
To: Medpace Clinical Pharmacology Unit

From: Zachary Prensky, CEO - LB Pharmaceuticals

Date: March 12, 2020

RE: Clarification Memo #4

LB-102-001: A Randomized, Double-Blinded, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LB-102 Administered Orally to Healthy Subjects

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The intent of this protocol clarification memo is to provide clarification for the LB-102-001 protocol (Protocol Version 3, 06 February 2020). All items listed below will be incorporated into the next amendment. The protocol amendment will be sent after it is filed with FDA.

***Section 1 - Endpoints - Safety***

***Original Wording***

- *ECG*
  - *Part A: Screening, Check-in, Day 1 at pre-dose and at 2, 4, 6, and 24 (Day 2) hours (±30 min) post-dose on Day 1.*
  - *Part B: Screening, Check-in, Day 1 prior to the first dose and at 2, 4, and 6 hours (±30 min) post first dose on Day 1 prior to first dose on Days 2-7, and Day 8 (24 hours post-dose Day 7; ±30 min).*

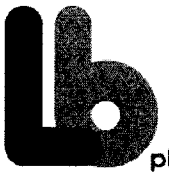
***Revised Wording***

- *ECG*
  - *Part A: Screening, Check-in, Day 1 at pre-dose and at **1**, 2, **3**, 4, **5**, 6, **8** and 24 (Day 2) hours (±30 min) post-dose on Day 1.* ***ECG will be measured once at each time point for Cohorts 1-4 and in triplicate (approximately 1 min apart) for Cohort 5.***
  - *Part B: Screening, Check-in, Day 1 prior to the first dose and at **1**, 2, **3**, 4, **5**, 6, **and 8** hours (±30 min) post first dose on Day 1 prior to first dose on Days 2-7, and Day 8 (24 hours post-dose Day 7; ±30 min).* ***ECG will be measured in triplicate (approximately 1 min apart) at each time point.***

***Section 1 - Diagnosis and Main Criteria for Eligibility***

***Original Wording***

***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, 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.*
4. *History or presence of psychiatric or neurological disease or condition.*
5. *History of seizures.*
6. *Subject with any history or current evidence of suicidal behavior.*
7. *Unwilling to complete any planned study assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS).*
8. *Recent history of alcohol or drug abuse (within the last two years).*
9. *Any use of tobacco or tobacco-containing products (cigarettes, pipes, etc.) within one month prior to Screening.*
10. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*
11. *Have received treatment with an investigational drug or device within 60 days prior to Screening.*
12. *Use of any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration.*
13. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
14. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
15. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*
16. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*
17. *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)*

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


***Revised Wording***

***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, 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.*
4. *History or presence of psychiatric or neurological disease or condition.*
5. *History of seizures.*
6. *Subject with any history or current evidence of suicidal behavior.*
7. *Unwilling to complete any planned study assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS).*
8. *Recent history of alcohol or drug abuse (within the last two years).*
9. *Any use of tobacco or tobacco-containing products (cigarettes, pipes, etc.) within one month prior to Screening.*
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11. *Have received treatment with an investigational drug or device within 60 days prior to Screening.*
12. *Use of any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration.*
13. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
14. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
15. *The subject has a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5% at Screening.*
16. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*
17. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening* ***(ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate (approximately 1 min apart) in Part A for Cohort 5 and Part B, mean values will be used for following criteria):***
    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)*

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


***Table 1: Schedule of Events for Part A***

***<u>Original Wording</u>***

***Table 1: Schedule of Events for Part A***

***Notes to the Schedule of Events for Part A:***

*BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic*

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

*[2] Vital Signs will be measured at Screening, Check-in, Day 1 at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 (±30 min) hours post-dose, and at Follow-up (Day 8).*

*[3] ECG will be measured at Screening, Check-in, Day 1 at pre-dose and 2, 4, 6, and 24 (±30 min) hours post-dose.*

*[4] Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 8 for all females of childbearing potential.*

*[5] FSH test for postmenopausal women.*

*[6] Plasma PK samples will be collected on Day 1 at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose.*

*[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.*


***Revised Wording***

***Table 1: Schedule of Events for Part A***

***Notes to the Schedule of Events for Part A:***

*BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic*

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

*[2] Vital Signs will be measured at Screening, Check-in, Day 1 at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 (±30 min) hours post-dose, and at Follow-up (Day 8).*

*[3] ECG will be measured at Screening, Check-in, Day 1 at pre-dose and* ***1,*** *2,* ***3,*** *4,* ***5,*** *6,* ***8,*** *and 24 (±30 min) hours post-dose.* ***ECG will be measured once at each time point for Cohorts 1-4 and in triplicate (approximately 1 min apart) for Cohort 5.***

*[4] Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 8 for all females of childbearing potential.*

*[5] FSH test for postmenopausal women.*

*[6] Plasma PK samples will be collected on Day 1 at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose.*

*[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.*


***Table 2: Schedule of Events for Part B***

***<u>Original Wording</u>***

***Table 2: Schedule of Events for Part B***

***Notes to the Schedule of Events for Part B:***

*BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic*

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

*[2] Vital Signs will be measured at Screening, Check-in, Day 1 prior to the first dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up.*

*[3] ECG will be measured at Screening, Check-in, Day 1 prior to the first dose and 2, 4, and 6 hours (±30 min) post first dose, prior to first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).*

*[4] Serum pregnancy test at screening and Urine pregnancy test at Day 0 and Day 15 for all females of childbearing potential.*

*[5] FSH test for postmenopausal women.*

*[6] Plasma PK samples will be collected on Day 1 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours (±15 min) post first dose, Days 2-6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose.*

*[7] Subjects are required to fast for approximately 12 hours prior to the first Day 1 dose. On Days 1-6, subjects will receive 2 doses per day (8 AM and 8 PM ±1 hour) separated by approximately 12 hours. On Day 7, subjects will receive 1 dose (8 AM ±1 hour).*

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


***Revised Wording***

***Table 2: Schedule of Events for Part B***

***Notes to the Schedule of Events for Part B:***

*BMI = Body Mass Index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; FSH = Follicle-Stimulating Hormone; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetic*

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

*[2] Vital Signs will be measured at Screening, Check-in, Day 1 prior to the first dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up.*

*[3] ECG will be measured* ***in triplicate (approximately 1 min apart)*** *at Screening, Check-in, Day 1 prior to the first dose and* ***1,*** *2,* ***3,*** *4,* ***5,*** *6,* ***and 8*** *hours (±30 min) post first dose, prior to first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).*

*[4] Serum pregnancy test at screening and Urine pregnancy test at Day 0 and Day 15 for all females of childbearing potential.*

*[5] FSH test for postmenopausal women.*

*[6] Plasma PK samples will be collected on Day 1 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours (±15 min) post first dose, Days 2-6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose.*

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

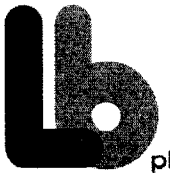

***Section 5.1 - Overall Study Design and Plan***

***Original Wording***

*In Part A, eligible subjects, in 5 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 40 subjects. Four (4) visits will occur as follows: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-3), and Follow-up (Visit 4, Day 8). The study procedures for these visits are presented in detail in Table 1. Dosage of LB-102 will begin at 50 mg/day and subsequent groups will administered 100, 200, 400, and 800 mg/day, respectively. In Cohort 1 (Part A), dosing of the first 2 subjects (1 active and 1 placebo) will commence at least 24 hours prior to the remaining 6 subjects. Dosing of the remaining subjects in the cohort may proceed if no safety issues are identified for the first 2 subjects. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 at 8 AM (±1 hour). For each cohort, blood samples for PK will be collected on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post-dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours (±30 min) post-dose, and at the Follow-up visit (Day 8). 12-lead ECG will be done on at Screening, Check-in, Day 1 at pre-dose and 2, 4, 6, and 24 hours (±30 min) post-dose. Clinical labs (hematology, chemistry, urinalysis) will be assessed at Screening, Check-in, Day 2, and Follow-Up. Hemoglobin A1c (HbA1c) will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 3, and Day 8. C-SSRS will be assessed at Screening and Day 3. Subjects will remain in the clinic from Check-in to Discharge on Day 3 for additional safety assessment and then return for a Follow-up Visit on Day 8. Subsequent groups will follow the same study procedures.*

*In Part B, eligible subjects, in 3 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 24 subjects. Four (4) visits will be scheduled for this study: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-9), and Follow-up (Visit 4, Day 15). The study procedures for these visits are presented in detail in Table 2. Dosage of LB-102 will be based on the PK observed in a minimum of two Part A cohorts. Subjects will receive 2 doses of placebo or LB-102, first dose at 8:00 AM (±1 hour) and second dose approximately 12 hours later, on Days 1-6 and one dose at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. The first dose on Day 1 will occur following a 12 hour, overnight fast. For each cohort, blood samples for PK will be collected at multiple timepoints starting on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose. On Days 2-6, blood samples for PK will be collected prior to the first dose. On Day 7 blood samples for PK will be collected pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, at pre-dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up. 12-lead ECG will be done at Screening, Check-in, Day 1 at pre-dose and 2, 4, and 6 hours (±30 min) post first dose, prior to first dose on Days 2-7, and on Day 8 (24 hours (±30 min) post-dose Day 7). Clinical labs will be assessed at Screening, Check-in, prior to first dose on Day 4, Day 8, and at Follow-up. HbA1c will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 9, and Day 15. C-SSRS will be assessed at Screening, Day 4, and Day 8. Subjects will remain in the clinic from Check-in to Discharge on Day 9 for additional safety assessment and then return for a Follow-up Visit on Day 15. Subsequent groups will follow the same study procedures.*

***Revised Wording***

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*In Part B, eligible subjects, in 3 cohorts, will be randomized on Day 1 (pre-dose) to placebo (n=2) or LB-102 (n=6) treatment for a total of 24 subjects. Four (4) visits will be scheduled for this study: Screening (Visit 1, Days -28 to -1), Check-in (Visit 2, Day 0), Treatment Evaluation (Visit 3, Days 1-9), and Follow-up (Visit 4, Day 15). The study procedures for these visits are presented in detail in Table 2. Dosage of LB-102 will be based on the PK observed in a minimum of two Part A cohorts. Subjects will receive 2 doses of placebo or LB-102, first dose at 8:00 AM (±1 hour) and second dose approximately 12 hours later, on Days 1-6 and one dose at 8 AM (±1 hour) on Day 7 for a total of 13 oral doses. The first dose on Day 1 will occur following a 12 hour, overnight fast. For each cohort, blood samples for PK will be collected at multiple timepoints starting on Day 1 at pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose. On Days 2-6, blood samples for PK will be collected prior to the first dose. On Day 7 blood samples for PK will be collected pre-dose and at 15, 30, and 45 minutes (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 hours (±15 min) post first dose. Vital signs will be recorded for each subject at Screening, Check-in, Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours (±30 min) post first dose on Day 1, at pre-dose and 2 hours (±30 min) post first dose on Days 2-7, 24 and 48 hours (±30 min) post Day 7 dose, and at Follow-up. 12-lead ECG will be done* ***in triplicate (approximately 1 min apart)*** *at Screening, Check-in, Day 1 at pre-dose and* ***1,*** *2,* ***3,*** *4,* ***5,*** *6,* ***and 8*** *hours (±30 min) post first dose, prior to first dose on Days 2-7, and on Day 8 (24 hours (±30 min) post-dose Day 7). Clinical labs will be assessed at Screening, Check-in, prior to first dose on Day 4, Day 8, and at Follow-up. HbA1c will be measured in serum at Screening. Prolactin will be measured in serum at Screening, Day 9, and Day 15. C-SSRS will be assessed at Screening, Day 4, and Day 8. Subjects will remain in the clinic from Check-in to Discharge on Day 9 for additional safety assessment and then return for a Follow-up Visit on Day 15. Subsequent groups will follow the same study procedures.*

***Section 5.4.2 – Exclusion Criteria***

***<u>Original Wording</u>***

*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.*
4. *History or presence of psychiatric or neurological disease or condition.*
5. *History of seizures.*
6. *Subject with any history or current evidence of suicidal behavior.*
7. *Unwilling to complete any planned study assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS).*
8. *Recent history of alcohol or drug abuse (within the last two years).*
9. *Any use of tobacco or tobacco-containing products (cigarettes, pipes, etc.) within one month prior to Screening.*
10. *Have a history of blood donation in excess of 500 mL of blood within 30 days prior to Screening.*
11. *Have received treatment with an investigational drug or device within 60 days prior to Screening.*
12. *Use of any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration.*
13. *Have a positive test for Human Immunodeficiency Virus (HIV) antibodies 1 and 2, Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus (HCV) antibody.*
14. *Any subject who is known to be allergic to the study drug or any components of the study drug.*
15. *The subject has a fasting blood glucose ≥126 mg/dL or hemoglobin A1C ≥6.5% at Screening.*
16. *The subject has a history of QT prolongation or dysrhythmia or a family history of prolonged QT interval or sudden death.*
17. *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*

***Revised Wording***

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

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

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

15. *The subject has a fasting blood glucose ≥126 mg/dL or hemoglobin A1C ≥6.5% at Screening.*

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

17. *Clinically significant abnormal finding on ECG and/or evidence of any of the following cardiac conduction abnormalities at Screening* ***(ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate (approximately 1 min apart) in Part A for Cohort 5 and Part B, mean values will be used for following criteria)****:*

    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*

***Section 7.1.1 - Screening (Visit 1, Days -28 to -1)***

***Original Wording***

*The following procedures will be performed:*

- *Administration of informed consent.*
- *Review inclusion and exclusion criteria.*
- *Record medical history, including prior and current therapies (e.g., prescription and non-prescription concomitant medications).*
- *Collect demographic information.*
- *Physical examination including weight, height, and BMI.*

- *Vital signs.*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).*
    - **Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.*
- *12-lead ECG.*
- *Alcohol Breathalyzer.*
- *Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).*
- *C-SSRS*

***Revised Wording***

*The following procedures will be performed:*

- *Administration of informed consent.*
- *Review inclusion and exclusion criteria.*
- *Record medical history, including prior and current therapies (e.g., prescription and non-prescription concomitant medications).*
- *Collect demographic information.*
- *Physical examination including weight, height, and BMI.*
- *Vital signs.*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).*
    - **Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.*
- *12-lead ECG.* ***In Part A, ECG will be measured once at each time point for Cohorts 1-4 and in triplicate (approximately 1 min apart) for Cohort 5.***
- *Alcohol Breathalyzer.*
- *Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).*


- *C-SSRS*

***Section 7.1.3 - Treatment Evaluation (Visit 3, Day 1)***

***Original Wording***

*Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:*

- *Administer dose of study drug.*
- *Vital Signs (at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post-dose).*
- *12-lead ECG (at pre-dose and at 2, 4, and 6 hours (±30 min) post-dose).*
- *Plasma sample for PK analysis (at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post-dose).*
- *Record concomitant medication use.*
- *Assess and record AEs.*

***Revised Wording***

*Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:*

- *Administer dose of study drug.*
- *Vital Signs (at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post-dose).*
- *12-lead ECG (at pre-dose and at **1**, 2, **3**, 4, **5**, 6, **and 8** hours (±30 min) post-dose).*
- *Plasma sample for PK analysis (at pre-dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post-dose).*
- *Record concomitant medication use.*
- *Assess and record AEs.*

***Section 7.2.1 Screening (Visit 1, Days -28 to -1)***


***Original Wording***

*The following procedures will be performed:*

- *Administration of informed consent.*
- *Review inclusion and exclusion criteria.*
- *Record medical history, including prior and current therapies (e.g., prescription and non-prescription concomitant medications).*
- *Collect demographic information.*
- *Physical examination including weight, height, and BMI.*
- *Vital signs.*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).*
    - **Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.*
- *12-lead ECG.*
- *C-SSRS.*
- *Alcohol Breathalyzer.*
- *Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).*

***Revised Wording***

*The following procedures will be performed:*

- *Administration of informed consent.*
- *Review inclusion and exclusion criteria.*
- *Record medical history, including prior and current therapies (e.g., prescription and non-prescription concomitant medications).*
- *Collect demographic information.*
- *Physical examination including weight, height, and BMI.*

- *Vital signs.*
- *Collect blood and urine samples for clinical laboratory tests (hematology, clinical chemistry, urinalysis, HbA1c, prolactin*, urine drug screen, and HIV, HBsAg, and HCV screen).*
    - **Prolactin note: This result will serve as the baseline for assessing potential post-dose changes and will not be de-identified.*
- *12-lead ECG.* ***In Part B, ECG will be measured in triplicate (approximately 1 min apart) at each time point.***
- *C-SSRS.*
- *Alcohol Breathalyzer.*
- *Serum pregnancy test for all females of childbearing potential (FSH test for postmenopausal women).*

***Section 7.2.7 – Treatment Evaluation (Visit 3, Day 1)***

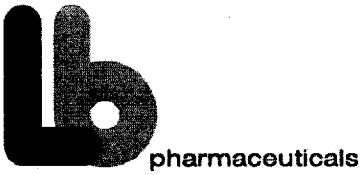
***Original Wording***

*Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:*

- *Administer study drug.*
- *Vital Signs (prior to the first dose and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post first dose).*
- *12-lead ECG (prior to the first dose and at 2, 4, and 6 hours (±30 min) post first dose).*
- *Plasma sample for PK analysis (prior to the first dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose).*
- *Record concomitant medication use.*
- *Assess and record AEs.*

***Revised Wording***

*Subjects are considered randomized after all pre-dose evaluations are completed, including review of admission laboratory results, and the subject remains eligible. The following procedures will be performed on Day 1:*




- *Administer study drug.*
- *Vital Signs (prior to the first dose and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±30 min) post first dose).*
- *12-lead ECG (prior to the first dose and at **1**, 2, **3**, 4, **5**, 6, **and 8** hours (±30 min) post first dose).*
- *Plasma sample for PK analysis (prior to the first dose, 15, 30, and 45 minutes (±5 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 hours (±15 min) post first dose).*
- *Record concomitant medication use.*
- *Assess and record AEs.*

***Section 8.5.6 - QT Prolongation Stopping Criteria***

***Original Wording***

*Dosing of an individual subject will cease if any of the following criteria are met:*

- *An increase in QTcF to > 500 msec for male and female subjects.*

*OR*

- *An increase in QTcF of > 60 msec over baseline.*

*A confirmation of an abnormal finding meeting the stopping criteria will be required within 15 minutes of the initial QTcF reading.*

***Revised Wording***

*Dosing of an individual subject will cease if any of the following criteria are met:*

- *An increase in QTcF to > 500 msec for male and female subjects.*

*OR*

- *An increase in QTcF of > 60 msec over baseline.*

***ECG will be measured once in Part A for Cohorts 1-4. ECG will be measured in triplicate (approximately 1 min apart) in Part A for Cohort 5 and Part B, mean QTcF values will be used for Stopping Criteria.** A confirmation of an abnormal finding meeting the stopping criteria will be required within 15 minutes of the initial QTcF reading.*

***Section 8.5.11 - Electrocardiogram***

pharmaceuticals

***Original Wording***

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

*Part A: Screening, Check-in, Day at pre-dose and 2, 4, 6, and 24 hours (±30 min) post-dose.*

*Part B: Screening, Check-in, Day 1 Pre-dose and 2, 4, and 6 hours (±30 min) post-dose, prior to the first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).*

***Revised Wording***

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

*Part A: Screening, Check-in, Day* ***1*** *at pre-dose and* ***1,*** *2,* ***3,*** *4,* ***5,*** *6,* ***8,*** *and 24 hours (±30 min) post-dose.* ***ECG will be measured once at each time point for Cohorts 1-4 and in triplicate (approximately 1 min apart) for Cohort 5.***

*Part B: Screening, Check-in, Day 1 Pre-dose and* ***1,*** *2,* ***3,*** *4,* ***5,*** *6,* ***and 8*** *hours (±30 min) post-dose, prior to the first dose on Days 2-7, and Day 8 (24 hours (±30 min) post Day 7 dose).* ***ECG will be measured in triplicate (approximately 1 min apart) at each time point.***

ZACHARY PRENSKY

Zachary Prensky, CEO | Signature | 3/13/2020 Date