STUDY PROTOCOL AND STATISTICAL ANALYSIS
PLAN
13 December 2019 FINAL

# A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED INSULIN TOLERANCE TEST STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF PITOLISANT IN PATIENTS WITH TYPE 1 DIABETES

PROTOCOL NUMBER FPITO-T1D-01.01

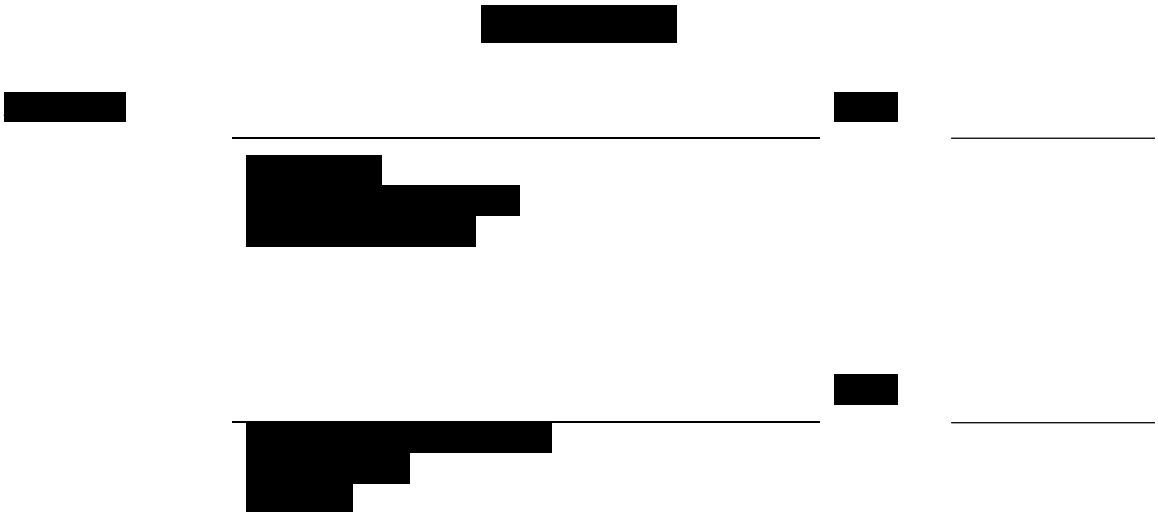
SPONSORED BY

Ferox Therapeutics LLC

PREPARED BY

## DOCUMENT VERSION CONTROL

| Version Number | Date | Comments/Changes |
|---|---|---|
| 1.0 | 13 December 2019 | Original |



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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ARS | abbreviated study report |
| ATC | Anatomical Therapeutic Chemical |
| BMI | body mass index |
| CGM | continuous glucose monitor(ing) |
| CRU | clinical research unit |
| DKA | diabetic ketoacidosis |
| ECG | electrocardiogram |
| GAD | generalized anxiety disorder |
| HbA1c | glycosylated hemoglobin |
| HIV | human immunodeficiency virus |
| HYPO Log | hypoglycemia log |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| ITT | insulin tolerance test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MITT | Modified Intent to Treat |
| PCSV | potentially clinically significant value |
| PHQ | Patient Health Questionnaire |
| PT | preferred term |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOC | system organ class |
| T1D | type 1 diabetes |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |

# 1. PURPOSE OF THE ANALYSES

The statistical analysis plan (SAP) has been developed based on the Ferox Therapeutics, LLC (Ferox) protocol FPITO-T1D-01.01 (April 29, 2019). The SAP contains detailed information to aid in the implementation of the statistical analyses and reporting of the study results for use in the abbreviated study report (ASR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be analyzed and the patient characteristics and parameters that will be evaluated. The details of the specific statistical methods that will be used are provided in this SAP.

# 2. PROTOCOL SUMMARY

## 2.1 Study Objectives

### 2.1.1 Primary Objectives

In subjects with type 1 diabetes (T1D) and on insulin for ≥ 4 years.

- To determine the effect of 7 days of pitolisant treatment on peak glucagon response to hypoglycemia during an insulin tolerance test (ITT)
- To assess the safety and tolerability of pitolisant administered orally for 7 days

### 2.1.2 Secondary Objectives

- To determine the effect of pitolisant on time to return to euglycemia during the ITT
- To determine the effect of pitolisant on the plasma glucose nadir during the ITT
- To determine the effect of pitolisant on plasma glucose area under the curve during the ITT

## 2.2 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled parallel study design to be conducted in patients with T1D to determine the effect of pitolisant on glucagon secretion during insulin-induced hypoglycemia.

Pitolisant 36 mg per day or placebo will be administered daily orally for 7 days. Patients may have their study drug dose adjusted downward at Visit 4 to 18 mg if the 36 mg dose is not tolerated.

Patients will undergo screening and baseline evaluation for study eligibility from day -21 (Visit 1) to day -1 (Visit 3). Eligible patients will have CGM (Dexcom G6) instruction and sensor placement on day -9 (Visit 2) and will continue to wear the study CGM until day -1 (Visit 3). Glucose values will be masked to patients and select study staff evaluating patient adverse events (AEs). Study staff will assess CGM data sufficiency at Visit 3 and patients with data sufficiency greater than 70% will be admitted to the clinical study unit for randomization and the baseline ITT the following morning.

Eligible patients will be admitted the night before the baseline ITT study, where they will receive an overnight continuous intravenous (IV) infusion of regular insulin to maintain glucose levels at target range (100–120 mg/dL) on the morning of the ITT. The ITT will not begin if three consecutive glucose determinations made every 5 minutes are outside

the 100-120 mg/dL range. The continuous IV insulin infusion also must not have been adjusted by more than approximately 10% during the final hour before beginning the ITT.

All patients will be studied after an overnight fast and in the supine position. In the morning of the baseline ITT, two baseline blood samples 10 minutes apart will be obtained for plasma glucose and glucagon. Plasma and serum samples will be archived.

Site personnel having direct contact with patients will be blinded to patient treatment assignments. Only the study site pharmacist and Ferox study personnel will be unblinded to treatment assignments. At least one study nurse, Principal Investigator (PI), and one study physician will be unblinded to bedside glucose monitoring to manage insulin dosing during the inpatient periods. The study PI who is conducting the ITT and the physician assessing AEs will remain blinded to treatment assignment. Plasma glucose and glucagon will be masked to all site personnel until the end of the study. Safety and tolerability will be assessed by treatment-emergent adverse events (TEAEs), physical exam, vital signs, electrocardiogram (ECG), and laboratory and clinical evaluation. Patients will be asked to report all AEs experienced from the time of informed consent until their end of study visit. Hypoglycemia will be further assessed using the Hypoglycemia Log (HYPO Log).

Serum and plasma samples will be aliquoted and archived for additional research studies.

Up to 14 patients will be enrolled to obtain 12 evaluable patients. Two additional patients may be randomized to replace patients who drop out prior to the first ITT.

The study duration is up to 37 days.

## 2.3 Study Population

Men and women, ages 18-65 years inclusive, with a history of T1D and on insulin for 4 or more years with glycosylated hemoglobin (HbA1c) ≤ 10.0%. Patients with a history of hypoglycemia unawareness, cardiovascular disease, or recent (7 days) antihistamine intake will be excluded. Women of childbearing potential must use effective methods of pregnancy prevention.

Additional inclusion and exclusion criteria for the study are enumerated in Section 4.2 of the protocol.

## 2.4 Treatment Regimens

Pitolisant 36 mg per day or placebo will be administered daily orally for 7 days. Patients may have their study drug dose adjusted downward at Visit 4 to 18 mg if the 36 mg dose is not tolerated.

## 2.5 Treatment Group Assignments or Randomization

Up to 14 patients will be randomized in a 2:1 ratio to receive either pitolisant or placebo according to a randomization scheme provided by the unblinded pharmacist (or qualified designee). All site personnel will be blinded to subject treatment assignment, except for the designated study pharmacist(s). Ferox study personnel will be unblinded to subject treatment assignment. Unblinding of treatment assignment for a subject may be necessary due to a medical emergency or any other significant medical event (e.g., pregnancy).

## 2.6 Sample Size Determination

A sample size of 8 pitolisant and 4 placebo subjects is sufficient to evaluate the efficacy of pitolisant. Patients who drop out of the study without completing the initial ITT may be replaced but the number of replacements will not exceed 2. The study is 80% powered at a two-sided 0.05 alpha level and is predicted to detect a peak glucagon of 208 pg/mL in the pitolisant group, assuming the placebo group has a peak of 123 pg/mL, with placebo having a mean change of 65 and a SD of change of 49 pg/mL, and both have a baseline glucagon of 58±41 pg/mL

See protocol Section 9.2 for justification of sample size.

# 3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

Tabular summaries will include a column for each treatment group and a total column combining patients across all treatment groups.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)." All percentages will be rounded to one decimal place. If a count is 0, no percentage will be shown. If a percentage is 100%, 100.0% will be shown. To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a value in a particular category.

All continuous variables will be summarized using number of patients with non-missing data, mean, SD, minimum, maximum, and median. The mean and median will be reported to 1 more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.

All analysis will be performed using SAS® System version 9.4 or later.

Dates in listings will be displayed as yyyy-mm-dd (e.g., 2015-01-24).

Age will be calculated in years using the date of birth and the date of first dose as [(date of first dose – date of birth+1)]/365.25, rounded down to the nearest integer using the floor function.

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of the investigational product.

Laboratory values with "<" or ">" signs will be analyzed without the signs in tabular summaries.

# 4. ANALYSIS POPULATIONS

## 4.1 Safety Analysis Population

The safety analysis population includes all randomized subjects who receive at least one dose of randomized drug and will be based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the safety analysis set.

## 4.2 Modified Intent to Treat (MITT) Analysis Population

The MITT primary efficacy analysis population includes all randomized subjects who completed the baseline and day 7 ITT.

# 5. STUDY SUBJECTS

## 5.1 Disposition of Subjects

Summaries will be provided based on all screened subjects regardless of the treatment group.

- The number of screened subjects who signed the informed consent form (ICF)
- The number (n) and percentage (%) of subjects randomized
- The number (n) and percentage (%) of subjects not randomized
- The number (n) and percentage (%) of subjects who were not randomized by the reasons

Summaries will be provided based on all randomized subjects.

- The number of subjects randomized and randomized but not receiving study treatments.
- The number (n) and percentage (%) of subjects randomized and receiving study treatments
- The number (n) and percentage (%) of subjects who completed treatment and discontinued treatment, respectively, and the reasons for discontinuation
- The number (n) and percentage (%) of subjects who completed the study and discontinued the study, respectively, and the reasons for discontinuation

A single listing will be provided for subjects who failed during the screening period, who were randomized, and who were not randomized but received study treatments separately.

## 5.2 Protocol Deviations

Protocol deviations will be categorized into major or minor protocol deviations. A single listing of subjects with protocol deviations will be provided.

See Section 9.5 of the protocol for additional information on protocol deviations.

# 6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summaries of demographic and baseline characteristics and randomized subject disposition will be presented for pitolisant and placebo.

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to administration of the investigational product.

## 6.1 Demographic Characteristics

Demographic characteristics will include age, sex, race, weight, height, body mass index (BMI), age of onset of T1D, years on insulin, history of diabetic ketoacidosis (DKA), hypoglycemia frequency and severity, and diabetes complications. Age (years) will be calculated using the date of first dose and the date of birth. Race will have potential values of White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, or Other.

Demographic characteristics will be summarized in a table.

## 6.2 Medical History

Medical history will be collected at the Screening Visit. Medical history data will be coded using MedDRA version 22.0.

A listing for medical history will be provided by treatment group.

## 6.3 Prior and Concomitant Medications

Medication use will be collected at all visits.

Prior and concomitant medications will be coded using the WHODRUG Global Version B3 March 2019 World Health Organization (WHO) Drug Dictionary.

All prior and concomitant medications will be listed by subject. A flag will be added to the listing to denote a concomitant medication administered to treat an AE and a separate flag denoted if a concomitant medication was a prohibited medication.

The daily insulin dose taken by patients will be captured on their HYPO Log and recorded in an insulin-specific eCRF.

If the start date of a prior or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of investigational product, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

### 6.3.1 Prior Medications

Prior medications are defined as any medications with a start date prior to the first day of dosing.

### 6.3.2 Concomitant Medications

Concomitant medications are defined as any medications that are taken on or after the day of first dose of study drug. This includes medications that were started before the study and are ongoing during the study. In general, if it is not clear whether a medication is concomitant due to missing or incomplete medication start and/or end dates, the medication will be considered to be concomitant unless the non-missing portions of the start and end dates indicate otherwise.

# 7. MEASUREMENTS OF TREATMENT COMPLIANCE AND DRUG ADMINISTRATION

At Days 1, 3, and 7 subjects are to be dosed at the study site under the supervision of appropriate study personnel. At Days 2, 4, 5 and 6 patients will self-administer the study drug in the AM. Study drug adherence will be assessed at Day 3 and Day 6. All drug compliance records will be kept current and will be made available for inspection by the Collaborator and regulatory agency inspectors.

# 8. SAFETY EVALUATION

## 8.1 Overview of Safety Analysis Methods

The safety analyses will be performed using the safety analysis set for safety measures, which include adverse events (AEs), vital signs, clinical laboratory data, electrocardiograms (ECG), body weight, and physical exam.

Thresholds for treatment-emergent PCSV are defined in Appendix 4 of the protocol for laboratory variables, hematology variables, urinalysis, vital sign variables, and ECG variables.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be performed.

### 8.1.1 Primary Endpoint

1. Incidence and severity of treatment-emergent adverse events (TEAEs) through end of study (day 37)

Incidence and severity of treatment-emergent adverse events will be descriptively summarized by treatment group. Incidence tables will reflect a count and percentage of subjects experiencing at least 1 AE in each SOC, PT and grouping or severity. Evaluation will be performed on the safety analysis set.

## 8.2 Adverse Events

For safety variables, 2 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of investigational product.
- The on-treatment period is defined as the time from first dose of investigational product to the last study visit or early termination.

Treatment-emergent AEs (TEAEs) are AEs that develop or worsen in severity on or after the dosing of study treatment through the end of study. Non-treatment AEs are those that occur from signing the ICF up to the first dose of study drug. The half-life of the investigational product is 12 hours. AEs occurring between Day 10 and Day 16 are considered at or below detectable drug levels.

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Coding will be to the lowest level terms.

Primary SOCs will be sorted according to the order described in the Guideline on summary of product characteristics (December 1999, European Commission), with the

total overall classes coming first and labeled "Any class". Within each primary SOC, PTs will be sorted by decreasing frequency of investigational product.

If the start date of an AE is incomplete or missing, it will be assumed to have occurred on or after the first dose of investigational product, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

By-subject listings of AEs will include all events regardless of treatment emergence.

Rules for Severity and Relationship of Adverse Events

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

If a subject experiences the same adverse event multiple times, the event with the strongest severity or relationship to study drug will be counted.

Planned Summaries of Adverse Events

- Total number of TEAEs
- Total number of serious TEAEs
- Total number of study drug-related TEAEs
- The number (n) and percentage (%) of subjects with at least 1 TEAE
- The number (n) and percentage (%) of subjects with serious TEAEs
- The number (n) and percentage (%) of subjects with study drug-related TEAEs
- The number (n) and percentage (%) of subjects with TEAEs leading to discontinuation
- The number (n) and percentage (%) of subjects with TEAEs leading to death
- The number (n) and percentage (%) of subjects with TEAEs of special interest

An overall summary showing the number and percentage of subjects with a TEAE, a serious TEAE, a treatment- related TEAE, a TEAE leading to treatment discontinuation, a TEAE resulting in death, and a TEAE of special interest. This summary will be presented on an overall basis.

All percentages will use the number of safety analysis set subjects as the denominator.

No statistical tests will be performed on adverse events.

## 8.3 Patient Record Hypoglycemia

Subject recorded hypoglycemia in the HYPO Log will be defined as outlined below. Severe hypoglycemia events recorded in the Hypo Log by the subject that were not spontaneously reported may be used to report these AEs in the Hypo eCRF, if deemed a severe hypoglycemia event by the blinded investigator.

- Level 1: Glucose < 70 mg/dL and glucose ≥ 54 mg/dL
- Level 2: Glucose < 54 mg/dL
- Level 3: A severe event characterized by altered mental and/or physical status requiring assistance

## 8.4 Clinical Laboratory Evaluation

For continuous clinical laboratory test measurements, results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics; for categorical or ordinal data, frequencies and percentages will be provided for each category.

The number and percentage of patients with at least 1 post-baseline value outside the normal range will be summarized for each clinical laboratory test with a normal range supplied by the central lab.

The number and percentage of patients meeting the predefined criteria for potentially clinically significant value (PCSV) at any post-baseline time point, including unscheduled visits, will be summarized for each clinical laboratory test.

### 8.4.1 Pregnancy Tests

A serum pregnancy test will be administered at the Screening Visit. A urine pregnancy test will be administered at Day -1, Day 6, and Day 16.

## 8.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

### 8.5.1 Vital Signs

Vital signs will be measured at all visits and will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. Change from

baseline summaries will only include subjects with a baseline value and at least one post-baseline value. In addition, the number and percentage of subjects with at least 1 treatment-emergent PCSV at any post-baseline time point will be summarized and a listing for subjects with at least 1 treatment-emergent PCSV provided.

The following vital signs will be recorded during this study:

- Pulse rate
- Respiratory rate
- Blood pressure (systolic and diastolic in mmHg)
- Temperature

### 8.5.2 Physical Examinations

A complete physical examination will be conducted at the Screening Visit, Day 7, and Day 16.

### 8.5.3 12-Lead ECGs

12-lead ECGs will be obtained in triplicate at the Screening Visit, Day 1, Day 7, and at Day 16.

Electrocardiogram variables including ventricular heart rate (bpm), RR interval (msec), PR interval (msec), QRS interval (msec), QT interval (msec), and QTcF interval (msec) and will be listed by subject.

### 8.5.4 Other Safety Measures

Other safety measures include body weight.

# 9. EFFICACY EVALUATION

## 9.1 Handling of Dropouts or Missing Data

There will be no imputation for missing data.

## 9.2 Analysis Methods

The MITT analysis population will be used in all ITT related primary, secondary, and exploratory endpoints. The safety analysis population will be used for the safety and hypoglycemia endpoints. The primary hypothesis that in patients with T1D, treatment with pitolisant 36 mg once daily orally for 7 days will increase peak glucagon response to insulin-induced hypoglycemia will be analyzed using a t-test.

### 9.2.1 Primary Endpoint

1. Change in peak plasma glucagon during the ITT

The ITT will occur at baseline (Day 1) and at Day 7. Glucagon will be measured at timepoints -10, 0, 15,30, 45, 60, 90, 120, and 180 minutes and peak plasma glucagon will be identified for each subject at both baseline and Day 7. Change from baseline will be calculated for each subject.

Difference in mean change from baseline of peak plasma glucagon between treatment groups will be analyzed by the two-tailed t-test for independent samples of equal variance (pooled variance). Treatment difference results (p-value, 95% confidence interval) will be presented.

Mean change from baseline of peak plasma glucagon within treatment groups will be analyzed for each group by the two-tailed t-test for paired samples. Treatment difference results (p-value, 95% confidence interval) will be presented for each group.

Sample data distributions will be visually inspected for skewness and/or outliers. Non-parametric tests will be used if the sample data suggests that the t-test normality assumption cannot be defended.

No adjustments for multiple comparisons will be made. Both analyses will use PROC TTEST, SAS, version 9.4 or greater, SAS Institute, Inc., Cary, North Carolina.

A figure illustrating the time course of mean plasma glucagon by group will be presented for Day 1 and Day 7.

### 9.2.2 Secondary Endpoints

1. Time to return to plasma glucose ≥ 70 mg/dL during the ITT on Day 1 and Day 7
2. Plasma glucose nadir during the ITT on Day 1 and Day 7
3. Glucose area under the curve, calculated from time 0 minutes to 180 minutes for the ITT period on Day 1 and Day 7

The ITT will occur at baseline (Day 1) and at Day 7. Glucose will be measured at timepoints -10, 0, 15,30, 45, 60, 90, 120, and 180 minutes.

Summary statistics using n, mean, standard deviation, minimum, median, and maximum by treatment group will be provided for all secondary endpoints

Glucose area under the curve (AUC) is defined as the area under the glucose curve for the ITT period. It is calculated from time 0 to 180 minutes using the trapezoidal rule. A figure illustrating the time course of mean glucose plasma by group will be presented for Day 1 and Day 7.

### 9.2.3 Exploratory Endpoints

1. Glucagon area under the curve, calculated from time 0 minutes to 180 minutes for the ITT period on Day 1 and Day 7

2. Hypoglycemia counts < 54 mg/dL and ≥ 54 and < 70 mg/dL by Dexcom G6 CGM in each study period

Additional CGM exploratory endpoints:

a. Data sufficiency (% time CGM active)
b. Mean glucose
c. Standard deviation
d. Coefficient of variation
e. Time in ranges (< 54 mg/dL, < 70 mg/dL, 70-180 mg/dL, > 180 mg/dL, > 250 mg/dL)
   - For values < 54 mg/dL
     - average minutes/day
     - mean number of episodes/day/period
     - mean duration of each episode in minutes/day

Hypoglycemia will also be assessed using the Hypoglycemia Log (HYPO Log) which includes patient self-report of hypoglycemic events using their usual method of self-monitoring as well as their daily insulin dose. Summary statistics will be performed on

masked Dexcom G6 CGM data according to study period: baseline, on active treatment, and off treatment using the standard data reporting endpoints. However, this analysis may not by conducted if the primary endpoints are not met.

Glucagon area under the curve (AUC) is defined as the area under the glucagon curve for the ITT period. It is calculated from time 0 to 180 minutes using the trapezoidal rule.

## 10. OTHER ANALYSES

Not applicable.

# 11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

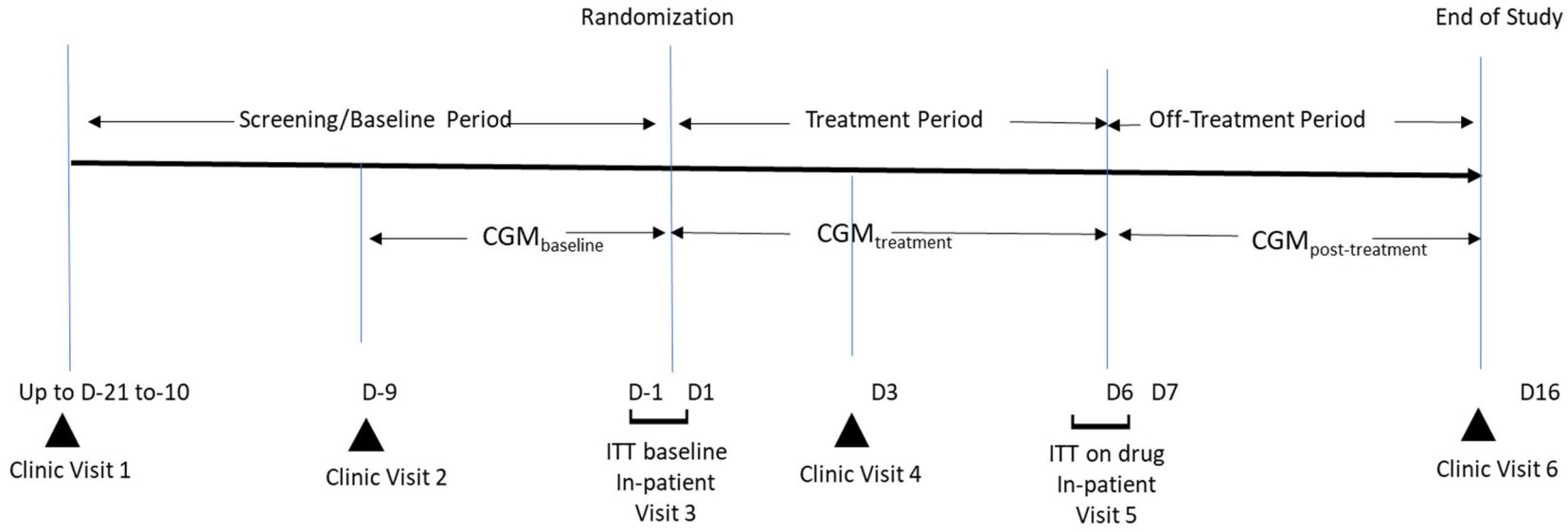
Not applicable.

## 12. REFERENCES

Not applicable.

# 13. APPENDICES

## 13.1 Study Flow Chart



## 13.2 Schedule of Events

| Activity | Screening | CGM | Inpatient Baseline ITT | | Out-patient | Resupply | Out-patient | Inpatient Treatment ITT | | Out-patient | End of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Visit 1** | **Visit 2** | **Visit 3** | | | **Visit 4** | | **Visit 5** | | | **Visit 6** |
| | *Day -21 to -10* | *Day -9* | *Day -1* | *Day 1* | *Day 2* | *Day 3* | *Day 4, 5* | *Day 6* | *Day 7* | *Day 8-15* | *Day 16* |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion | X | X | X | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | | X | | X | X | | X |
| Vital Signs | X | X | X | X | | X | | X | X | | X |
| Height, Weight, BMI [a] | X | | | X | | | | | X[a] | | X |
| Physical Examination [a] | X | | | | | | | | X | | X |
| 12-lead Electrocardiogram | X | | | X | | | | | X | | X |
| Adverse Events | | X | X | X | | X | | X | X | | X |
| PHQ-9 and GAD-7 | X | | | | | | | | | | |
| Admission to CRU | | | X | | | | | X | | | |
| Intravenous catheter placement | | | X | | | | | X | | | |
| Overnight Intravenous Insulin Infusion | | | X | | | | | X | | | |
| ITT [b] | | | | X | | | | | X | | |
| Randomization | | | | X | | | | | | | |
| Dispensing of Study Drug | | | | X | | X | | | | | |
| Administration of Study Drug | | | | X | X | X | X | X | X | | |
| Study Drug Adherence | | | | | | X | | X | | | |

| Activity | Screening | CGM | Inpatient Baseline ITT | | Out-patient | Resupply | Out-patient | Inpatient Treatment ITT | | Out-patient | End of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | | | Visit 4 | | Visit 5 | | | Visit 6 |
| | *Day -21 to -10* | *Day -9* | *Day -1* | *Day 1* | *Day 2* | *Day 3* | *Day 4, 5* | *Day 6* | *Day 7* | *Day 8-15* | *Day 16* |
| HbA1c [c] | X | | | | | | | | | | |
| C-peptide [c] | X | | | | | | | | | | |
| Hepatitis and HIV Screening[c] | X | | | | | | | | | | |
| Hematology (complete blood count)[c] | X | | | X | | | | | X | | X |
| Fasting Plasma Glucose [c,d] | X | | | X | | | | | X | | X |
| Blood Chemistry Panel[c] | X | | | X | | | | | X | | X |
| Fasting lipid Panel [c,d] | X | | | | | | | | | | X |
| Urinalysis (dip stick and microscopy)[c] | X | | | X | | | | | X | | X |
| Serum Pregnancy Test[c] | X | | | | | | | | | | |
| Urine Pregnancy Test | | | X | | | | | X | | | X |
| Glucagon[c] | X | | | X | | | | | X | | X |
| Histamine[c] | X | | | | | | | | | | |
| Archived Research Sample[c] | X | | | X | | | | | X | | X |
| Masked CGM training/education | | X | X | | | X | | X | | | |
| Masked CGM sensor insertion[e-g] | | X | X | | | | | X | | | |
| Masked CGM | | X | X | X | X | X | X | X | X | X | X |
| Masked CGM upload | | | X | | | | | X | | | X |
| Provide HYPO Log with instruction | X | X | | X | | X | | | X | | |

| Activity | Screening | CGM | Inpatient Baseline ITT | | Out-patient | Resupply | Out-patient | Inpatient Treatment ITT | | Out-patient | End of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Visit 1** | **Visit 2** | **Visit 3** | | | **Visit 4** | | **Visit 5** | | | **Visit 6** |
| | *Day -21 to -10* | *Day -9* | *Day -1* | *Day 1* | *Day 2* | *Day 3* | *Day 4, 5* | *Day 6* | *Day 7* | *Day 8-15* | *Day 16* |
| Patient to Record in HYPO Log | X | X | X | X | X | X | X | X | X | X | X |
| Turn in HYPO Log completed record | | X | X | | | X | | X | | | X |
| Discharge from CRU | | | | X | | | | | X | | |

BMI = body mass index; CGM = continuous glucose monitoring; CRU = clinical research unit; HbA1c = glycosylated hemoglobin; HIV = human immunodeficiency virus; HYPO Log = Hypoglycemia Log; ITT = insulin tolerance test

[a] Height and BMI captured at screening only, all other time points only weight is collected. Full physical exam at baseline and Day 16 or End of Study; Abbreviated physical exam at day 7.

[b] ITT Glucose must be 100-120 mg/dL; insulin dose during last hour of intravenous insulin must be stable (not >10% change); ITT sampling timepoints -10, 0, 15, 30, 45, 60, 90, 120, 180 for plasma glucose and glucagon. Study drug administered after ITT completed on day 1. Study drug administered 1 hour before ITT -10-minute blood draw on day 7.

[c] Laboratory samples will be sent to and analyzed at LabCorp with the exception of glucagon sample that will be sent to Mercodia. Histamine samples and archive research samples will be stored at the local laboratory until end of study.

[d] Laboratory samples to be obtained after an 8 hour fast.

[e] Day -9 to -1 baseline CGM period

[f] Day 1 to +6 on-drug CGM period

[g] Day 7 to +16 off-drug CGM period

## 14. ATTACHMENTS

Not applicable.