Study Title	Randomized Crossover Euglycemic Clamp Study in Adult Patients with Type 1 Diabetes to Assess Pharmacokinetics and Pharmacodynamics of Subcutaneously Infused Insulin Using an Investigational Extended Wear Continuous Subcutaneous Insulin Infusion Cannula Compared to a Commercial Infusion Set
NCT Number	NCT04398030
Document Description	STATISTICAL ANALYSIS PLAN
Document Date	20 JUNE 2021

STATISTICAL ANALYSIS PLAN

Trial ID: CapBio 150-1022

Randomized Crossover Euglycemic Clamp Study in Adult Patients with Type 1 Diabetes to Assess Pharmacokinetics and Pharmacodynamics of Subcutaneously Infused Insulin Using an Investigational Extended Wear Continuous Subcutaneous Insulin Infusion Cannula Compared to a Commercial Infusion Set

Approval:	LEI SHI	Digitally signed by LEI SHI DN: cn=LEI SHI, o=Integrated Medical Development, LLC, ou=Biometrics, email=lshi@imdcro.com, c=US Date: 2021.06.23 14:15:52 -04'00'	
	Statistician/Name	Signature	Date
Approval:	Douglas B. Muchmore Senior Consultant	Douglas B. Muchmore Douglas B. Muchmore (Jun 30, 2021 08:24 PDT)	Jun 30, 2021
	Clinical Monitor/Name	Signature	Date
Approval:	Alayne Lehman Alayne Lehman	Alayne Lehman Alayne Lehman (Jun 29, 2021 18:10 PDT)	Jun 29, 2021
	Role/Name	Signature	Date

TABLE OF CONTENTS

ABBREVIATION AND DEFINITIONS

- **AE:** Adverse Event
- **AUC:** Area under the curve
- **BG:** Blood Glucose
- **CGM:** Continues Glucose Monitor
- **C_{max}:** Maximum Concentration
- **CV:** Coefficient of variation
- **DOI:** Day of Insertion
- **EDC:** Electronic Data Capture
- **ITT:** Intent to Treat
- **MRT:** Mean-Residence Time
- **N/A:** Not Applicable
- **PD: Pharmacodynamics**
- **PK: Pharmacokinetics**
- **PP:** Per Protocol
- **SD**: Standard Deviation
- **SOC:** system organ class
- **T1DM:** Type 1 Diabetes Mellitus
- **t_{max}:** Time to Maximum Concentration
- **VAS:** Visual Analog Scale

1 OVERVIEW

1.1 INTRODUCTION

This documentation describes the planed data analyses for the CapBio 150-1022 Clinical Study.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the reliability of insulin delivery using the investigational Achilles infusion set by evaluating the rate of decline of the glucose lowering effect of insulin from DOI through day 7 (0, 3, 5, and 7 days post insertion) compared to the commercially available control infusion set.

2.2 Secondary Objectives

Secondary objectives include:

- To assess other pharmacodynamics (PD) parameters of insulin within and across treatments following subcutaneous delivery using Achilles vs Teflon control set on DOI (day 0) and days 3, 5, and 7 post insertion
- To assess pharmacokinetic (PK) parameters within and across treatments following subcutaneous insulin delivery using Achilles vs Teflon control set on DOI and days 3, 5 and 7 post insertion.
- To assess continuous glucose monitoring (CGM) data, comparing data within and across treatments.
- To assess performance of the investigational infusion set on DOI (day 0) through day +7 (8^{th} calendar day of wear) for each treatment

2.3 Safety Objectives

- To assess safety and tolerability of the investigational infusion set on DOI through day +7 post insertion (8^{th} calendar day of wear) for each treatment as measured by infusion set failure.

2.4 Analysis Software

SAS 9.4 (or later) Windows.

2.5 MODIFICATIONS FROM THE STATISTICAL SECTION IN THE PROTOCOL

After the 7^{th} subject completed the study, sponsor decided to terminated the study. Thus :

- The analyses carries out using all available data will be considered as final analyses. No intrime analyses will be carried out.
- All analyses defined in this SAP will be done. However, it is expected some of them may not have results/outputs generated due to the small sample size.

3 INVESTIGATIONAL PLAN

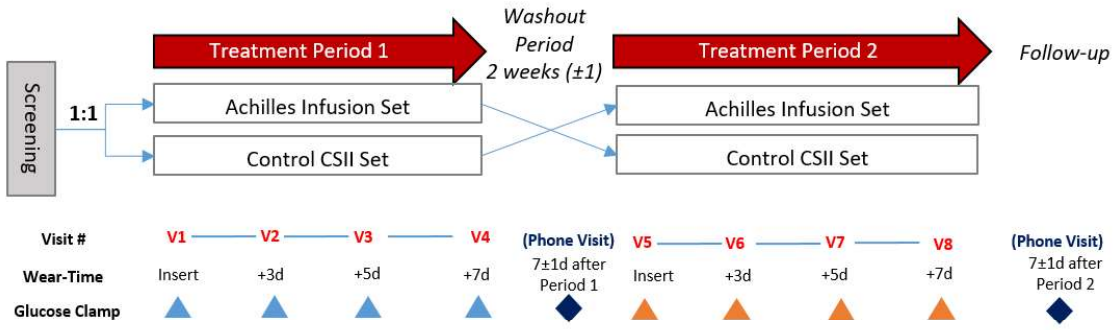
3.1 STUDY DESIGN AND RANDOMIZATION

3.2 Study Design

This is an open, single-center, 2-way randomized, cross-over trial investigating the survivability, consistency, efficacy, and safety of an extended wear time investigational insulin infusion set (CapBio Achilles). This is achieved by measuring PK and PD profiles of a bolus of rapid acting insulin on 4 separate days of CSII set wear time during 2 separate wear periods in up to 30 adult patients with T1DM.

3.3 Randomization

Participants will be randomized at Visit 1 1:1 to either undergo glucose clamp testing with the Achilles investigational cannula or commercially available control CSII set. If participant is randomized into the Achilles infusion set treatment group during Treatment Period 1, they will undergo Treatment Period 2 with the Teflon control set and vice versa. This allows the participant to act as his/her own control and minimizes user bias.



3.3.1 Study Visit Window

Study visit windows have has been defined for each visit as in the table below where day 0 is the day of the first set insertion (DOI).

Visit	Visit Window
Screening/Baseline	-28 to -1 days
Wear Period	DOI to +7 days inclusive in each treatment period
Study Completion	8^{th} calendar day or upon infusion set failure in each treatment Period
Follow-up	Patients will receive follow-up phone call by staff 1 day after each period

3.4 SAMPLE SIZE JUSTIFICATION

A sample size of 24 participants is sufficient to generate 90% power for a 2-tailed p=0.05 comparison of the $\ln(AUC_{0\text{-}300(GIR)})$ slope contrasts (=control minus Achilles), within this 2x2 crossover design. In addition to the usual regularity assumptions for the 2x2 crossover design (i.e. no carryover effects), this computation was based on the following assumptions:

1. The $\ln(AUC_{0\text{-}300(GIR)})$ values are normally distributed.
2. The within participant variance is 40% of the total variance.
3. The study day correlation matrix of the within-participant $\ln(AUC_{0\text{-}300(GIR)})$ assessments is AR (autoregressive model) with correlation r=0.5.
4. The within plus among participant variance for the $\ln(AUC_{0\text{-}300(GIR)})$ values is 0.21 (based on previous studies).
5. The difference in slopes (Achilles minus control) is at least 0.07.

4 STATISTICAL AND ANALYTICAL PROCEDURES

4.1 ANALYSIS POPULATIONS

4.1.1 Safety Population

The safety population includes all patients who had either an investigational or control cannula implanted.

4.1.2 Intent-to-Treat (ITT) Population

The intent-to treat (ITT) population includes all patients that meet all inclusion criteria and none of the exclusion criteria and are randomized to treatment sequence and complete at least one glucose clamp procedure will be included in the ITT population.

4.1.3 Per-Protocol (PP) Population

The per-protocol population includes all patients who completed both treatment sequences with no major protocol violations.

4.1.4 Populations Used for Analyses

The primary effectiveness analysis will be based on the ITT population. Sensitivity analyses of the primary effectiveness endpoint will be generated based on the PP population.

The demographics and baseline characteristics will be based on ITT Population.

The safety analysis will be based on the Safety population.

All secondary effectiveness analyses will use ITT population , with sensitivity analyses using the PP population (similar to the primary effectiveness analysis).

4.2 Data Handling Conventions

4.2.1 Missing Data

- Any blank value will be treated as missing (unknown)
- Blank values will be left as blank in the data listings.
- Missing data will not be imputed unless specified

4.2.2 Per Protocol Time Points Vs Actual Time Points

Actual time points will be used for the all parameter calculation unless otherwise specified. Per protocol time may be used if the by each time point summary is needed.

4.2.3 Inconsistent Time Points between CRF and Lab Transferred Data

N/A.

4.2.4 Repeated and Unscheduled Visit

4.2.4.1 Repeated Visit

A repeated visit is defined as a visit done at different date/time but is considered the same visit by the study site.

The principle of 'last observation priority' will be used to handle the situation of repeated visits unless there is a specific instruction from the study site. There are some general recommendations:

- If a variable (except dates and all lab transferred data) is newly measured/collected at the repeated visit, the value of that variable will be replaced with the value from the repeated visit.
- Dates and lab transferred data will be determined case by case based on their medical importance/meaning.
- If a variable is not measured/collected at the repeated visit, then the value from the original visit will be kept intact.

4.2.4.2 Unscheduled Visit

Unscheduled visit is visit dimmed as out of schedule by the investigational site. Data collected during unscheduled visits should be handled case by case. The following are some general recommendations:

- Data from unscheduled visit will only be used in listings.
- Data from unscheduled visit might be used to substitute a missing value in a scheduled visit as long as it is authorized and appropriately documented by the medical monitor.

4.2.5 Major Protocol Violations and Minor Protocol Deviations

All Protocol violations will be recorded but any Major Protocol Deviation will be evaluated by the scientifically responsible person (usually the medical monitor) and the statistician, for the purpose of excluding subjects from the per protocol population, before breaking the blinding.

4.2.6 Unexpected switch of the infusion set

Anytime when the participant switched the use of the study infusion set to other infusion set, it is considered the study infusion set is removed for the corresponding period regardless if the study infusion set is used again or not.

4.3 ANALYSIS (Efficacy) VARIABLES

4.3.1 Baseline Characteristics

Baseline characteristic variables such as demographics are captured in the EDC. No conversion will be done unless specified.

If age is captured in the EDC, the reported Age will be used. Otherwise, age can be calculated as

- *Age = (date of randomization - Date of birth) / 365.25, if Day is catured*
- *Or Age = (Year of randomization x 12 + Month of randomization - Year of birth x 12 - Month of birth) / 12, if Day is catured due to privacy concern*

Age will be calculated in years with decimal points for more accurate results.

4.3.2 Efficacy Variables

4.3.2.1 Handling of (Possible) Multiple Peaks of GIR and Insulin Curve.

We expect the GIR and insulin curve to have a single peak. However, it is possible that multiple peaks or no peak will be observed. The following are ways to handle GIR curves:

1. Determination of single peak/no peak/Multi-peak will be based on the plot of the GIR/insulin curve
    a. The statistician will make the judgement based the visual observation of each plot of the GIR/insulin curve
2. No peak. (i.e. the variables keeps rising up to 300 minutes)
    a. The Maximum, Time to Maximum, Time to Half-Maximum will be set as missing. We will consider these variable as undefined.
    b. The AUC_{0-t} will be calculated but the $AUC_{0-\infty}$ will be set as missing.
3. Multi-peak.
    a. If the same Maximum value appears at two or more time point, the Time to Maximum, Time to Half-Maximum will be estimated based on the first occurrence.

All of the following GIR and PK parameters, including the primary variable, will be calculated after this data handling.

4.3.2.2 Handling of (Possible) non-response (0) GIR or Insulin Curve.

It is possible that some subjects do not respond to the bolus insulin which resulted in all GIR to be 0 or Insulin to be 0. In such case, the derived variable of this GIR / Insulin profile will be censored out from all analyses.

4.3.2.3 Variables for Primary Efficacy: Area Under the Curve (AUC) of the Glucose Infusion Rate (GIR)

The variable for Primary Efficacy is the $AUC_{0\text{-}300}$. It is estimated using the methods described in the following section 4.3.2.3.3.

4.3.2.3.1 GIR_{max}

GIR_{max} will be the maximum GIR readings from time 0 to time 300 minutes.

- In a "No Peak" case, this will be set as missing.

4.3.2.3.2 Terminal Rate Constant λ

Terminal rate constant λ is needed before we estimate $AUC_{0\text{-}t}$. It is estimated by:

a. Find the GIRs after GIR_{max} (section 4.3.2.3.1)
    i. If there only 1 or 0 available GIR reading after GIR_{max}, then λ will be set as missing.
b. Do a regression of log-transformed GIR vs Time
c. λ is the slope from this regression
d. In a "No Peak" case, λ will be set as missing

4.3.2.3.3 $AUC_{0\text{-}t}$

The $AUC_{0\text{-}t}$ of GIR over wear time will be calculated using trapezoid rule and the actual time points. Missing data for the calculation of the AUC will be handled as followed:

1. If the reading for Time 0 is missing, it will be the average of up to 3 prior readings. However, it there is no prior readings available, it will be assumed to be 0
2. If the reading at (actual) time t (t < 300 min) is missing, it will be imputed with linear interpolation
3. If the reading at t=300 min is missing:
    a. The reading at t=300 min will be imputed using the regression line obtained when estimate λ (section 4.3.2.3.1).
    b. If λ is missing, $AUC_{0\text{-}t}$ will be set as missing.

4.3.2.3.4 $AUC_{0\text{-}\infty}$

$AUC_{0\text{-}\infty}$ is estimated as

$$AUC_{0-\infty} = AUC_{0-last} + AUC_{last}, \text{ where } AUC_{last} = GIR_{last}/\lambda$$

If λ is missing, then $AUC_{0-\infty}$ is set as missing.

4.3.2.3.5 Baseline Adjusted AUC_{0-t}

The baseline adjusted AUC_{0-t} is calculated as

$BaseAdjAUC_{0-t} = AUC_{0-t} - GIR_0 * t$

4.3.2.3.6 Baseline Adjusted $AUC_{0-\infty}$

The baseline adjusted $AUC_{0-\infty}$ is calculated as

$$BaseAdjAUC_{0-\infty} = (AUC_{0-last} - GIR_0 * t_{last}) + (GIR_{last} - GIR_0/\lambda)$$

4.3.2.4 Other GIR Parameters

4.3.2.4.1 Time-to-Maximum GIR ($t_{max(GIR)}$)

$t_{max(GIR)}$ is the minute between the time corresponding to GIR_{max} and Time 0. Actual time will be used in this calculation.

- If GIR_{max} is missing, $t_{max(GIR)}$ will also be set as missing.
- If the same Maximum value appears at two or more time point, the Time to Maximum will be estimated based on the first occurrence of maximum value.

4.3.2.4.2 Time to Half-Maximal GIR, Both Early and Late ($t_{50(GIR),early}$ & $t_{50(GIR),late}$)

$t_{50(GIR),early}$ is the time in minutes from 0 min to the time when GIR rises to half way to the maximum. It is calculated as followed:

- $t_{50(GIR),early}$ = Time corresponding to $\frac{(GIR_{max} - GIR_0)}{2}$ - t_0.
- If GIR_{max} is missing, $t_{50(GIR),early}$ will also be set as missing.

$t_{50(GIR),late}$ is the, It is estimated as:

- $t_{50(GIR),late}$ = Time corresponding to $\frac{(GIR_{max} - GIR_{300})}{2}$ - t_0.
- If GIR_{300} is missing, it will be imputed as described in section 4.3.2.2.3.

All calculation will be based on the actual time.

4.3.2.4.3 Onset of Insulin Action

The onset of insulin action is defined as the time in minutes from the beginning of baseline to the first occurrence of a drop in blood glucose concentration by 5 mg/dL from its maximum. It will be based on the actual time.

- If the blood glucose never dropped by 5 mg/dL from time 0, it will be set as missing.

4.3.2.4.4 Duration of Insulin Action

Duration of insulin action is calculated similar to Mean Residence Time (MRT). It is calculated as:

$$\text{Duration of insulin action} = \frac{AUMC_{0-300}}{AUC_{0-300}}$$

AUMC is the area under curve of GIR_t*t, and is estimated using the same method as described for AUC in section 4.3.2.1.

4.3.2.4.5 Percentage of $AUC_{0\text{-}300}$ and Coefficient of Variability (CV) AUC

$$\text{Percentage of } AUC_{0\text{-}300} = 100 \times \frac{AUC_{0-t}}{AUC_{0-300}}$$

CV of AUC is calculated per week for each subject and,

$$\text{CV} = \frac{Standard\ Deviaition\ of\ AUC\ each\ week}{Mean\ of\ AUC\ each\ week}$$

4.3.2.5 PK Parameters

4.3.2.5.1 $AUC_{0\text{-}t}$

$AUC_{0\text{-}t}$ is calculated using the same methods as described in section 4.3.2.1.

4.3.2.5.2 Baseline Adjusted $AUC_{0\text{-}t}$

Baseline adjusted $AUC_{0\text{-}t}$ is calculated using the same methods as described in section 4.3.2.3.5

4.3.2.5.3 $AUC_{0\text{-}60}$

$AUC_{0\text{-}60min}$ is calculated using the same methods as described in section 4.3.2.1.

- If the “60 minute” insulin value actual collection time is before 55 minutes or after 65 minutes, then $AUC_{0\text{-}60}$ will be set as missing.
- However, if the “60 minute” reading actual collection time is between 55 and 65 minutes, the $AUC_{0\text{-}60}$ will be calculated using the available value.

4.3.2.5.4 Percentage of AUC_{0-300} and Coefficient of Variability (CV) AUC

These parameters will be calculated with the same methods as described in section 4.3.2.4.5

4.3.2.5.5 Mean-Residence Time (MRT) of Insulin

MRT of insulin will be calculated with the same methods as described in section 0.

4.3.2.5.6 Maximum Insulin Concentration (C_{max})

C_{max} will be the will be calculated with the same methods as described in section 4.3.2.3.1

4.3.2.5.7 Time-to-Maximum Insulin Concentration (T_{max})

T_{max} will be calculated with the same methods as described in section 4.3.2.4.1.

- If C_{max} is missing, $t_{max(GIR)}$ will also be set as missing.

4.3.2.5.8 Time-to-50% Maximum Insulin Concentration [$t_{50,early}$ & $t_{50,late}$]

$t_{50,early}$ & $t_{50,late}$ will be calculated with the same methods as described in section 4.3.2.4.2.

4.3.2.6 Continues Glucose Monitor (CGM) Blood Glucose (BG)

Blood glucose concentration is captured in a commercial CGM device and the data is exported into a csv or excel file and imported into SAS.

- CGM is coming from two sources: Dexcom CGM and Medtronic CGM using by some automatic Pump.
- The data from Dexcom CGM will be used for analyses, only if there are missing data in Dexcom CGM, the data from Medtronic Pump CGM will be used for substitution.

The mean daily CGM glucose, standard deviation (SD) of daily CGM glucose and time (%) spent in glucose range of daily CGM glucose will be summarized.

All CGM parameters will be based on out-patient days' data only.

4.3.2.6.1 Evaluable CGM Days

The CGM glucose is recorded every 5 minutes. Thus, for each day (24 hours, 0:00-23:59), there should be 288 data points recorded. However, in some cases, there might be fewer data points reported. In such case, using a 24-hour CGM interval with less than 288 data points will result in bias, as blood glucose concentrations may vary throughout the day.

For this reason, we will use the following process to select the evaluable CGM day (24-hour interval):

1. For each subject, we will use cubic spline to interpolate any missing intervals that are less than or equal to 2 hours (or 24 data points).
2. Then an evaluable CGM day will be the interval with at least 276 data points (or at least 23 hours).
3. We will only use these evaluable CGM day in the following analyses. The choice of the number 276 is arbitrary and based on past experience of CGM analyses.

In some rare cases, we may have duplicated glucose readings of the CGM. Duplication is defined as two or more records with the exact same subject ID, date and time (including sections).

- Duplications will be averaged and the mean glucose concentration will be used as the reading for this date and time of the subject.

4.3.2.6.2 Mean Daily CGM Glucose

The mean daily CGM glucose is calculated as:

$$Mean\ Daily\ CGM\ BG = \frac{Sum\ of\ (all\ avaliable\ CGM\ BG)}{\#\ of\ all\ avaliable\ CGM\ BG}$$

4.3.2.6.3 SD of Daily CGM Glucose

Let $N = \#\ of\ all\ avaliable\ CGM\ BG,\ i = index\ of\ each\ BG$, then SD of Daily CGM Glucose is calculated as:

$$SD\ of\ Daily\ CGM\ BG = \sqrt{\frac{\sum_{i=1}^{N}(\ BG_i - MeanBG)^2}{(N-1)}}$$

4.3.2.6.4 Time (%) Spent in Glucose Range

The time (%) spent in glucose range is estimated as:

$$Time(\%)\ in\ BG < 54\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings < 54\ mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG < 70\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings < 70\ mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG \geq 70\ and \leq 140\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings \geq 70\ and \leq 140\ mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG \geq 70\ and \leq 180\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings \geq 70\ and \leq 180\ mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG > 140\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings > 140 mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG > 180\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings > 180 mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

$$Time(\%)\ in\ BG > 240\ mg/dL = \frac{\#\ of\ CGM\ BG\ readings > 240 mg/dL}{\#\ of\ all\ avaliable\ CGM\ BG\ readings}$$

4.3.2.6.5 Coefficient of Variability (CV) CGM BG

$$CV\ of\ Daily\ CGM\ BG = \frac{SD\ of\ Daily\ CGM\ BG}{Mean\ of\ Daily\ CGM\ BG}$$

4.3.2.7 Performance of the Investigational Infusion Set

4.3.2.7.1 Daily Insulin Infusion Set Survival Rate

Infusion set failure is defined as an episode of unexplained hyperglycemia that did not respond to a correction bolus, hyperglycemia associated with elevated serum ketone measurement in the absence of evidence of intercurrent illness, evidence of infusion site infection, or non-resolvable insulin infusion pump occlusion alarm. These conditions indicate failure of the system at the level of the subcutaneously indwelling infusion cannula.

Infusion sets can also fail to provide insulin as a result of other system performance issues, such as failure of the insertion attempt to pierce the skin, accidental removal of the set by inadvertent application of tension to the tubing (e.g. “tubing caught on a doorknob”), or failure of the adhesive to secure the cannula housing to the skin for the full duration of study.

The daily infusion set survival rate is calculated by the # of non-fail infusion sets on that day divided by the total # of infusion sets inserted. Survival curves will be generated for both "infusion set failure" episodes and all failures combined ("infusion set failure" combined with "other system performance issues" as defined above).

The day will be normalized to the day of the insertion where first day is set to Day 0.

4.3.2.7.2 Time (h) to Device Failure

Time to device failure = date/time when device fails – date/time of Day 0 (as defined in section 4.3.2.7.1) . It will then be transformed to hours.

4.3.2.7.3 Pump Bolus Occlusion Alarms

of pump bolus occlusion alarms will be counted for each day.

4.3.2.7.4 Pump Basal Occlusion Alarms

of pump basal occlusion alarms will be counted for each day.

4.3.3 Safety Variables

4.3.3.1 Device Malfunctions

4.3.3.1.1 Hyperglycemia (Glucose >250 mg/dL) not Responsive to Correction Bolus

This hyperglycemia episode is reported by the investigational site. Occurrence of these cases will be counted. A subject without any reported cases will have a count of 0.

4.3.3.1.2 Hyperglycemia with Elevated Ketones (Glucose >250 mg/dL and a Ketone Value ≥0.6 mMol/L) in the Absence of Evidence of Intercurrent Illness.

This hyperglycemia episode is reported by the investigational site. Occurrence of these cases will be counted. A subject without any reported cases will have a count of 0.

4.3.3.1.3 Evidence of Infection or Clinically Meaningful Inflammation at the Infusion Site

This is reported by investigational site and the occurrence of these cases will be counted. The number of hours following cannula insertion will be reported for each occurrence. A subject without any reported cases will have a count of 0.

4.3.3.1.4 Cannula Dislodgement

It is reported by investigational site and the occurrence of these cases will be counted. A subject without any reported cases will have a count of 0.

4.3.3.1.5 *Cannula other Malfunctions*

It is reported by investigational site and the occurrence of these cases will be counted. A subject without any reported cases will have a count of 0.

4.3.3.2 Visual Analog Scale (VAS) for Pain Assessment

The VAS score will be normalized to 100 mm based on the reported pain score length and the total line length.

The mean VAS score of each subject is calculated as:

$$Mean\ VAS = \frac{Sum\ of\ (all\ avaliable\ VAS\ Score)}{\#\ of\ all\ avaliable\ VAS\ Score}$$

4.3.3.3 Exposure (h) to Study Device

The exposure of the device will be in days and calculated as:

The date/time of last device removal – the date/time of first device insertion

It will then be transformed to hours.

4.3.3.4 Adverse Events (AE)

All observed or volunteered adverse events regardless in the treatment group or suspected causal relationship to the investigational device are captured in the EDC. The adverse events will be coded using Medra Coding.

4.3.3.5 ECG

ECG is captured in the EDC and will be reported.

4.3.3.6 Vital Sign

Vital signs, including blood pressure, are captured in the EDC and will be reported.

4.4 STATISTICAL Analyses

4.4.1 Study Days

Days as defined in the protocol (and in SAP section 3.3.1) will be used.

Additionally, for the calculation related to infusion set insertion, Day 0 will be the day of insertion.

4.4.2 General Consideration of Descriptive Summary

The following rules will be used, unless specific described, for any descriptive summary.

1. Descriptive summary will be by treatment and by period
2. For continuous variables: mean, SD, median, minimum and maximum will be reported. Two decimal points will be used unless specified.
3. For category variables: count, percentage, and the total used as a denominator will be reported. One decimal point will be used unless specified.

4.4.3 Baseline Characteristics Analyses

4.4.3.1 Demographics

Demographics table includes summaries for age, sex, race, and euthenics. A descriptive summary will be provided.

Population	ITT

4.4.3.2 Subject Disposition

Subject disposition will be presented descriptively. It will show the # of subjects using each device.

Population	ITT

4.4.3.3 Physical Exam

The physical exam includes height, weight and a systematic body exam. A descriptive summary will be provided.

Population	ITT

4.4.3.4 Medical History

The physical exam includes a pregnancy test, The medical history includes the patient's insulin correction factor and previous medical conditions. A descriptive summary will be provided.

Population	ITT

4.4.3.5 Prior and Concomitant Medications

Both prior and concomitant medications will be listed.

Population	ITT

4.4.4 Efficacy analyses

4.4.4.1 Analyses of Primary Endpoints

Our primary endpoint is the failure rate of infusion set. A descriptive summary of infusion set failures will be provided. The summary will be reported for each period.

The $AUC_{0\text{-}300(GIR)}$ on day of insertion (day 0) and days 3, 5, 7 in periods 1 and 2 will be calculated using the trapezoidal rule as described in section 4.3.2.1.

The nature log of AUC: $\ln(AUC_{0\text{-}300(GIR)})$ will then be calculated.

A mixed-effects (repeated-measures) linear model with *treatment* and *period* as fixed effects and participant as a random effect will then be fit to this data. Estimates of the slopes by treatment will be generated as contrasts based on the least squares means.
The contrast is: the difference in slopes (control minus Achilles) of $AUC_{0\text{-}300(GIR)}$ versus day, computed from the least squares means of $AUC_{0\text{-}300(GIR)}$ at each study day within each of the 2 periods.

Treatment comparisons and confidence bounds on the difference in slopes will be presented.

The primary analysis will be conducted on the ITT population using all available data within the mixed model repeated measures framework. Missing an $AUC_{0\text{-}300(GIR)}$ assessment will be assumed missing at random (MAR). However, a sensitivity analysis will be done to check the extent to which the missing data could have made a difference in the conclusions of the analysis.

Additionally, the same analyses will be repeated on the baseline adjusted $AUC_{0\text{-}300}$ and ITT population.

Population	ITT and PP (ITT is the primary , PP is the sensitivity)

4.4.4.2 Analyses of Secondary Endpoints

4.4.4.2.1 Daily Insulin Infusion Set Survival Rate

The survival of the Achilles and control infusion sets will be compared using a discrete lifetable analysis over study days 0, 3, 5, and 7 and the discrete form of the log-rank test.

4.4.4.2.2 PK Parameters

All pharmacokinetic parameters will be presented descriptively.

Additionally, AUCs, t_{50}, C_{max}, t_{max}, and MRT will be tested for treatment effects. The effects between Achilles and control set will be compared in a mixed-effects (repeated-measures) linear model with *treatment* and *period* as fixed effects and *participant* as a random effect. Log-transformation will be applied if data distribution is found to be highly skewed.

The mean difference between treatments (or on the log-scale) will be compared with a two-sided test using significance level α=0.05. Then mean ratio and its 95% confidence interval will be calculated

- Inverse-transforming will be done if the variable was log-transformed.

Population	ITT and PP (ITT is the primary , PP is the sensitivity)

4.4.4.2.3 PD Parameters

All PD parameters will be presented descriptively.

Additionally, AUCs, t_{50}, GIR_{max}, $t_{max(GIR)}$, and Duration of Insulin Action will be tested for treatment effects. The effects between Achilles and control set will be compared in a mixed-effects (repeated-measures) linear model with *treatment* and *period* as fixed effects and *participant* as a random effect. Log-transformation will be applied if data distribution is found to be highly skewed.

The mean difference between treatments (or on the log-scale) will be compared with a two-sided test using significance level α=0.05. Then mean ratio and its 95% confidence interval will be calculated

- Inverse-transforming will be done if the variable was log-transformed.

Secondary analyses will use the both ITT and PP populations for analysis. Multiple comparisons may raise these tests. We are not considering any correction in this SAP.

Population	ITT and PP (ITT is the primary , PP is the sensitivity)

4.4.4.2.4 Other Efficacy Endpoints

For other efficacy endpoints listed in section 4.3.2, descriptive summary will be presented.

Population	ITT

4.4.5 Safety Analysis

4.4.5.1 Adverse Events

Adverse events will be listed only if the total # of AE in the whole study is less than 5.

Otherwise, they will be summarized by presenting, for each dose/treatment group, the number and percentage of participants experiencing any adverse event, experiencing an adverse event in each system organ class (SOC) and experiencing each individual adverse event.

- If two events of the same symptom of the same subject happens within 5 minutes, it will be considered as a single event in the summary.

Subgroups of intensity and subgroups of device-related tables should also be presented.

Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Population	Safety

4.4.5.2 Vital Signs

Vital signs include blood pressure, pulse/heart rate, respiration rate and temperature. A descriptive summary will be provided.

Population	Safety

4.4.5.3 ECG

ECG includes PR, QRS, RR and QT intervals. Descriptive summary will be provided.

Population	Safety

4.4.5.4 Device Malfunctions

Device malfunctions as specified in section 4.3.3.1 will be presented descriptively

Population	Safety

4.4.5.5 Exposure to Study Device

Participant exposure to study device will be presented descriptively

Population	Safety

4.4.5.6 VAS

VAS pain score will also be presented descriptively.

Population	Safety

5 INTERIM ANALYSIS

Interim analysis was planned in SAP V1. However, because the study is terminated after 7th subject completed, we will not carry out interim analysis. All analysis will be considered as final.

6 LIST OF PLANNED LISTINGS, TABLE AND FIGURES

Please see the attached Table of Contents Excel file for the list of planned listings, tables and figures.

Note that this is the planned Table of Contents, based on the actual data. Table numbers, names and structures may change.

The Table of Contents is the same as in SAP V1, however:

- As mentioned in section 2.5, some analyses may not generate results due to inadequate sample size. In such case, no corresponding table/listing/figure will be presented.
- A listing of such table/listing/figure will be given and the reason will be presented.

7 SOFTWARE DOCUMENTATION

- PC SAS – Windows version 9.4 or higher.
- [PC R - Windows version 12.0 or higher.]
- Excel - Microsoft Excel 2007 or higher.

8 REFERENCES

None.