**Xeris Pharmaceuticals, Inc.**

**Statistical Analysis Plan**
Protocol No: XSMP-204
Product: Glucagon RTU
Version: 1.0
Date: 04 Dec 2019

# A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Parallel Study to Evaluate Glucagon RTU (Glucagon Injection) Compared to Standard of Care for the Prevention of Exercise-Induced Hypoglycemia During Regular Aerobic Exercise in Adults with Type 1 Diabetes



| | | |
|---|---|---|
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**REVISION HISTORY**

| Version | Date | Author | Reasons |
|---|---|---|---|
| 1.0 | 05 Dec 2019 | Roman Ganzha | Initial version |
| | | | |
| | | | |

# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| AOC | Area Over the Curve |
| $AUC_{0\text{-}xh}$ | Area under the plasma concentration vs time curve from time 0 to X hours post-dose (where x=1 hour, 2 hours, 4 hours post-dose). $AUC_{0\text{-}xh}$ is estimated using the trapezoidal method. |
| BGM | Blood Glucose Monitoring |
| BGMT | Blood Glucose Measurement |
| BMI | Body Mass Index |
| CBP | Childbearing potential |
| CGM | Continuous Glucose Monitoring |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV% | Coefficient of Variation expressed as a percentage |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| ER | Extended Analysis |
| FDA | United States Food and Drug Administration |
| GCP | Good Clinical Practice |
| HR | Heart Rate |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IG | Interstitial Glucose |
| IMP | Investigational Medicinal Product |
| ITT | Intent-to-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |

| **Abbreviation or special term** | **Explanation** |
|---|---|
| PP | Per Protocol |
| PROs | Patient Reported Outcomes |
| PT | Preferred Term |
| QTc | Corrected QT interval |
| QTcF | QT interval corrected for heart rate using Fridericia's method |
| RBC | Red Blood Cell |
| RTY | Ready To Use |
| SAE | Serious Adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| WBC | White Blood Cell |
| WHO | World Health Organization |
| YSI | Yellow Springs Instrument |

# INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide the details of the planned statistical analyses that were outlined within the protocol for the study "A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Parallel Study to Evaluate Glucagon Ready-to-Use (RTU) (Glucagon Injection) Compared to Standard of Care for the Prevention of Exercise-Induced Hypoglycemia During Regular Aerobic Exercise in Adults with Type 1 Diabetes", XSMP-204, version 4.0 dated 20 June 2019. The SAP will further define and expand those analyses. The SAP will take precedence over the protocol.

# 1. STUDY DETAILS

## 1.1 STUDY OBJECTIVES

### Primary Objectives

The primary objective of this study is:

1. To evaluate if the subcutaneous administration of Glucagon RTU (Glucagon Injection) just before exercise, with or without a 50% reduction in basal rate insulin, compared to a 50% basal rate insulin reduction alone, prevents the occurrence of hypoglycemia (i.e., blood glucose ≤ 70 mg/dL; 3.89 mmol/L) measured by blood glucose meter (BGM) during and after moderate-to-high intensity aerobic exercise by adult subjects with T1D in an outpatient setting.

### Secondary Objectives

1. To evaluate how Glucagon RTU (Glucagon Injection) contributes to prevention of hypoglycemia during exercise and post exercise recovery.
2. To evaluate the effect of Glucagon RTU (Glucagon Injection) on insulin utilization during exercise.
3. To evaluate the effect of Glucagon RTU (Glucagon Injection) on PROs: Barriers to Physical Activity in Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS-II), and Hypoglycemic Confidence Scale (HCS) after 12 weeks of outpatient exercise.

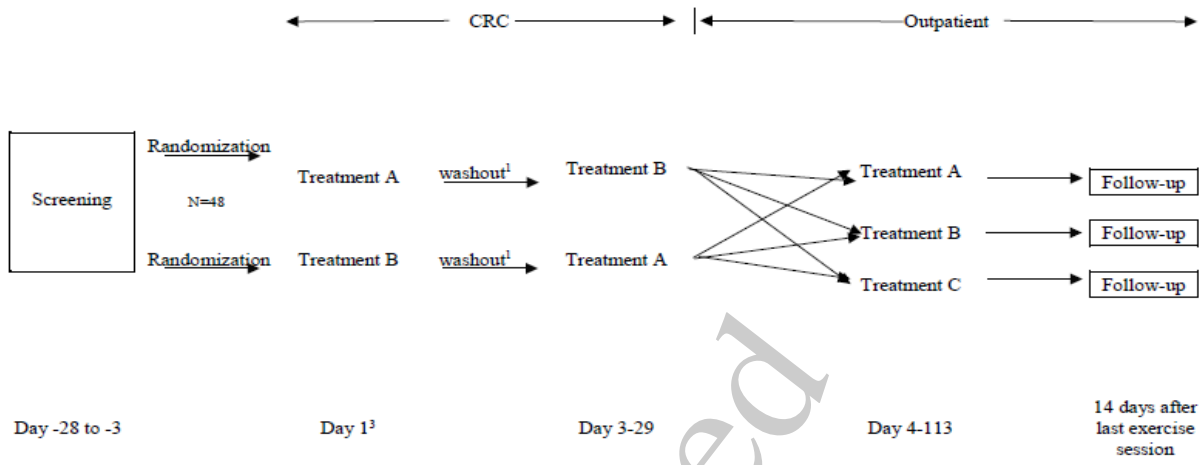
**Exploratory Objectives**

1. To evaluate the glycemic time in range associated with exercise sessions and post exercise.
2. To evaluate the impact of Glucagon RTU (Glucagon Injection) on the quantity of glucose tabs used over time during exercise sessions.
3. To evaluate weight loss or weight maintenance over time.
4. To examine food intake both before and after exercise.
5. To examine the effect of exercise and Glucagon RTU on overnight hypoglycemia following episodes of exercise.
6. To evaluate the effects of exercise and Glucagon RTU use upon changes in hemoglobin A1c.
7. To evaluate the intensity and duration of the frequent exercise sessions.
8. To evaluate overall frequency of aerobic exercise over study period.
9. To evaluate effects on exercise duration and intensity as well as daily activity metrics.

**1.2 STUDY DESIGN:**

This study is a randomized, placebo-controlled, double-blind, two-treatment, two-period, crossover comparison in a clinical research center (CRC) setting, followed by a randomized, placebo-controlled, partially double-blinded, 3-arm parallel comparison in an outpatient setting to evaluate the preliminary efficacy and safety of Glucagon RTU to prevent exercise-induced hypoglycemia (EIH) in adults with Type 1 diabetes mellitus (T1D), who perform regular, moderate-to-high intensity aerobic exercise.

**Figure 1. Schema of Study Design**






The CRC Stage will involve two daytime clinical research centers (CRC, or comparable setting) exercise sessions 2-28 days apart, in a morning exercise session, for the following treatment assignments:

- Insulin pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise placebo injection (30 µL vehicle), or
- Insulin pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise Glucagon RTU (30 µL active - 0.15 mg).

At Investigator discretion, the insulin pump rate can be reduced overnight based on subject's medical history for the duration of the study.

BGM assessments during CRC visits will be at -15, 0, 30, 45 and 75 minutes from the start of exercise. Venous Blood Glucose assessments (Yellow Springs Instrument [YSI] readings) during CRC visits will be at -15, 0, 15, 30, 45, 60 and 75 minutes from the start of exercise. Subjects will also wear unblinded continuous glucose monitoring (CGM) both the CRC and Outpatient Stages of the study.

The Outpatient Stage will be 12 weeks in duration during which subjects are randomized to one of three parallel treatment arms, two of which are double-blinded, and one is open-label.

During the Outpatient Stage, subjects will receive one of the following randomly assigned treatments:

- Insulin Pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise placebo injection (30 µL vehicle), or
- Insulin Pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise Glucagon RTU (30 µL active - 0.15 mg), or
- Pre-exercise Glucagon RTU (30 µL active - 0.15 mg) without pump changes.

Subjects will measure blood glucose using BGM at -15 and 0 minutes (just before exercise) to establish baseline, at 30 minutes of exercise, at the end of exercise, and 30 minutes post-exercise. Subjects will also wear unblinded CGM during the conduct of the study.

**Table 1. Schedule of Activities**

| **Assessment** | **Visit 1** | **Visit 2** | **Visit 3[o] CRC 1** | **Visit 4[o] CRC 2** | **Visits 5 to 10 Outpatient Phase** | **Visit 11 Follow-up[f] /ET** |
|---|---|---|---|---|---|---|
| | **Screening Day–28 to –3** | **CGM Placement Day –2 to –1** | **Treatment Period 1 (Days 1[a,b,c])** | **Treatment Period 2 Day 3 to 29[d]** | **Treatment Period 3 Day 4 to 113[e]** | |
| Informed consent | X | | | | | |
| Medical History/ Demographics | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| Concomitant medications (including insulin pump data) | X | X | X | X | X | X |
| Height, weight and physical examination | X | | | | | X |
| 12-lead ECG | X | | | | | X |
| Vital signs | X | | X | X | X | X |
| Urine pregnancy test | X | | X | X | X | X |
| Urine drug screen | X | | | | | |
| Hematology | X | | | | | X |
| Clinical chemistry | X | | | | | X |
| HbA1c | X | | | | | X |

| Assessment | Visit 1<br>Screening<br>Day–28 to –3 | Visit 2<br>CGM Placement<br>Day –2 to –1 | Visit 3[o]<br>CRC 1<br>Treatment Period 1<br>(Days 1[a,b,c]) | Visit 4[o]<br>CRC 2<br>Treatment Period 2<br>Day 3 to 29[d] | Visits 5 to 10<br>Outpatient Phase<br>Treatment Period 3<br>Day 4 to 113[e] | Visit 11<br>Follow-up[f] /ET |
|---|---|---|---|---|---|---|
| Plasma Glucose | X | | | | | X |
| C-peptide | X | | | | | X |
| Immunogenicity[g] | | | X | | X | X |
| CGM | | X[d] | X[h] | X[h] | X[h] | X[h] |
| Exercise[i,o] | | | X | X | | |
| BGM[k] | | | X | X[j] | X[j] | X[j] |
| Study drug administration | | | X | X[l] | X | |
| Wearable Activity Monitors (Fitbit Ionic and Polar Beat H10) | | | X[m] | X[m] | X[n] | X[n] |
| HBV, HCV, HIV Screen | X | | | | | |
| Outpatient Study Training | | | | X | | |
| Diary[i] | | | X | X | X | X |
| Glucose Tabs Log | | | X | X | X | X |
| Randomization | | | X | | | |
| 8-Hour fast | X | | X | X | | X |
| Venous blood glucose (YSI) | | | X | X | | |
| BAPAD-1 Questionnaire | | | X | | | X |
| Draize Scale | | | X | X | | |
| HFS | | | X | | | X |
| Hypoglycemia Confidence Scale | | | X | | | X |
| Injection Site Discomfort Description and Duration Questionnaire | | | X | X | | |
| Adverse event review | X | X | X | X | X | X |

*Visits will occur every 2 weeks during the out-patient phase. The visit window is +/- 3 days for the outpatient visits.

BAPAD-1 = Barriers to Physical Activity in Type 1 Diabetes Scale; BGM = blood glucose monitor; CRC = Clinical Research Center; CGM = continuous glucose monitor; ECG = electrocardiogram; HBV = hepatitis B

virus; HCV = hepatitis C virus; HFS = Hypoglycemia Fear Survey; HIV = human immunodeficiency virus; YSI = Yellow Springs Instrument

a. As long as the subject has 2 days of rest between each CRC visit.
b. Subjects will be instructed not to exercise between Visit 2 and Visit 3.
c. Questionnaires to be completed are Barriers to Physical Activity Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS) and Hypoglycemia Confidence Scale (HCS).
d. CGM will be placed approximately 24-48 hours prior to data collection at CRC Visit 2.
e. Collection timepoints ± 2 minutes are: -15 minutes, 0 minutes (just before initiation of exercise), and at 15, 30, 45, 60 and 75 minutes after initiation of exercise.
f. Follow-Up occurs 14 days after the last exercise period.
g. An immunogenicity sample will be drawn before the first dose of investigational product, every four weeks (28 days +/- 2 days) and at the End of Study visit.
h. CGM data will be downloaded.
i. During the CRC Phase of the study, subjects will perform moderate-to-high-intensity exercise of at least 45 minutes duration, with each exercise session separated by at least 2 days during the inpatient phase of the study. During the Outpatient Phase of the study, subjects will be asked to maintain a weekly exercise average of 2 to 3 sessions weekly of at least 30 minutes. Exercise data will be downloaded from the wearable device. Data include heart rate, calories burned, daily steps, floors climbed, distance covered, active minutes.
j. BGM Measurements will be performed at the following timepoints during CRC visits, ± 2 minutes:
    - -15 minutes (both YSI and BGM)
    - Time 0 (immediately before exercise) (both YSI & BGM))
    - 15 minutes (YSI only)
    - 30 minutes (both YSI & BGM)
    - 45 minutes (both YSI & BGM, end of exercise)
    - 60 minutes (YSI only)
    - 75 minutes (both YSI & BGM, thirty minutes after completion of exercise)
k. BGM data will be downloaded at each patient visit.
l. Investigational Product (IP) for first outpatient visit will be dispensed at the end of visit 4.
m. Subject will wear both Fitbit Ionic and Polar Beat H10 heart rate sensor during this visit.
n. Subject will wear only the Fitbit Ionic during these visits.
o. Prior to beginning the exercise session, if the subject's blood glucose is below 100 mg/dL the subject is allowed to take dextrose tabs (e.g., 2-4 tabs) to raise the blood glucose, and the blood glucose verified to be within 100-180 mg/dL (5.56 – 10 mmol/L). The number of dextrose tabs and time administered are recorded. Prior to beginning the exercise session, if the blood glucose is >180 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 100 to 180 mg/dL.

At discretion, the investigator may reschedule the visit to occur after a minimum wait of 24 hours. The visit should be re-scheduled so it occurs within the originally defined visit window. For example, a rescheduled Visit 3 (CRC 1) should occur within 28 days of Visit 1 (Screening), while a rescheduled Visit 4 (CRC 2) should occur within 28 days of a completed Visit 3 (CRC 1).

## 1.3 DETERMINATION OF SAMPLE SIZE

The primary endpoint of the study is the incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session, which occurred within the 12-week outpatient follow-up, as measured by BGM. The null hypothesis is that there is no difference between the treatment groups in the incidence of exercise-associated hypoglycemia, and the alternative is there is a difference between the treatment groups in terms of the incidence of exercise-associated hypoglycemia. With an effect size estimate of 0.262 (variance of means 59, common standard deviation 15), 80% power and an alpha of 0.05, using a one-way analysis of variance, 14 subjects per treatment group in the Outpatient Stage is required. Accounting for 15% attrition, a total of 48 subjects will be randomized.

### 1.3.1 Randomization and Blinding

The study statistician will create the randomization schedule for the study. The randomization assignment for the subject will be conducted once at the time of enrollment and confirmation of eligibility. The CRC assignments will be by random assignment during the first session to either Glucagon RTU or Placebo. At the second session, the subject will be crossed over to the other treatment assignment. At the completion of the CRC visits, the subject will then have his/her treatment assignment applied for the parallel group study.

The cross-over study is blinded to the extent possible since all subjects will receive both Glucagon RTU and placebo. All staff, subjects and study team members will know that the subject will receive both study treatments during the CRC sessions. During the outpatient study, two of the treatments will be blinded to the study staff, subjects and Sponsor. One arm of the study will be open label. It is imperative for the study staff to remain blinded to treatment assignment prior to randomization and during the study treatment periods as not to bias the outcome.

Glucagon RTU and Placebo will be prepared and administered so that the two will be indistinguishable.

Blinding of study treatment is critical to the integrity of this clinical trial. It is expected that in the majority of cases, AEs can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual subject's treatment

assignment is considered critical to the subject's management, the treating physician may unblind the treatment assignment. The investigator should contact the responsible Medical Director to discuss the subject and circumstances requiring the unblinding. The blind will be broken only for the specific subject under discussion. The Sponsor will remain blinded to the treatment assignment. Every effort will be made to restrict knowledge of the treatment assignment to the investigator only.

## 2. STATISTICAL AND DATA ANALYSIS CONSIDERATION

The statistical analyses will be performed by EmpiriStat, Inc., using SAS Version 9.3 (or higher). All tables, listings and figures (TLFs) will be produced in landscape format. In general, all data will be listed by the subject and visit/time point where appropriate.

Data will be summarized by treatment/treatment sequence and by period where appropriate. The total number of subjects in the study group (N) under the stated population will be displayed in the treatment sequence/treatment header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise stated, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. In case of n<2, where n indicates the number of evaluable subjects at the particular time point, only n, mean, minimum and maximum will be displayed. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/subjects, if any at that visit, and presented as a summary statistic only for the resulting time points.

**Decimal Precision Convention:** The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects in the respective treatment sequence [N]. Percentage will be obtained by: % = (n/N)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

The closest non-missing measurement (whether from scheduled or unscheduled visit) taken prior to the first dose administration will be considered as the baseline value. The Post-baseline values are defined as measurements taken after the first administration of study drug. For summarizing vital signs follow-up visits, screening value will be considered as baseline, and change from baseline to follow-up visit is the change in measurement from baseline (screening) to follow-up visit. For other visits, baseline is the measurement taken at pre-dose in each period and change in measurement from baseline (pre-dose) to each post-dose in each period.

The following conventions will be applied to analyses/data presentation:

All dates will be displayed in DDMMMYYYY format.

All unscheduled visit data will be presented in Listings, and last repeated unscheduled visit data (if applicable) which will be flagged as analysis value will also be used in summarizing data for Tables and Figures.

For Listings, data will be presented by subject, sequence, treatment, period, parameter, assessment date in chronological order, but not limited to the above variables. The number of variables presented in each listing can vary. Please refer to the Mock tables, listings and figures.

**2.1 Protocol Deviation:**

The Principal Investigator must sign the protocol and its amendments (if any) before initiating the study at a particular site. The Investigator will make all reasonable efforts to comply with the written protocol. Protocol modifications to ongoing studies that affect the safety of subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosing, study assessments, the number of subjects exposed to test drug, or subject selection criteria must be made only after consultation between Xeris and the Investigator. All protocol modifications must be reviewed and approved by the IRB/IEC before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to subjects do not require preapproval by the IRB/IEC. However, the IRB/IEC must be notified in writing as soon as possible after the modification has been made. A copy of this communication must be forwarded to Xeris. All departures from the protocol must be fully documented in the source documents and the eCRFs of the subjects involved. Protocol deviations will be tracked in an electronic system implemented by the Sponsor or designated representative. Protocol Deviations

will be summarized as per the impact (Major/Minor) and category across the treatments throughout the different phases of the study. This classification is designated by the Sponsor and documented prior to locking and unblinding the study.

A summary of protocol deviations will be created for the CRC phase and Outpatient phase of the study using the ITT and Safety population for each phase.

A listing of subjects with Protocol Deviations (PD) will be provided for both CRC phase and Outpatient phase.

**2.2 Handling of Missing Data:**

Imputation of missing data will not be performed.

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "January."
3. If the day is unknown, then assign "01."

For partial end dates:

4. If the year is unknown, then do not impute the date but assign a missing value.
5. If the month is unknown, then assign "December."
6. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is considered to be concomitant while the AE is defined by start date.

If the Adverse Event Relationship flag is missing, the relationship for adverse event will be defined as related. If the Adverse Event Severity flag is missing, the severity for adverse event will be defined as severe.

**2.3 Treatment Group Labelling in TFLs:**

The Treatments in the CRC phase will be labelled as "Treatment A" and "Treatment B"

The Treatments in the Outpatient phase will be labelled as "Treatment A," "Treatment B," "Treatment C" in the footnote for the respective TFLs. A Footnote will be added for the treatment columns as below:

"Treatment A" = "Glucagon RTU (30 µL active - 0.15 mg) with 50% insulin pump reduction"

"Treatment B" = "Placebo injection (30 µL vehicle) with 50% insulin pump reduction"

"Treatment C" =" Glucagon RTU (30 µL active - 0.15 mg) without 50% insulin pump reduction"

**2.4 Definition**

**Baseline for CRC Phase:**

The Baseline for the CRC Phase is defined as the latest assessment prior to the first administration of the study drug in the CRC Phase for period 1, and the first assessment prior to the first administration of the study drug in period 2 for the analysis pertaining to CRC Phase, unless otherwise stated.

Baseline will be calculated as the average of the blood glucose measurements at: -15 minutes (both YSI and BGM) and Time 0 (immediately before exercise) (both).

**Baseline for Outpatient Phase:**

The Baseline for Outpatient Phase is defined as the latest assessment prior to the first administration of the study drug in the Outpatient Phase for the analysis pertaining to Outpatient Phase, unless otherwise stated.

If the assessment occurs on the same day as the first study drug administration for either of the phases, then the time of assessment should be compared to the time of first dose administration for both CRC and Outpatient Phase.

Baseline will be calculated as the average of the blood glucose measurements (BGMT) at: -15 minutes and just before the exercise session (Time 0).

**Change from Baseline:** The change from baseline values will be calculated as post baseline value minus the baseline value.

If BGM readings are missing from the CRC phase, the YSI readings can be used.

**Shift from Baseline:** The shift from baseline is defined as a change in categorical variable from baseline to subsequent visits for each subject.

**Percentage Change from Baseline:** The percentage change from baseline is defined as the ratio of change (Analysis value – Baseline value) and baseline value expressed in terms of percentage. % Change from Baseline = ((value – baseline) /baseline) *100;

**Treatment Emergent Adverse Event (TEAE):** TEAE is any AE does not present prior to the initiation of IMP (Investigation Medicinal Product) administration at CRC phase or any event already present that worsens in either intensity or frequency following exposure to the IMP at CRC phase.

An SAE is any AE that results in death, is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant

disability/incapacity, is a congenital anomaly/birth defect, is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above).

**Qualified Exercise Session:** For inclusion in the statistical analysis for the per protocol population (defined in section 4.1) a qualified exercise session will be defined. Exercise sessions will be performed in both the CRC and Outpatient phases. In the CRC phase, a qualified exercise session will be defined as the subject having (1) a blood glucose value of 100-180 mg/dL (5.56 - 10 mmol/L) prior to starting exercise, (2) completed 45 minutes of exercise (not including breaks), (3) achieved a target heart rate of 80% of maximum calculated heart rate at least once during the workout session, and (4) fasted at least 8 hours prior to that exercise session.
Primary analysis in the CRC Phase will be based on the above definition of qualified exercise session. Additional subgroup analysis will be applied to analyze exercise sessions in which subjects achieved a target heart rate of 80% of maximum calculated heart rate for 30% and 505 of the exercise time.

In Outpatient phase, a qualified exercise session will be defined as the subject having (1) a confirmed blood glucose value of 100-180 mg/dL (5.56 - 10 mmol/L) prior to starting exercise, (2) self-administered the study drug no more than 10 minutes prior to exercise (five minutes is the target), (3) conducted a protocol allowed exercise for moderate to high intensity for at least 30 minutes and no longer than 75 minutes, and (4) achieved a target heart rate of 80% of maximum calculated heart rate at least once during the session. If a subject has more than one exercise session in a day that is deemed a qualified exercise session, only the first qualified exercise session that day will be used in the analysis.
Primary analysis in the Outpatient Phase will be based on the above definition of qualified exercise session. Additional subgroup analysis will be applied to analyze exercise sessions in which subjects achieved a target heart rate of 80% of maximum calculated heart rate for 30% and 50% of the exercise time.

**Target Heart Rate:** Per protocol, the goal is to achieve a target of 80% of maximum calculated heart rate during the session as shown by the following equation:

- Target Heart Rate = 0.80 x (220 – Age in Years)

**Overnight Hypoglycemia:** Throughout the study, overnight hypoglycemia will be defined as any instance of a subject's CGM reading changing from being above 70 mg/dL (> 3.89 mmol/L) to at or below 70 mg/dL ( ≤ 3.89 mmol/L) between Midnight and 6am (T00:00 – T06:00). Please note this definition will enable analysis of multiple instances in a given night.



## 3. STUDY ENDPOINTS

As applicable, the 2 (CRC phase) or 3 (Outpatient phase) treatment groups will be compared based on the following primary, secondary and exploratory endpoints.

**Primary Endpoint:**

The primary endpoint is the incidence of hypoglycemia (i.e, blood glucose ≤70 mg/dL; 3.89 mmol/L) associated with an exercise session across 12 weeks of outpatient treatment as measured by blood glucose meter (BGM).

For primary endpoint analysis the exercise session must meet the criteria defined in Section 2.4 as being a 'qualified exercise session' by requiring (1) a confirmed blood glucose value of 100-180 mg/dL (5.56 – 10 mmol/L) prior to starting exercise, (2) self-administered the study drug no more than 10 minutes prior to exercise (five minutes is the target), (3) conducted a protocol allowed exercise for moderate to high intensity for at least 30 minutes and no longer than 75 minutes, and (4) achieved a target heart rate of 80% of maximum calculated heart rate at least once during the session.

**Secondary Endpoints:**

1. Interstitial glucose (IG) levels below target range, measured by unblinded CGM (inpatient and outpatient), defined as both time (in minutes) and mean decremental area over the curve (AOC (0-300 min) in minutes*mg/dL) during exercise:
    - Below range, as defined by IG ≤ 70 mg/dL (≤ 3.89 mmol/L)

- Below range, as defined by IG between 54 to 70 mg/dL (3–3.89 mmol/L)
- Below range, as defined by IG < 54 mg/dL (<3 mmol/L)
- Proportional time (percentage time within hypoglycemia IG ≤ 70 mg/dL (3.89 mmol/L) and clinically significant hypoglycemia IG < 54 mg/dL (3mmol/L)).

2. Insulin utilization as reported by subject at baseline, and weeks 4, 8 and 12 in the outpatient setting.
3. Change from Baseline to the end of the Outpatient Phase in PROs: Barriers to Physical Activity in Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS-II), and Hypoglycemic Confidence Scale (HCS).

**Other Secondary Endpoints:**

Change from Baseline in insulin utilization as reported by the subject at Weeks 4, 8, and 12 in the Outpatient Phase.

**Exploratory Endpoints:**

1. Mean time and mean proportional time (%) within range, as defined by IG between 70 and 180 mg/dL (3.89 to 10 mmol/L) (CGM, 0 to 300 minutes with exercise), across the 2 CRC treatment arms.
2. Time, proportional time (percentage), and mean incremental Area Under Curve, plasma glucose > 180 mg/dL (10 mmol/L), and (AUC (0-300 min) in minutes*mg/dL) during exercise, across the 2 CRC treatment arms and the 3 outpatient treatment arms.
3. The time, proportional time (percentage), and mean incremental area under the curve (AUC) during which plasma glucose >250 mg/dL (AUC (0-300 min) in minutes*mg/dL) during exercise, across the 2 CRC treatment arms and the 3 outpatient treatment arms.
4. Incidence of overnight hypoglycemia as measured by CGM, across the 2 CRC treatment arms and the 3 outpatient treatment arms.
5. Compare the glucose tablet utilization during exercise, across the 2 CRC treatment arms and the 3 outpatient treatment arms.

6. Compare food (carbohydrate) intake pre/post exercise, across the 3 outpatient treatment arms.

7. Compare number of exercise sessions performed across the 3 outpatient treatment arms.

    a. Conduct subgroup analysis for:

        i. comparison of the number of qualified exercise sessions out of total number of exercise sessions conducted

        ii. comparison of the number of qualified sessions meeting less than 30% proportional time at target HR

        iii. comparison of the number of qualified sessions meeting greater than or equal to 30% proportional time at target HR

8. Compare number of minutes of exercise performed per week, across the 3 outpatient treatment arms.

9. Compare caloric expenditure during exercise, across 3 treatment arms.

10. The change from Baseline to end of study in body weight will be measured and analyzed across the 3 treatment arms.

11. Compare number of steps taken, and the distance achieved during exercise sessions across the 3 outpatient treatments arms.

12. The following assessments during exercise sessions will be captured from the wearable activity monitor: heart rate, daily steps, calories burned, distance covered, floors climbed, active minutes.

13. Change from baseline in HbA1c.

**Safety Variables:**

- AEs, SAEs (incidence, frequency, severity), and AEs leading to discontinuation.
- Vital signs (heart rate, blood pressure, respiration rate, temperature).

- 12-Lead ECG.
- Clinical laboratory tests (clinical chemistry, hematology, urinalysis).
- Physical examination findings.
- Draize Scales, Injection Site Discomfort and Duration Questionnaires.

# 4. STATISTICAL METHODOLOGY

## 4.1 Definition of Analysis Population

**All Screened Subjects:** All Screened subjects will include any subject who signed the informed consent form.

**Intention to Treat (ITT) Population:** All randomized subjects regardless of whether they received Study Drug.

**Per Protocol (PP) Population:** ITT participants who completed a qualified exercise session, and who was dosed within the study window and did not meet any of the key exclusion criteria at screening. The definition of qualified exercise is defined in Section 2.4.

**Safety Population:** All randomized subjects who received any amount of Study Drug.

## 4.2 Coding Dictionaries Used

Adverse events and Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1.

Prior & concomitant medication will be coded using World Health Organization-Drug Reference List (WHO-DRL) (Version WHODD-B3-MAR 2019).

## 4.3 Wearable Monitoring Devices

There are three wearable devices used for collection and analysis of metrics related to the study endpoints. Each subject has data collected from a wearable fitness tracker (Fitbit Ionic), continuous glucose meter (CGM), and a blood glucose meter (BGM). Endpoint Analysis will require confluence of data from these sources and therefore understanding of each is imperative.

### 4.3.1 Fitbit® Ionic

The Fitbit is used to collect exercise session metrics, daily activity metrics, and a daily food log. Data collected from this source is based on the reporting capabilities of the online portal fitabase. The Sponsor Study Specific Procedure-002 defines the process for collecting reports from the fitabase source. The metrics collected for analysis are as follows:

- The Activity Log report is collected to capture Date, Start Time, Duration (in milliseconds), Steps, Distance (in kilometres), Elevation Gain (in meters), Calories (in kilocalories), Average Heart Rate (beats per minute), and Active Minutes (in minutes) for each tracked exercise session. Active Minutes are separated into three categories titled Lightly Active, Fairly Active, and Very Active. Specific details for collection and data entry related to the Activity Log report are summarized in the 4-Sep-2019 Xeris Memorandum titled 'Fitbit Data Entry Clarification'.
- The Food Log report is collected to capture Date and the Nutritional Value of the food item in Grams of Carbohydrates. Specific Time of food consumption is not tracked. For analysis, cumulative carbohydrate intake will be summarized each day of a qualified session and compared across the treatment arms.
- The Heart Rate report is collected to capture Date, Time, and Heart Rate Value. Instances of heart rate are collected every minute and will be used to determine qualified exercise sessions.



**4.3.2 Dexcom® G5 Continuous Glucose Meter**

The CGM is used to collect interstitial glucose measurements on a continuous basis. The source data is stored in the cloud-based portal Dexcom CLARITY and outputted as .csv. The Sponsor Study Specific Procedure-001 and Study Specific Procedure-003 define the process for collecting this data and cleaning it to assure integrity. The metrics collected for analysis are as follows:

- Date and Time of Reading, Event Type (EGV or Calibration reading), and Glucose Value (in mmol/L).

Glucose Values for this device are only recorded in the range of 2.2-22.2 mmol/L. Values less than 2.2 will be recorded as "Low" and values greater than 22.2 will be recorded as "High."

**4.3.3 Blood Glucose Meter: Bayer® Contour Next One**

The BGM is used to collect blood glucose values during exercise sessions and to confirm blood glucose levels indicated by CGM. These data are being transferred by the Sponsor to the CRO. Variables included in this transfer are:

Date and Time of Reading to 1-minute precision, Blood Sugar (in mmol/L), and Control (binary indicator of whether the reading was a controlled calibration). Control readings will be excluded from analysis.

**4.3.4 Duplicate Timestamps:**

Some of the reports collected from the wearable devices are related to a specific timestamp. Upon routine data management review, it has been identified that some reports contain duplicate timestamps and therefore have multiple results tied to one unit of time. Whenever duplicate timestamps are encountered in analysis, the mean of all duplicate instances will be calculated and used as the result at that given timestamp. The mean result will be rounded to as many decimals as the original data.

**4.3 Statistical Methods and Data Analysis**

**4.3.1 Disposition**

The number and percentage of screened subjects, screen failures, subjects who entered the CRC phase, completed the CRC phase, and subjects included in each of the study populations will be summarized using the ITT population for CRC phase.

The number and percentage of subjects who entered the Outpatient phase, completed the Outpatient phase and subjects included in the various study populations will be summarized using the ITT population for Outpatient phase.

The number and percentage of subjects who prematurely discontinued from the CRC Phase along with reasons for study discontinuation will be summarized by last treatment received using the ITT population for CRC phase.

The number and percentage of subjects who prematurely discontinued from the Outpatient phase along with reasons for study discontinuation will be summarized by last treatment received using the ITT population for Outpatient phase.

For all subjects, analysis population inclusions, disposition and reason for discontinuation will be listed for both CRC and Outpatient phase.

A listing of the subject eligibility (inclusion/exclusion met/not met, reasons for screen failure) at CRC phase will be provided.

**4.3.2 Demographics and Baseline Characteristics**

Demographic and baseline characteristics (age [years], sex, ethnicity, race, body weight [kg], height[cm], and body mass index [BMI; kg/m2], will be summarized by treatment for the CRC phase and Outpatient phase separately using descriptive statistics for subjects in the safety population. Qualitative variables (gender, ethnicity, race, CBP, contraceptive methods) will be summarized using frequencies, while quantitative variables (age, weight, height, BMI) will be summarized using mean, SD, median, minimum, and maximum.

The screening tests such as Urine Pregnancy Test (women of childbearing age), HIV, HbA1c, C-peptide, HCV, HBV and urine drug screen will be listed using all screened subjects for the applicable phase (Screening and/or Treatment) of the study.

**4.3.3 Study Drug Administration and Accountability**

A listing will be provided for both CRC and Outpatient phases for study drug administration information, including date and time of dosing, dose administered and comment in case dose was not administered.

**4.3.4 Medical History**

Listings of Medical History will be provided for all screened subjects. Summary table of Medical History will be provided using Safety population. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1.

**4.3.5.1 Prior and Concomitant Medications**

All prior and concomitant medications will be presented in separate listings for CRC phase and Outpatient phases of the study using Safety population.

Each medication will be classified as prior, concomitant or both and will be assigned to CRC Stage, Outpatient Stage or both.

Any medication taken within 4 weeks before first study drug administration will be considered as prior.

Any medication taken on or after the first study drug administration or with a start date prior to and ongoing at the time of the first dose will be considered as concomitant.

In case when start/stop date is incomplete, or medication is ongoing, the following assumption will be made for Prior/Concomitant classification:

- If there is reasonable possibility that medication was taken within 4 weeks (28 days) before study drug administration, the medication will be considered as prior;
- If there is no evidence that medication was taken before the drug administration, medication will not be classified as prior;

Use of prohibited concomitant medications will be listed using ITT population. Also, prior medications will be presented as a separate listing.

The medication name, dose, units, route, frequency, indication or reason taken, start and end dates will be presented.

Prior and concomitant therapy will be coded using World Health Organization-Drug Reference List (WHO-DRL) (Version WHO-DDE Mar-2019).

#### 4.3.5.1 Rescue Medications

Standard of care for patients with symptoms of hypoglycemia and confirmed (BGM) blood glucose ≤70 mg/dL (3.89 mmol/L) is to take 16g (4 tabs, 4 g/tab) of glucose tabs, and repeat the 16-g carbohydrate serving every 15 minutes until blood glucose is >70 mg/dL (3.89 mmol/L).
Use of rescue medications will be presented in separate listings using Safety population.



### 4.3.6 Primary Endpoint Analysis:

The primary efficacy hypothesis test for the study is as follows:

Null Hypothesis: There is no difference between the treatment groups in the mean incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session occurring within the 12 weeks of out-patient treatment as measured by BGM.

Alternative Hypothesis: There is a difference between treatment groups in the mean incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session occurring within the 12 weeks of out-patient treatment as measured by BGM.

Incidence rate per subject is calculated by summing the number of exercise sessions completed within 12 weeks and dividing this denominator by the number of hypoglycemic events that

occurred during those exercise sessions (Incidence Rate = number of exercise sessions / inter/post-exercise hypoglycemic events). Events associated with an exercise session are defined as hypoglycemic events that occur during or within 30 minutes of exercise completion.

The primary efficacy analysis will be analyzed by ANOVA comparing the mean incidence rate between the three treatment groups. All statistical significance testing will be two-sided with a p-value <0.05. Efficacy endpoints will be analyzed using the ITT and PP analysis populations for Outpatient phase, if performed F-test yields an overall p-value less than 0.05 ($p<0.05$), post-hoc analysis of groups means will be conducted to statistically determine which group means differ.

Parameters that do not meet normality criterion will be analyzed non-parametrically. Overall treatment effect will be assessed using Friedman's test. If the overall treatment effect is significant in the Friedman's test, pairwise treatment comparisons will be assessed using the following tests.

- If the difference between two treatments is normally distributed (i.e., the p-value is ≥0.05 for Shapiro-Wilk test, the Tukey Test will be used.
- If the difference between two treatments is not normally distributed and the distribution is highly skewed, then the sign test/Kruskal Wallis test will be used.

Example of SAS syntax code that can be used for primary endpoint analysis is provided in APPENDIX 1.



**4.3.7 Secondary Endpoint Analysis:**

Glucose levels below target range will be measured and analyzed as the mean decremental area over the curve (AOC(0-5hrs) in minutes*mg/dL) during exercise. AOC will be estimated using Trapezoidal Rule.

Analysis will be conducted for glucose levels below range (interstitial glucose ≤70 mg/dL (3.89 mmol/L), interstitial glucose between 54-70 mg/dL (3 – 3.89 mmol/L), <54 mg/dL (3 mmol/L)) using a contingency table and treatment difference will be calculated using Chi square/Fisher's exact test.

Proportional time (percentage within serious hypoglycemia <54 mg/dL (3 mmol/L)) will be calculated and treatment difference will be calculated using ANOVA/Kruskal–Wallis test, based on whether the data is normally distributed or not respectively.

Insulin utilization as reported by subjects in Outpatient phase and change from baseline will be analyzed using ANOVA.

The Questionnaires will be analyzed using T Test/ANOVA for CRC/outpatient phase. For ANOVA, significant value will lead to a post hoc analysis for identifying the treatment pairs which are significantly different.

Changes from baseline in questionnaire values (numeric) will be analyzed by the ANCOVA model using treatment arm at Outpatient phase, treatment sequence in CRC phase, sex as factors with age, weight and baseline value as covariates.

Example of SAS syntax code that can be used for secondary endpoint analysis is provided in APPENDICES 2.

**4.3.8 Exploratory Analysis:**

Glucose levels within range, >180 mg/dl, >250 mg/dl will be measured and analyzed as the mean incremental area under the curve (AUC(0-5hrs) in minutes*mg/dL) during exercise.

Time and Proportional time (percentage within range, >180 mg/dl, >250 mg/dl) will be calculated and treatment difference will be calculated using ANOVA/Kruskal–Wallis test, based on whether the data is normally distributed or not respectively.

Generally, unless otherwise stated, the mean incidence rates will be compared using the T tests/ ANOVA or ANCOVA models using treatment arm at Outpatient phase, treatment sequence, obtained by combining the received treatments at CRC and Outpatient phase, sex as factors with, if applicable, age and weight as covariates.

Glucose tablet utilization during exercise, food (carbohydrate) intake pre/post exercise, number of exercise sessions completed across the 3 outpatient treatment arms , number of minutes exercised per week, number of calories burned per exercise sessions, number of steps, distance

covered, heart rate, floors climbed and change from Baseline in body weight will be compared for the treatment arms using T tests/ ANOVA at CRC/ Outpatient phase.

Incidence of overnight hypoglycemia will be compared for the treatment arms using Chi-Square/Fisher's exact tests at CRC/ Outpatient phase.

HbA1c data will be summarized using descriptive statistics (n, mean, SD, median, min, and max) for each scheduled study assessment, as well as change from baseline, will be summarized using ITT and PP Population.

Example of SAS syntax code that can be used for exploratory analysis is provided in APPENDIX 3.



**4.3.9 Safety Analysis**

**Adverse Events:**

All analyses will be conducted in the safety population. Adverse events will be recorded from the time of consent until completion of study. The number and percentage of subjects with AEs will be displayed by body system and preferred term (MedDRA), by study treatment. Summaries in terms of severity and relationship to Study Drug will also be provided. All SAEs will be summarized in a similar manner. Participant listings of all AEs causing discontinuation of study medication and SAEs will be produced.

All AEs will be listed for individual subjects showing both verbatim and preferred terms. Separate summaries of treatment emergent SAEs and TEAEs related to Study Drug will be generated.

AEs will be summarized separately during the CRC treatment visits. Any AE that occurs after administration of study drug at Visit 3 and prior to administration of the alternate study drug at Visit 4 will be treatment emergent with respect to the study drug received at Visit 3. Any AE that occurs after administration of study drug at Visit 4 and prior to the first administration of study drug in the out-patient phase will be treatment emergent for the study drug received at Visit 4. Any event reported on the eCRF that occurs at the time of or after the initiation of Study Drug in the out-patient phase is defined as treatment-emergent for that study drug. Additionally, an AE that was reported to have started on Day 1 without an associated onset time is assumed to have

occurred after the initiation of Study Drug. Hence, AEs occurring on Day 1 with no associated onset time are assumed to be treatment emergent.

SAEs associated with a protocol specified procedure and occurring after the time of consent but before administration of first dose of Study Drug are defined as Non-Treatment Emergent AEs (NTEAE).

**Physical Examination:**

All physical examination findings will be provided in the listings.

**12-Lead ECG:**

ECG results will be summarized using frequency counts for Overall Evaluation (normal, abnormal NCS, and abnormal CS) by treatment for Screening and EOS using Safety Population.

All ECG data will be listed for each subject with abnormal values flagged in the listing.

**Vital Signs:**

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature) will be summarized using the descriptive statistics for each vital sign measurement and change from baseline by treatment and timepoint for CRC phase and Outpatient phase using the Safety Population.

Vital Sign data will be listed by timepoint for each parameter and subject by treatment.

**Laboratory:**

Laboratory evaluation results for observed values and change from baseline will be summarized descriptively by treatment and visit using Safety Population. Unless otherwise specified, all continuous laboratory data will be summarized using descriptive statistics (n, mean, SD, median, min, and max) for each scheduled study assessment as well as change from baseline by parameter class (Hematology and Biochemistry). Abnormal laboratory values will be summarized using frequency and percentage using the safety population.

Hematology and Chemistry data will be summarized by displaying shifts from baseline value (low/normal/high or Normal/Abnormal as applicable) to subsequent assessment.

Safety laboratory data (Hematology and Chemistry) will be listed by timepoint for each parameter and subject. All abnormal values will be flagged on the listing. Serology, HbA1c and C-peptide data will also be listed.

**Draize Scales, Injection Site Discomfort and Duration Questionnaire:**

Erythema formation, Edema formation and Injection Site Discomfort data will be summarized at CRC phase using Safety population.

The Injection Site Discomfort Description and Duration Questionnaire is a 3-question instrument that assesses a subject's level of discomfort and its duration post-injection. There are 5 responses for each of the first 2 questions, which address the level of discomfort and the duration of the discomfort, respectively, for each injection. For the 3rd question, the total time for the duration of discomfort is to be provided.

All categorical data will be summarized by using and frequency and percentage and continuous data will be summarized using descriptive statistics.

### 4.3.10 Immunogenicity

Details and results for immunogenicity sample analysis will be provided in a separate analysis document.

### 4.3.11 Interim Analysis

There are no planned interim analyses for this study.

## 4.4 CHANGES FROM PROTOCOL

NA

## 4.5 REFERENCES

NA

## 4.6 APPENDICES

### 4.6.1 APPENDIX 1. Example of SAS syntax code for primary endpoint analysis.

The following SAS syntax code can be referred to during programming of primary endpoint analysis:

```
PROC ANOVA DATA = clover;
        CLASS trt_o;
        MODEL param = trt_o;
RUN;
```

Alternative:

```
PROC GLM DATA = xx;
        CLASS trt_o;
        MODEL param = trt_o/ ss3;
        LSMEANS trt_o / PDIFF CL ALPHA=0.05;
RUN;
```

Alternative:

```
PROC MIXED DATA=school METHOD=type3;
        CLASS trt_o;
        MODEL param= trt_o;
RUN;
```

The following SAS syntax example code can be referred to during testing the normality of the residuals using the Shapiro-Wilk W-test.

```
PROC UNIVARIATE DATA=xxxxx NORMAL PLOT;
        VAR yyyyy;
        QQPLOT yyyyy /NORMAL (MU=EST SIGMA=EST COLOR=RED L=1);
RUN;
```



### 4.6.2 APPENDIX 2. Example of SAS syntax code for secondary endpoint analysis.

The following macro can be used for the calculation of area over the curve (AOC):

```
%macro auc (dsn);
      data auctree;
            set &dsn;
            if concentration = 0 and time > tlast then delete;
            x = time;
            y = concentration;
            xpre = lag(x);
            ypre = lag(y);
            xdif = x - xpre;
            if x <= tmax or y = ypre or y =0 or ypre = 0 then do;
                  auc = xdif * (( y + ypre ) / 2 );*linear rule;
            end;
            else do;
                  auc = xdif * ((y - ypre) / log (y / ypre));
```

```
            end;
      run;

      proc summary data = auctree noprint;
            var auc;
            output out = aucest sum = aucL;
      run;

      proc sort data = auctree out = part1 nodupkey ;
            by subject ;
      run;
      data AUCs&i (keep = subject period aucL);
            merge part1 aucest;
      run;
%mend auc;
```

The following macro can be used to perform estimation according to Trapezoidal Rule:

```
%macro trap(a,b,n, function);
      data f1;
            do i = 0 to &n ;
                  if i = 0 then do;
                        x = &a ;
                        y = ((&b - &a)/&n )*( &function / 2 );
                        output;
                  end;
                  else if i = &n then do;
                        x = &b ;
                        y = ((&b - &a)/&n )*( &function / 2 );
                        output;
                  end;
                  else do;
                        x = ( &a + i * (( &b - &a) / &n ) );
                        y = ((&b - &a) / &n) * &function;
                        output;
                  end;
            end;
      run;
      proc summary data=f1;
            var y;
      output out=p1 sum=areau;run;
      proc print data=p1;
      run;
%mend;
```

The Chi-Square/Fisher's exact test can be done using the following SAS code example:

```
PROC FREQ DATA = data;
      TABLES param*trt / CHISQ FISHER EXPECTED;
```

```
      WEIGHT count;
RUN;
```

Kruskal Wallis test can be performed in SAS using the following reference code:

```
PROC NPAR1WAY DATA=soil WILCOXON;
        CLASS location;
        EXACT WILCOXON / MC;
        VAR claypct;
RUN;
```

T test within the cross over design in CRC phase can be done with the help of the following reference code:

```
PROC TTEST DATA=data PLOTS=interval;
        VAR aval1 aval2 / CROSSOVER = (TrtA TrtB);
RUN;
```



### 4.6.3 APPENDIX 3. Example of SAS syntax code for exploratory analysis.

The ANCOVA model can be analyzed using the following SAS code example:

```
 PROC MIXED DATA= XXXX;
                CLASS SUBJECT TREATMENT trtSEQ sex;
                MODEL &par= TREATMENT trtSEQ sex age weight/DDFM=SATTERTH;
                RANDOM SUBJECT (SEQ);
                REPEATED / GROUP=TREATMENT SUB=SUBJECT R;
                LSMEANS TREATMENT / CL;
                LSMESTIMATE TREATMENT 'Treatment A vs. Treatment B' 1 1 0 /
                CL ALPHA=0.025 E LOWER;
RUN;
```

## 5. LIST OF TABLES, LISTINGS AND FIGURES

The following is the list of anticipated Tables, Listings and Figures for the study. Modifications may be made to this list to follow the SAP and for revisions with the Sponsor. If any new endpoints or new analyses are requested, they will be evaluated for whether an Amendment to the SAP is required.

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| Table 14.1.2.1.1 | Summary of Demographic and Baseline Characteristics for CRC Phase |

| Number | Title |
|---|---|
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| Table 14.2.3.1.2.1 | Summary of Incidence of Overnight Hypoglycemia at CRC Phase ITT Population |
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| Number | Title |
|---|---|
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| Table 14.2.3.2.2.1 | Summary of Incidence of Overnight Hypoglycemia at Outpatient Phase ITT Population |
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