilized: hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit] or postmenopausal. Menopause is defined as being amenorrhoeic for at least 2 years with plasma follicle-stimulating hormone (FSH) levels in the post-menopausal range at screening, based on the central laboratory's rang****es; OR***

    b. ***Females of child-bearing potential mus****t have a negative pregnancy test and be not breastfeeding at Screening and use either abstinence or an accepted contraception method during the treatment period and for an additional period of 30 days after the end of investigational treatment. For this study, accepted contraception methods include:*

        i. *condom plus spermicide*

        ii. *condom plus diaphragm*

        iii. *condom plus cervical cap or female condom*

        iv. *hormonal contraceptives*

        v. *intrauterine device*

        vi. *partner vasectomy and a use of barrier contraception methods*

8. *If male, subject must be surgically sterile or practicing at least 1 of the following methods of contraception, from initial study drug administration through 90 days after administration of the last dose of study drug:*

    a. *Have had a vasectomy (at least 6 months earlier);*

    b. *Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream with or without a diaphragm);*

    c. *Partner use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal) for at least 3 months prior to study drug administration;*

    d. *Partner use of an intrauterine device;*

    e. *Complete abstinence from sexual intercourse;*

f. *Male subjects not practicing complete abstinence must use a condom as a required form of birth control (in addition to at least 1 of the other methods listed above, if desired) in order to protect partners of male participants from exposure to study drug.*

9. *If male, subject must agree to abstain from sperm donation through 90 days after administration of the last dose of investigational drug.*

Section 5.2.2 - Exclusion Criteria

Original Wording

A subject will be excluded from the study if he or she meets the following criteria:

1. *Are pregnant or lactating.*
2. *Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or neurological disorders which, in the opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.*
3. *Clinically significant abnormal findings on physical examination or vital signs as determined by the PI.*
4. *Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.*
5. *History or presence of psychiatric or neurological disease or condition as determined by the PI.*
6. *History of seizures.*
7. *Subject with any history or current evidence of suicidal behavior.*
8. *Unwilling to complete any planned study assessments.*
9. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*
10. *Have received treatment with an investigational drug or device within 30 days prior to Screening.*
11. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
12. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
13. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*

14. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*

15. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:*

    a. *Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)*

    b. *QTcF interval > 450 msec for males and females*

    c. *PR interval ≥ 200 msec*

    d. *Intraventricular conduction delay with QRS duration > 120 msec*

    e. *Evidence of second- or third-degree atrioventricular block (AVB)*

    f. *Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB*

16. *Any subject who has a positive Urine Drug Screen test on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*

17. *Any subject who has an Alcohol Breathalyzer test result deemed positive by the Investigator (Principal Investigator or Sub-Investigator) on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*

Revised Wording

A subject will be excluded from the study if he or she meets the following criteria:

1. *Are pregnant or lactating.*

2. *Have a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or neurological disorders which, in the opinion of the Investigator, increases the risk of the study drug or may confound the interpretation of study measures.*

3. *Clinically significant abnormal findings on physical examination or vital signs as determined by the* ***Principal Investigator (****PI****).***

4. *Individuals with pacemakers, aneurysm clips, shrapnel, or other restricted implanted metallic devices will be excluded from study. All subjects complete the standard MRI screening questionnaire prior to MRI.*

5. *History or presence of psychiatric or neurological disease or condition as determined by the PI.*

6. *History of seizures.*

7. *Subject with any history or current evidence of suicidal behavior.*

8. *Unwilling to complete any planned study assessments.*

9. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*

10. *Have received treatment with an investigational drug or device within 30 days prior to Screening.*

11. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*

12. *Any subject who is known to be allergic to the study drug or any components of the study drug.*

13. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*

14. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*

15. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening:*

    a. *Heart rate < 40 bpm and > 100 bpm (based on the ECG reading)*

    b. *QTcF interval > 450 msec for males and females*

    c. *PR interval ≥ 200 msec*

    d. *Intraventricular conduction delay with QRS duration > 120 msec*

    e. *Evidence of second- or third-degree atrioventricular block (AVB)*

    f. *Electrocardiographic evidence of complete left bundle branch block (LBBB), complete right bundle branch block (RBBB), or incomplete LBBB*

Note: If the PI determines that an abnormal ECG is borderline, the PI may conduct an additional ECG. Clinically significant abnormal findings and/or evidence cardiac abnormalities (see 15 a-f) on the second ECG will be exclusionary.

16. *Any subject who has a positive Urine Drug Screen test on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub-Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*
17. *Any subject who has an Alcohol Breathalyzer test result deemed positive by the Investigator (Principal Investigator or Sub-Investigator) on the Day 0 or Day 1 Visit, unless in the Investigator's (Principal Investigator or Sub Investigator) documented opinion, the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results. The Investigator (Principal Investigator or Sub-Investigator) must provide their documented opinion to the Sponsor's Medical Monitor, and then the Sponsor (CMO) within 24 hours of their decision.*

Section 6.3 – Treatment Administration

Original Wording

Subjects from Cohorts 1-3 will be dispensed LB-102 capsule(s) based on their assigned treatment at 9 AM (±1 hour) on Day 1. For Cohort 4, subjects will receive LB-102 capsules BID at 9 AM and 9 PM (±1 hour) from Days 1-4, and once at 9 AM (±1 hour) on Day 5. 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. Subjects must fast approximately 12 hours prior to receiving the first dose of LB-102.

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)*

Revised Wording

*Subjects from Cohorts 1-3 will be dispensed LB-102 capsule(s) based on their assigned treatment at 9 AM (±1 hour) on Day 1. For Cohort 4, subjects will receive LB-102 capsules BID at 9 AM and 9 PM (±1 hour) from Days 1-**34**, and once at 9 AM (±1 hour) on Day **~~45~~**. 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. Subjects must fast approximately 12 hours prior to receiving the first dose of LB-102.*

*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~~ all previous cohort(s) (PET data from at least 3 subjects per cohort)**are obtained.*

Cohort	***Treatment***
1 (n=4)	*LB-102 50 mg x 1 day*
2 (n=4)	*LB-102 **~~XX~~100 mg** x 1 day*
3 (n=4)	*LB-102 **~~XX~~75 mg** x 1 day*
4 (n=4)	*LB-102 XX mg, **34** x BID (Days 1-**34**) and 1 x QD (Day **~~45,~~** AM dose; i.e., a total of **~~79~~** doses)*

Section 7.3.3 - Treatment Evaluation (Visit 3, Days 1-4)

Original Wording

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

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.*

Revised Wording

Section 7.3.3 - Treatment Evaluation (Visit 3, *Days 1-**~~45~~**)*

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

*The following procedures will be performed on Days 1-**~~45~~**:*

- *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-**~~45~~** (AM **dose** only on Day **~~45~~**).*
- *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 **~~45~~** 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; **~~dependent on data from Cohorts 1-3~~2.5 h (±30 min) post LB-102 dose**).*
- *Undergo post-dose PET/CT scan (scan 3; **~~dependent on data from Cohorts 1-3~~7.5 h (±30 min) post LB-102 dose**).*
- *Subjects will be monitored on an in-patient basis beginning on Day 1 until completion of the final scan on Day **~~5~~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, **3,** 4, 8, **~~and~~** 24, **and 25** h (Day 2).*
- *On Day 4 plasma samples for PK analysis at pre-dose and at the following times post dose (±15 min): 0.5, 1, 2, **3,** 4, and 8 h.*

Section 7.3.4 - Discharge (Visit 4, Day 5)

Original Wording

Section 7.3.4 - Discharge (Visit 4, Day 6)

The following procedures will be performed on Day 6:

- *Vital signs (at the time of the PET scan, ±30 min).*
- *Undergo post-dose PET/CT scan (scan 4; 23.5 h (±30 min) post LB-102 dose).*
- *12-lead ECG (24 h post-dose, ±30 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

*Section 7.3.4 - Discharge (Visit 4, Day **56**)*

*The following procedures will be performed on Day **56**:*

- *Vital signs (at the time of the PET scan, ±30 min).*
- *Undergo post-dose PET/CT scan (scan 4; 23.5 h (±30 min) post LB-102 dose).*
- *12-lead ECG (24 h post-dose, ±30 min).*
- *On Day **56** plasma samples for PK analysis at the following times post dose (±15 min): 24 **and 25** 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 7.3.5 - Follow-Up Visit (Visit 5, Day 6)

Original Wording

Section 7.3.5 - Follow-Up Visit (Visit 5, Day 7)

Revised Wording

*Section 7.3.5 - Follow-Up Visit (Visit 5, Day **67**)*

Section 7.3.6 – Pregnancy Follow-Up Visit (Visit 6, Day 34)

Original Wording

Section 7.3.6 – Pregnancy Follow-Up Visit (Visit 5, Day 35)

Revised Wording

*Section 7.3.6 – Pregnancy Follow-Up Visit (Visit 5, Day **3435**)*

Section 8.1 – Dopamine PET Receptor Measures

Original Wording

The PET-CT Vision will be the primary research scanner employed (Biograph as a back-up scanner should there be any delayed down time for the former PET scan). Following a CT attenuation scan, each research subject will receive the IV bolus high specific activity ^{11}C Raclopride (15mCi) followed immediately by dynamic scans of about 30 frames in increasing length from about 20-30 sec to up to 3 minutes in length over 90 minutes in list mode and then framed up to about 30-32 frames on PET-CT vision.

Regions of interest (ROIs) will be drawn on PET images using the co-registered structural MRI. ROIs will be placed on the right and left caudate nuclei, putamen, and cerebellar cortices. Time-activity curves (TACs) will be obtained for the ROIs over the entire dynamic scan described above, and decay corrected for the time after tracer injection. Each PET scan for each of the chosen regions (caudate, putamen, thalamus and temporal cortex) will be used as the target region (highest concentration of D2/D3 receptors) and the cerebellum (devoid of Dopamine D2/D3 receptors) will be used as the reference region and a binding potential (BP_{ND}) (Innis et al., 2007) at each of the four scans using established reference tissue kinetic models as Dr. Wong has employed in the past (e.g., SRTM, MRTM2, etc.) (Wong et al., 2013).

Revised Wording

*The PET-CT Vision will be the primary research scanner employed (Biograph as a back-up scanner should there be any delayed down time for the former PET scan). Following a CT attenuation scan, each research subject will receive the IV bolus high specific activity ^{11}C-Raclopride (15mCi **±15%**) followed immediately by dynamic scans of about 30 frames in increasing length from about 20-30 sec to up to 3 **min** in length over 90 **min** in list mode and then framed up to about 30-32 frames on PET-CT vision.*

***A standard template region of interest (ROI; Hammers et al., 2003) will be used following these steps: T1-weighted MR images will be used for co-registration of PET. Next, the co-registered PET images will be normalized into a standard space so that the standard template ROI definitions can be used to extract the time-activity curve and subsequent ROI occupancy calculations. This way, ROI-specific measures are consistent across subjects and can be fairly compared.** ROIs will be placed on the right and left caudate nuclei, putamen, **thalamus, temporal cortex,** and cerebellar cortices. Time-activity curves (TACs) will be obtained for the ROIs over the entire dynamic scan described above, and decay corrected for the time after tracer injection. Each PET scan for each of the chosen regions (caudate, putamen, thalamus and temporal cortex) will be used as the target region (highest concentration of D2/D3 receptors) and the cerebellum (devoid of Dopamine D2/D3 receptors) will be used as the reference region and a binding potential (BP_{ND}) (Innis et al., 2007) at each of the four scans using established reference tissue kinetic models as Dr. Wong has employed in the past (e.g., SRTM, MRTM2, etc.) (Wong et al., 2013).*

Section 8.2 – Dopamine Receptor Occupancy

Original Wording

LB-102 binding potential and dopamine receptor occupancy will be measured as the amount of ^{11}C 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 1-2. 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 a 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 will be measured as the amount of ^{11}C-Raclopride displaced by LB-102 using PET at Day 0 (baseline), and at 2.5, 7.5, and 23.5 hours **(±30 min)** post oral dose of LB-102 for Cohorts 1-2. For Cohort 3, PET scans will occur at Day 0 (baseline), 2.5, 23.5, and 47.5 hours **(±30 min)** 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 **~~4~~5** and **~~5~~6** (two on Day **~~4~~5 [2.5 and 7.5 h after last LB-102 dose, ±30 min]** **~~post LB-102 dose [at times determined following Cohorts 1-3]~~** and one on Day **~~5~~6** [23.5 h after last LB-102 dose, **±30 min**]) 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.*

Section 8.4 - Blood Collection

Original Wording

For each subject in Cohorts 1-3, up to 20 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 blood samples will be collected during the study for clinical and PK analysis. For each subject in Cohort 4, up to **~~2~~3**0 blood samples will be collected during the study for clinical and PK analysis.*

Section 8.6.1 - Dosing

Original Wording

Subjects in Cohort 1 will be administered a single oral dose of 50 mg and PET data will be acquired. This will be an adaptive, open-label study, and doses and PET scan times for Cohorts 2-4 will be based on observations in prior cohorts. Doses of LB-102 in this study will not exceed 150 mg.

Revised Wording

*Subjects in Cohort 1 will be administered a single oral dose of 50 mg and PET data will be acquired. This will be an adaptive, open-label study, and doses and PET scan times for Cohorts 2-4 will be **~~based on observations in prior cohorts~~** **determined after PET data from all previous cohort(s) (PET data from at least 3 subjects per cohort) are obtained**. Doses of LB-102 in this study will not exceed 150 mg.*

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

Original Wording

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.*

Revised Wording

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 ***24 (Cohort 1-3) or 5~~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 **~~5~~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.*

pharmaceuticals

ZACHARY PRENSKY

Zachary Prensky, CEO	Signature	6/8/21
		Date