Protocol Number: XSGO-AF01

FIXED RATE CONTINUOUS SUBCUTANEOUS GLUCAGON INFUSION (CSGI) VS PLACEBO IN TYPE 1 DIABETES MELLITUS PATIENTS WITH RECURRENT SEVERE HYPOGLYCEMIA: EFFECTS ON COUNTER REGULATORY RESPONSES TO INSULIN INDUCED HYPOGLYCEMIA

STATISTICAL ANALYSIS PLAN

Prepared for:

Xeris Pharmaceuticals

Version 1.0

Date: 21 October 2019

Study Biostatistician
EmpiriStat, Inc.

_____ Date: _____

Medical
Xeris Pharmaceuticals

_____ Date: 10/22/2019

Clinical
Xeris Pharmaceuticals

_____ Date: 10/22/2019

Regulatory
Xeris Pharmaceuticals

_____ Date: 22 OCT 2019

Biostatistics
Xeris Pharmaceuticals

_____ Date: 22 OCT 2019

Table of Contents

1 LIST OF ABBREVIATIONS 3
2 INTRODUCTION 5
2.1 General Information 5
3 STUDY OBJECTIVES 5
3.1 Primary Objective 5
3.2 Secondary Objectives 6
3.2.1 Efficacy Objectives 6
4 ENDPOINTS 7
4.1 Primary Endpoint 7
4.2 Secondary Endpoints 7
4.2.1 Efficacy Endpoints 7
4.2.2 Safety and Tolerability Endpoints 8
4.2.3 Immunogenicity Endpoints 8
5 SAMPLE SIZE 8
6 RANDOMIZATION 8
7 PLANNED ANALYSES 8
7.1 Analysis Populations 9
7.1.1 Intent-to-treat Population (ITT or All Randomized) 9
7.1.2 Per-Protocol Population (PP Population) 9
7.1.3 Safety Population 9
7.2 Derived Data 9
7.2.1 Baseline 9
7.2.2 Duration/Study Day/Time 10
7.2.3 Conventions for Missing and Partial Dates 10
7.2.4 Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications 10
7.2.5 Missing Diagnosis Dates 12
7.2.6 Duration of Study Drug Exposure 12
7.2.7 Inexact Values 12
7.2.8 Unscheduled Visits and Repeated assessments 12
7.2.9 Counter Regulatory Hormones 12
7.2.10 CGM Derived Parameters 13
7.2.11 Hypoglycemia Symptom Questionnaire 14
7.2.12 Local Tolerability 15
7.3 Conventions 15
7.3.1 Technical Requirements 15
7.3.2 Summary statistics 15
7.3.3 Decimal Places 16
7.4 Subject Disposition 17

7.5 Protocol Deviations 17
7.6 Demographic and Baseline Characteristics 17
7.7 Medical History 17
7.8 Prior and Concomitant Medications 18
7.9 Exposure to Study Drug 18
7.10 Efficacy Analyses 18
7.10.1 Primary Endpoint 18
7.10.2 Primary Efficacy Analysis 19
7.10.3 Sensitivity Analysis 19
7.10.4 Secondary Endpoints 19
7.10.5 Multiplicity 20
7.11 Safety Analyses 20
7.11.1 Adverse Events 20
7.11.2 Laboratory Data 21
7.11.3 Vital Signs 21
7.11.4 Electrocardiogram Data 22
7.11.5 Physical Examination 22
7.11.6 Local Tolerability 22
8 INTERIM ANALYSIS 22
9 DATA SAFETY MONITORING BOARD ANALYSIS 22
10 CHANGES TO PLANNED PROTOCOL ANALYSIS 23
11 REFERENCES 24
12 LIST OF TABLES, FIGURES AND LISTINGS 25

1 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
BSA	Body Surface Area
CGM	Continuous Glucose Monitor
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum Plasma Concentration
CSGI	Continuous Subcutaneous Glucagon Infusion
CSII	Continuous Subcutaneous Insulin Infusion
ECG	Electrocardiogram
GIR	Glucose Infusion Rate
HAAF	Hypoglycemia Associated Autonomic Failure
HbA1c	Glycated hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
IIR	Insulin Infusion Rate
IV	Intravenous
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
QTN	Quartesian LLC
PD	Pharmacodynamics
PG	PG
PGR	Positive Glucose Response
PK	Pharmacokinetic
RBC	Red Blood Cells
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
THC	Tetrahydrocannabinol
Tmax	Time to Maximum Plasma Concentration
T1D	Type 1 Diabetes Mellitus
VAS	Visual Analog Scale
WHO	World Health Organization

2 INTRODUCTION

This document describes the planned data analyses for clinical trial XSGO-AF01 sponsored by Xeris Pharmaceuticals, Inc.

This SAP should be read in conjunction with the amended version of study protocol (XSGO-AF01, Version 4.0, dated 21-Dec 2018). Any further changes to the protocol or eCRF may necessitate updates to the SAP.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different these differences will be identified. If additional analyses are required to supplement objectives described in the SAP, they may be performed and will be identified in the Clinical Study Report (CSR).

2.1 General Information

The proposed indication is for the management of blood glucose in type 1 diabetes patients.

Approximately 20% of the type 1 diabetes mellitus (T1DM) population suffers from recurrent severe hypoglycemia, which is of considerable consequence to the affected persons in rare cases leading to death and to the health care systems as the treatment often involves acute care and even hospitalization.

T1DM patients, with time, lose not only Langerhans' islet Beta-cell, but also Alpha-cell function leading to glucagon deficiency. Glucagon is the primary counterregulatory hormone to insulin. With fewer or no Alpha-cells, persons with diabetes who experience hypoglycemia have a delayed or insufficient glucagon response in order to both raise and normalize their blood glucose levels. Insufficient or deficient glucagon and other counter regulatory hormones response significantly increases the risk of persistent hypoglycemia in the setting of an excess exogenous insulin, that may progress to severe hypoglycemia. Hypoglycemia associated autonomic failure (HAAF) often occurs with recurrent episodes of hypoglycemia, a condition where the biologic stress response to hypoglycemia that includes loss of awareness to hypoglycemia and the corresponding loss of endogenous glucagon secretion. The pre-emptive administration of chronic exogenous glucagon, to partially replace the missing endogenous glucagon, may therefore normalize blood sugars to restore normal blood glucose over time, restore awareness, and ultimately restore autonomic function in the setting of hypoglycemia.

Xeris has used its biocompatible, non-aqueous peptide/protein reformulation technology to create a concentrated, low volume, stable glucagon formulation. Glucagon is indicated for the treatment of severe hypoglycemia in a 1 mg dose for adults and 0.5 mg for children >2 to 12 years, who are <45 kg. Additionally, Xeris glucagon has successfully been delivered for subchronic and chronic use, via the Omnipod® and vial & syringe, across multiple clinical programs.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to compare the plasma epinephrine concentration after 30 minutes of induced hypoglycemia (PG <50mg/dL) in adult T1D subjects with HAAF, who have received 4 weeks of treatment with either CSGI or placebo.

3.2 Secondary Objectives

3.2.1 Efficacy Objectives

1. Compare change in cumulative glucose infusion to maintain glucose at 50 mg/dL for the first 30 minutes after the 50 mg/dL is achieved.
2. Compare change in cumulative insulin infusion to maintain glucose at 50 mg/dL for the first 30 minutes after the 50 mg/dL is achieved.
3. Compare changes in the other counter-regulatory hormones: norepinephrine, glucagon, cortisol and growth hormone.
4. Compare changes from Induction 1 (baseline visit) to Induction 2 (visit 7, week 4) in subject responses to a validated hypoglycemia symptom questionnaire administered during induced hypoglycemia.
5. Compare changes from baseline to week 4 in CGM-derived hypoglycemia parameters of:
   a. Proportional time spent with interstitial glucose < 70, <60 and <50 mg/dL.
   b. Rate of hypoglycemic event episodes at plasma glucose < 70, <60, and <50 mg/dL.
   c. Area over the curve (AOC) of the reduction from baseline in the interstitial glucose from T0 (defined as the date/time of the CSGI injection) to Tx, where x corresponds to time when interstitial glucose < 70, <60 and <50 mg/dL is achieved.
6. Compare change from baseline to week 4 in CGM-derived parameters of:
   a. Average (mean) interstitial glucose and standard deviation
   b. proportional time with 70 ≤ interstitial glucose < 180 mg/dL,
   c. proportional time with interstitial glucose ≥ 180 mg/dL.
7. Describe subject reported hypoglycemic events
   a. Symptomatic events confirmed with self-monitored glucose < 70 mg/dL.
   b. Symptomatic events with no accompanying glucose meter reading or a reading ≥70 mg/dL.
   c. Asymptomatic events of self-monitored glucose < 70 mg/dL.
   d. Severe hypoglycemia as defined by affected consciousness of hypoglycemic origin confirmed by a glucose meter reading <50 mg/dL, requiring external assistance, or prompt recovery upon hypoglycemia treatment.
8. Describe change from Induction 1 (baseline visit) to Induction 2 (visit 7, week 4) of unawareness measured by the Gold scale.
9. Describe basal, bolus and total daily insulin dose changes by treatment group.
10. Describe the time course of the endpoints (primary and secondary 1-7) from week 4 through the rest of the study.
11. Describe non-serious and serious adverse events by treatment group.
12. Describe change from Induction 1 (baseline visit) through Induction 2 (visit 7, week 4) of serum concentrations of glucagon while still on the CSGI, and serum and plasma glucagon antibodies.

4 ENDPOINTS

4.1 Primary Endpoint

Percent change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with PG <50 mg/dL. The average of the non-missing results at each step will be used in analysis.

4.2 Secondary Endpoints

The secondary endpoints for this study include:

4.2.1 Efficacy Endpoints

- Absolute change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with PG <50 mg/dL. The average of the non-missing results at each step will be used in analysis.
- Percent change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with PG <50 mg/dL by Diabetes Duration Category (<15 years, ≥15 years). The average of the non-missing results at each step will be used in analysis.
- Intravenous glucose infusion rate (GIR) [time frame: 0-30 mins induced hypoglycemia] (cumulative glucose infusion rate required to maintain insulin-induced hypoglycemia).
- Intravenous insulin infusion rate [time frame: 0-30 mins induced hypoglycemia] (cumulative insulin infusion rate required to maintain insulin-induced hypoglycemia).
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in other counter regulatory hormones (norepinephrine, glucagon, cortisol and growth hormone plasma concentrations) after 30 mins of induced hypoglycemia.
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in Neuroglycopenic Symptom Scores (if hypoglycemia present) as documented using the hypoglycemia symptom questionnaire.
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in Autonomic Symptom Scores (if hypoglycemia present) as documented using the hypoglycemia symptom questionnaire.
- Change from baseline to Week 4 in CGM-derived hypoglycemia parameters of:
    - Proportional time spent with interstitial glucose (IG) <70, 60, and 50 mg/dL;
    - Rate of hypoglycemic event episodes at thresholds of plasma glucose <70, 60, and 50 mg/dL.
    - Area over the curve (AOC) of the reduction from baseline in the interstitial glucose from T0 (defined as the date/time of the CSGI injection) to Tx, where x corresponds to time when interstitial glucose < 70, <60 and <50 mg/dL is achieved.
- Change from baseline to Week 4 in CGM-derived parameters of:
    - Average interstitial glucose and standard deviation;
    - Proportional time within 70≤interstitial glucose<180 mg/dL;

- Proportional time with interstitial glucose ≥180 mg/dL.

- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in the Gold scale as a measure of hypoglycemia awareness.

4.2.2 Safety and Tolerability Endpoints

- Safety-related parameters including:
  - Reported hypoglycemic events;
  - Insulin dose (adjustments during the study);
  - Vital signs;
  - Physical exam;
  - ECG;
  - Standard safety laboratory parameters;
  - Incidence of adverse events (AEs) and serious adverse events (SAEs);
  - Subjective injection site discomfort as reported by subjects using a 100-mm VAS and other questionnaires;
  - Erythema and/or edema formation at site of injection assessed by an investigator using the modified Draize scale.

4.2.3 Immunogenicity Endpoints

- Plasma glucagon and serum glucagon antibodies;

5 SAMPLE SIZE

The primary hypothesis is to evaluate change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with plasma glucose <50mg/dL between treatment groups. Sample size is based on a closed hierarchical hypothesis test. Using this method, an alpha of 5% will be preserved for each hypothesis test where the next ordered test will only be conducted if statistical significance is achieved for that hypothesis.

Final calculations are based on 80% power and an alpha of 5%, to demonstrate a plasma epinephrine increase compared to placebo of 1.5 nmol/l given a SD of 1.34 nmol/l at an induced PG of 50 mg/dl. Sixteen subjects per treatment group (CSGI high dose, CSGI low dose, and placebo) are required based on the minimum sample size estimate for a comparison.

6 RANDOMIZATION

The randomization scheme is 1:1:1 for high dose, low dose and placebo. Each group will have 16 subjects, but the placebo group will be matched to high and low infusion rates (8 in each group). The randomization is stratified by site.

7 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

7.1 Analysis Populations

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2. Enrolled subjects are subjects that have signed ICF, been assigned a subject number and randomized.

7.1.1 Intent-to-treat Population (ITT or All Randomized)

The ITT population includes all randomized subjects. The ITT population will be analyzed according to the treatment group to which subjects were randomized.

ITT population will be used for primary and secondary efficacy endpoints.

7.1.2 Per-Protocol Population (PP Population)

The PP population will be a subset of the ITT population consisting of those subjects who:

- Satisfy all of the inclusion/exclusion criteria;
- Participate in the study through day 27 with no major protocol deviations

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a serious impact on the efficacy results will lead to the relevant subject being excluded from the PP population. Before database lock, potential subject exclusions from PP population will be reviewed by the Sponsor and documented in a subject evaluability document.

PP population will be used for sensitivity analysis of the primary efficacy endpoint.

7.1.3 Safety Population

All randomized subjects who received at least one study treatment application. Unless otherwise stated, the safety population will be the default analysis population for all safety and tolerability analyses. Analyses will be performed based on actual treatment received, even if different from treatment group to which subjects were randomized.

7.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

7.2.1 Baseline

For endpoints that are based on assessments that are collected once per visit, baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

For baseline of Counter regulatory hormone parameters see Section 7.2.9.

For baseline of CGM derived endpoints see Section 7.2.10.

For baseline of hypoglycemia symptom questionnaire parameters see Section 7.2.11.

7.2.2 Duration/Study Day/Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after day of first dose;
- date of event – date of first dose of study drug, for events before day of first dose.

7.2.3 Conventions for Missing and Partial Dates

All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be presented as recorded on the eCRF (i.e., not completed as per the below rules).

7.2.4 Missing/Partial Start/Stop Date of Adverse Events and Concomitant Medications

When the AE start date is incomplete, then it will be imputed for analysis purposes (e.g. when defining whether AE is treatment-emergent or not).

For concomitant medications, incomplete or missing start date and stop date will be imputed for analysis purposes (e.g. prior and concomitant medications). When the start date and the stop date are both incomplete for a subject, consider imputing the start date first.

Start and stop dates will be imputed as follows:

Incomplete Start Date

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the first dose will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

Missing start date

If the stop date is after the date of the first dose of investigational product, the date of the first dose of investigational product will be assigned to the missing start date

If the stop date is before the date of the first dose of investigational product, the stop date will be assigned to the missing start date.

Incomplete Stop Date

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of investigational product, then the day and month of the date of the last dose will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the last dose will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

7.2.5 Missing Diagnosis Dates

If the month and year are present but the day is missing, then diagnosis day will be set to "01". If only year is recorded, then diagnosis date and month will be set as "01-Jan" for that year.

7.2.6 Duration of Study Drug Exposure

Duration of study drug exposure will be calculated as date of last dosing minus the date of first dosing + 1. The exposure duration will not consider breaks in therapy.

7.2.7 Inexact Values

If a reported value of a clinical laboratory parameter cannot be used in a statistical summary table due, for example, to the fact that a character string is reported for a parameter of the numerical type, a coded value needs to be appropriately determined and used in the statistical analyses. Value of X+0.0001 will be used to impute ">X" character value and X-0.0001 will be used to impute "<X". That is, if X equal to 60, 60.0001 will be used to impute character value of ">60" and 59.999 will be used to impute "<60".

In the case where a laboratory value is recorded as "≥ X" or "≤ X", a value of X will be taken for analysis purposes.

However, the reported values will be presented in data listings.

7.2.8 Unscheduled Visits and Repeated assessments

Only scheduled post-baseline safety and tolerability values will be tabulated. If more than one value is available at scheduled visit, then the last one will be used for analysis.

7.2.9 Counter Regulatory Hormones

Hypoglycemia induction is conducted at

- Visit 3 Day 1 (baseline);
- Visit 7 (Week 4);
- Visit 9 (3 Month Follow-Up);
- Visit 11 (6 Month Follow-Up).

During the hypoglycemia induction, blood samples (2) for counter regulatory hormones (growth, cortisol, epinephrine, norepinephrine, glucagon) are drawn 10 minutes apart at the following steps after meeting target PG value for minimum amount of time:

- Baseline Stabilization (BS; defined as having PG between 90-110 mg/dL for at least 60 minutes, target PG value 100 mg/dL).
- Hypoglycemia induction and stabilization, 2nd step (HIS2, Subject has maintained a PG between 45-54 mg/dl for at least 30 minutes, target PG value 50 mg/dL)

The average of the non-missing results at each step will be used in analysis.

Assessments captured during the hypoglycemia induction at Visit 3, Day 1 are baseline values.

Counter regulatory hormone response to the induction is defined as the difference between HIS2 and BS value (e.g., response=HIS2 average value – BS average value).

7.2.10 CGM Derived Parameters

CGM readings occur every 5 mins. Hence in a complete 24-hour period, 288 CGM readings would be captured. The following endpoints will be calculated per day (e.g., 24-hour period starting from CSGI injection).

- Proportional time spent with interstitial glucose < 70 mg/dL;
- Proportional time spent with interstitial glucose < 60 mg/dL;
- Proportional time spent with interstitial glucose < 50 mg/dL;
- Proportional time within 70≤interstitial glucose<180 mg/dL;
- Proportional time with interstitial glucose ≥180 mg/dL.

Proportional time spent with IG < X mg/dL = (time spent with IG < X mg/dL (minutes) / total time spent with CGM (minutes)) * 100 where x = 70, 60 or 50, given the continuous CGM readings.

- Rate of hypoglycemic event episodes at thresholds of plasma glucose <70 mg/dL;
- Rate of hypoglycemic event episodes at thresholds of plasma glucose <60 mg/dL;
- Rate of hypoglycemic event episodes at thresholds of plasma glucose <50 mg/dL;

Rate of hypoglycemic event episodes at thresholds of <X mg/dL is defined as the number of episodes with PG < X mg/dL, where 70, 60 or 50. Subsequent PG measures with the result of < X mg/dL should be considered as the same episode.

- Average interstitial glucose;
- Interstitial glucose standard deviation;
- Area over the curve (AOC) of the reduction from baseline in the interstitial glucose from T0 (defined as the date/time of the CSGI injection) to Tx, where x corresponds to time when interstitial glucose < 70, <60 and <50 mg/dL is achieved.

AOC calculations will be done using the standard trapezoidal rule

$$\text{AOC} = -\left(\sum_{i=0}^{x}\left(\frac{abs(reduction\ in\ IG_i)+\text{abs}(reduction\ in\ IG_{i+1})}{2}\right) * (T_{i+1} - T_i)\right)$$

Where: abs(reduction in IGi) = absolute value of change from baseline in interstitial glucose at time i, and (Ti+1 – Ti) is the Time difference in minutes between time i and time i+1.

For endpoints that will be calculated per day - baseline will be based on the CGM data collected on the latest day prior to the date/time of the first CSGI injection. For the AOC endpoint baseline will be the latest interstitial glucose measure obtained prior to the date/time of the first CSGI injection.

7.2.10.1 Weekly endpoints

Additionally, all derived CGM endpoints will be derived on a weekly basis. The following weeks will be analyzed: Baseline (Week), Week 1, Week 2, Week 3, Week 4, Month 3 and Month 6. CGM-Derived parameters will be based on CGM data that fall in the following timeframe:

Week	Time window (Days)	
Baseline	7 days prior to day 1	
Week 1	1	7
Week 2	8	14
Week 3	15	21
Week 4	22	28
Month 3	7 days prior to date of Month 3 visit	
Month 6	7 days prior to date of Month 6 visit	

When deriving weekly endpoints - baseline will be based on the CGM data collected 7 days prior to the date/time of the first CSGI injection. For the AOC endpoint baseline will be the same as for the AOC calculated by day.

7.2.11 Hypoglycemia Symptom Questionnaire

This questionnaire measures the severity of 8 symptoms of hypoglycemia on a 1 (absent) to 6 (severe) scale. The symptoms are grouped by type of symptom (Neuroglycopenic or Autonomic) per following table:

Neuroglycopenic Symptoms (Score 1-6)	***Autonomic Symptoms (Score 1-6)***
Dizziness Blurred vision Difficulty in thinking Faintness	Sweating Tremor Palpitations Feeling of nervousness
Average Neuroglycopenic Symptom Score (ANS)	Average Autonomic Symptom Score (AAS)
Average Total Symptom Score (ATS)	
Overall Assessment of Hypoglycemia	
Do you currently feel hypoglycemic? (Yes/No)	

An average Neuroglycopenic Symptom Score (ANS), Autonomic Symptom Score (AAS) and Average Total Symptom Score (ATS) will be calculated from individual symptom scores. Average will be calculated if at least > 50% items in each group (Neuroglycopenic and Autonomic) will be not missing.

Overall Assessment of Hypoglycemia

will be treated as a categorical variable and analyzed with descriptive statistics by timepoints;

Gold Scale of Hypoglycemia unawareness

The questionnaire measures on a 7-point scale a subject's awareness of onset of hypoglycemia by asking a single question "To what extent are you aware of the onset of hypoglycemia?".

Baseline for all questionnaire measures is defined as the last value of obtained just before IV push dose of insulin at visit 3 (Day 1, Baseline).

A separate summary for Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS), Average Total Scores (ATS) and Overall Assessment of Hypoglycemia assessed with PG <70 mg/dl and PG <50 mg/dl will be presented.

7.2.12 Local Tolerability

7.2.12.1 Injection Site Discomfort Assessment

This assessment consists of a

- Visual Analog Scale (VAS) (0-100mm)
- Delivery Site Discomfort Description and Duration questionnaire that consists of the following questions:
    - Discomfort question with the following categories: Pain, Itching, (Tingling, twitching or numbness), Irritation and Other.
    - Question regarding how long after administration did the discomfort start and how long it lasted.

This assessment is administered at visit 3 (Day 1, Baseline) and Visit 4 (Day 7) with the VAS scale being administered at several timepoints and the discomfort questionnaire being administered at 10 mins following delivery of study drug.

7.2.12.2 Draize Scale

This scale measures presence/severity of Erythema and Edema Formation on a 0-4 scale (not present-severe) at Visit 4 (Day 7) and visit 7 (Day 28) at multiple timepoints.

7.3 Conventions

7.3.1 Technical Requirements

The statistical analyses will be performed by Quartesian Clinical Research, using SAS Version 9.4 (or higher). Datasets will be prepared using standards from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and ADaM (Analysis Dataset Model). Tables, figures and listings will be produced in landscape format if not specified otherwise.

7.3.2 Summary statistics

Data will be tabulated by time point where appropriate. The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables and figures.

All summaries will be presented by treatment group for baseline and each scheduled visit and timepoint, where applicable. If more than one assessment available per timepoint, then last assessment will be used for analysis.

Summaries will be presented by treatment group and overall. Treatment group labels will be displayed as follows:

CSGI				
Low Dose (20 ug/hr)	High Dose (80 ug/hr)	Combined (Low + High)	Placebo	Total

Listings will be sorted in the following order: subject, parameter, and visit unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment/sequence groups.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized with frequencies and percentages. For each variable, all pre-specified categories will be shown. Zero counts will be presented without percent.

N will be used as percentage denominator in descriptive summaries, if not specified otherwise.

Missing will be counted as difference of subjects at each visit and number of assessments. Note: Records collected from eCRF or eDT will not be used for 'Missing' statistics and can be used only for reference.

7.3.3 Decimal Places

Unless otherwise stated, continuous data will be summarized with the following descriptive statistics: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), median, minimum (Min), maximum (Max). For presentation, Min and Max will have the same number of decimal places as the original data; the mean, geometric mean and median will be presented to 1 decimal place greater than Min, Max; SD will be to 2 decimal places greater than Min, Max; percentages will be presented rounded to 1 decimal place. Number of decimals for descriptive statistics will be limited with 4 decimals. Minimum and maximum will be displayed with the number of decimals reported in CRF and can be limited to 3 decimals; converted or derived values will have from 3 to 4 significant digits in summary statistics and will be determined in case-by-case basis.

If some parameter contains original and calculated values or certain timepoints (e.g. hypoglycemia scores), then one decimal will be added to Min, Max for derived timepoints or parameters, not including other descriptive statistics.

P-values will be displayed with 3 decimal places. P-values that are less than 0.001 will be presented as "<0.001".

7.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who were screened, screen failures, randomized and who are in each analysis population will be summarized by treatment group and overall.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment group and overall for ITT population

7.5 Protocol Deviations

Protocol deviations will be identified during blinded data review by Sponsor and Medical Monitor and classified as major or minor. Subjects with major protocol deviations will be excluded from PP population..

The number of subjects with major and minor protocol deviations will be summarized descriptively with counts and percentages for ITT population and listed.

7.6 Demographic and Baseline Characteristics

Demographic characteristics will include:

- Age;
- Gender;
- Ethnicity;
- Race.

Baseline characteristics will include:

- Weight;
- Height;
- Body Mass Index (BMI);
- Body Surface Area (BSA);
- Gold scale for hypoglycemia unawareness;
- Glucose Correction Factor per Unit of Insulin (mg/dL);
- Hemoglobin A1C (%)
- Hemoglobin A1C (%) category (≤8%, >8%)
- Duration of diabetes (years)
- Duration of diabetes category (<15 yrs, ≥15 yrs)

Demographic and baseline characteristics will be listed and analyzed with descriptive statistics for Safety, ITT and PP population.

7.7 Medical History

Subjects will undergo a complete medical history at screening.

Medical history of each subject will be collected at screening visit and coded using the MedDRA 22.0 dictionary.

Medical history will be listed and analyzed with descriptive statistics by SOC and PT for ITT population.

7.8 Prior and Concomitant Medications

Subjects should be on a stable dose of all concomitant medications for at least 30 days prior to Screening. All subjects must have their concomitant medications reviewed at each visit. Medications taken within 4 weeks before Day 1 will be documented in the CRF. Any changes to a subject's concomitant medication regimen will be documented.

Prior medication is defined as any medication taken within 4 weeks before treatment administration.

Concomitant medication is defined as any non-study medication taken on or after blinded study treatment was administered.

If dates of medications are incomplete, missing, or medication is ongoing, the medication will be considered as concomitant if there is no evidence that medication intake stopped before study treatment. The medication will be considered as prior if there is an evidence that medication intake started before the study treatment, and there is a possibility that medication intake started not earlier than 6 months before screening.

Concomitant Medications, Drugs/Therapies will be coded using WHODrug Global B3 Mar 2019.

Prior and Concomitant medication will be summarized and listed with ATC level 2 and preferred term for the Safety population.

Patients may have more than one medication per ATC category and PT. At each level of patient summarization, a patient will be counted only once.

7.9 Exposure to Study Drug

Extent of exposure (number of days of exposure to study drug) will be presented for the Safety population.

7.10 Efficacy Analyses

7.10.1 Primary Endpoint

The primary endpoint is the percent change from Induction 1 (baseline visit) to Induction 2 (visit 7, week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with PG < 50 mg/dL.

Hypotheses of interest:

H_0: $\mu_x=\mu_y$ vs H_1: $\mu_x\neq\mu_y$

where the treatment comparison of interest (ranked in order of interest) is as follows:

- CSGI Combined vs placebo
- CSGI High vs placebo

- CSGI Low vs placebo
- CSGI High vs CSGI Low

For details regarding multiplicity please see section 7.10.5.

7.10.2 Primary Efficacy Analysis

The analysis of the primary endpoint will be performed using a two-group t-test for each treatment comparison of interest. The primary endpoint will also be analyzed, stratifying by duration of diabetes (<15 yrs, ≥15 yrs) as a secondary analysis.

A closed testing hierarchical procedure will be used to control for multiplicity. See section 7.10.5.

7.10.3 Sensitivity Analysis

The following Sensitivity analyses of the primary outcome in the PP population will be conducted:

- All subjects who are lost to follow-up or have missing outcome data will be considered to have a favorable outcome (e.g., value will be set to the largest (maximum) improved change in either treatment groups) in each treatment group
- Subjects who are lost to follow-up or have a missing primary endpoint at Day 27 in the high or low dose group will be considered to have an unfavorable outcome (e.g., value will be set to baseline outcome) whereas in the placebo group will be considered to have a favorable outcome
- Subjects who have a missing outcome data will be excluded from the analysis

7.10.4 Secondary Endpoints

- Intravenous glucose infusion rate (GIR) [time frame: 0-30 mins induced hypoglycemia] (cumulative glucose infusion rate required to maintain insulin-induced hypoglycemia)
- Intravenous insulin infusion rate [time frame: 0-30 mins induced hypoglycemia] (cumulative insulin infusion rate required to maintain insulin-induced hypoglycemia)
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in other counter regulatory hormones (norepinephrine, glucagon, cortisol and growth hormone plasma concentrations) after 30 mins of induced hypoglycemia
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in Neuroglycopenic Symptom Scores (if hypoglycemia present) as documented using the hypoglycemia symptom questionnaire
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in Autonomic Symptom Scores (if hypoglycemia present) as documented using the hypoglycemia symptom questionnaire
- Change from baseline to Week 4 in CGM-derived hypoglycemia parameters of:
    - Proportional time spent with interstitial glucose <70, 60, and 50 mg/dL

  - Rate of hypoglycemic event episodes at thresholds of plasma glucose <70, 60, and 50 mg/dL
  - Area over the curve (AOC) of the reduction from baseline in the interstitial glucose from T0 to Tx, where x corresponds to time when interstitial glucose < 70, <60 and <50 mg/dL is achieved.
- Change from baseline to Week 4 in CGM-derived parameters of:
  - Average interstitial glucose and standard deviation
  - Proportional time within 70≤interstitial glucose<180 mg/dL
  - Proportional time with intersititial≥180 mg/dL
- Change from Induction 1 (baseline visit) to Induction 2 (visit 7, Week 4) in the Gold scale as a measure of hypoglycemia awareness

Pharmacodynamic endpoints (e.g., CGM derived parameters, counter regulatory hormones, GIR, insulin infusion rate) will be analyzed using a 1-factor (treatment) analysis of variance (ANOVA) model with treatment as the main effect.

The change from baseline for Gold scale, Neuroglycopenic Symptom Score, and Autonomic Symptom Score endpoints will be analyzed using non-parametric analysis of variance (Wilcoxon rank-sum test).

7.10.5 Multiplicity

The analysis of the primary endpoint will be performed using a hierarchical hypothesis test in which an alpha of 5% will be preserved for each test. Testing will be employed in the following order:

• CSGI combined versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)

• CSGI high dose versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)

• CSGI low dose versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)

• CSGI high dose versus CSGI low dose

All secondary endpoints and the supportive analyses will be considered as descriptive evidence of efficacy and will be analyzed without any procedures to account for multiple comparisons.

7.11 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Population.

7.11.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug or
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug.

A treatment-related AE is defined as an AE as being related to the study drug if response to "Is there a reasonable possibility that the drug caused the event?" is Yes. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs:

- Overall incidence and the number of AEs, SAEs, TEAEs leading to withdrawal.
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment-related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- TEAE by system organ class, preferred term and maximum severity, incidence
- Treatment related TEAE by system organ class, preferred term and maximum severity, incidence
- TEAEs leading to early withdrawal by system organ class and preferred term, incidence
- Listing of Serious TEAEs (presented in the Table section of the appendices)
- Listing of Deaths (presented in the Table section of the appendices)

All AEs will be listed.

7.11.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, urinalysis and serum chemistry parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

7.11.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Body weight (kg).

7.11.4 Electrocardiogram Data

Overall ECG interpretation (Normal, Abnormal NCS, and Abnormal CS) data will be summarized by visit and treatment. Additionally, shift tables in relation to the overall interpretation from baseline to each follow-up visit will be presented.

7.11.5 Physical Examination

Physical examination data will be listed.

7.11.6 Local Tolerability

7.11.6.1 Injection Site Discomfort Assessments

Descriptive statistics for observed Visual Analog Scale (VAS) Score (mm; measure of discomfort) for injection Site discomfort will be presented by timepoint (10, 30, 60 and 180 minutes post-injection), visit and treatment group.

Number (percent) of subjects who had any discomfort when the pump administered study drug presented by visit and treatment group. For those with any discomfort, Incidence of type of discomfort (Categories: Pain; Itching; Tingling, twitching or numbness; Irritation (e.g., burning, stinging) and how long after study drug administration did the discomfort start (less than 1 minute, 1-2 minutes, 3-5 minutes, 6-9 minutes, at least 10 minutes) and Descriptive statistics for how long did the discomfort last (minutes) will be presented by visit and treatment group.

7.11.6.2 Draize Scale

Incidence of erythema will be presented by summarizing the Draize Scale Score for Erythema Formation by time point, visit and treatment group. The incidence if edema will be summarized similarly based on the Draize Scale Score for Edema Formation.

A shift table comparing Week 1, 10 minutes post-dose to Week 1, 60 minutes post-dose and Week 4, 10- and 60-minutes post-dose scores will be presented by treatment group.

8 INTERIM ANALYSIS

No interim analyses are planned. However, the primary endpoint analysis at Day 27 will be executed when the last subject data for this visit has been completed and monitored. Primary endpoint analysis results will only be unblinded at the treatment group level (CSGI high dose, CSGI low dose, placebo) and individual treatment assignments will remain blinded until the end of the study and the final database locked. Study investigators, study staff, subjects and the sponsor will remain blinded to individual group assignments. Primary endpoint analysis is defined as all analyses that include the evaluation of epinephrine (both primary and secondary designated analyses) and other corresponding counter regulatory hormones (norepinephrine, cortisol, glucagon and growth hormone).

9 DATA SAFETY MONITORING BOARD ANALYSIS

There is no data and safety monitoring board for this study.

10 CHANGES TO PLANNED PROTOCOL ANALYSIS

- Primary analysis endpoint updated to percent change from Induction 1 (baseline visit) to Induction 2 (visit 7, week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycemia with plasma glucose <50 mg/dL.
- Absolute change from Induction 1 (baseline visit) to Induction 2 (visit 7, week 4) in plasma epinephrine concentration after 30 minutes of induced hypoglycaemia with plasma glucose <50 mg/dL moved from primary to secondary endpoint.
- The primary analyses will also be performed by diabetes duration category (<15 yrs, ≥15 yrs) and included in the secondary analyses.
- The secondary endpoint of describing subject reported severe hypoglycemic events when glucose meter reading <36 mg/dL was updated to glucose meter reading <50mg/dL. This was a typo in the protocol.
- The Per-Protocol Population definition has been updated to include subjects who participate in the study through day 27 with no major protocol deviations because treatment compliance data was not captured for the study.

11 REFERENCES

SAS Institute Inc., Cary, NC, 27513, USA

12 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings (TFLs) for the study. Those marked with an asterisk (*) are planned for the primary endpoint analysis and presentation of the accompanying safety analysis for that time period (See Section 8).

Table Number	Table Title	Shell Number (if repeat)
14.1.1.1*	Summary of Subject Disposition - All Subjects	
14.1.1.2*	Summary of Analysis Populations - All Randomized Subjects	
14.1.2*	Summary of Protocol Deviations - Intent-to-Treat Population	
14.1.3.1*	Summary of Demographic and Baseline Characteristics - Safety Population	
14.1.3.2*	Summary of Demographic and Baseline Characteristics - Intent-to-Treat Population	14.1.3.1
14.1.3.3*	Summary of Demographic and Baseline Characteristics - Per Protocol Population	14.1.3.1
14.1.4*	Summary of Medical History - Intent-to-Treat Population	
14.2.1.1*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl Intent-to-Treat Population	
14.2.1.2*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl Per Protocol Population	14.2.1.1
14.2.1.3*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl, Sensitivity analysis 1* Per Protocol Population	14.2.1.1
14.2.1.4*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl, Sensitivity analysis 2* Per Protocol Population	14.2.1.1
14.2.1.5*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl, Sensitivity analysis 3* Per Protocol Population	14.2.1.1
14.2.2.1.1*	Absolute change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl Intent-to-Treat Population	14.2.1.1

Table Number	Table Title	Shell Number (if repeat)
14.2.2.1.2*	Absolute change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl Per Protocol Population	14.2.1.1
14.2.2.2.1*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl by Duration of Diabetes Category Intent-to-Treat Population	14.2.1.1
14.2.2.2.2*	Percent change from Induction 1 (Baseline visit) to Induction 2 (Visit 7, Week 4) in Plasma Epinephrine Concentration During Induced Hypoglycemia with PG <50 mg/dl by Duration of Diabetes Category Per Protocol Population	14.2.1.1
14.2.2.3.1*	Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones During Induced Hypoglycemia with PG <50 mg/dl - Intent-to-Treat Population	
14.2.2.3.2*	Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones During Induced Hypoglycemia with PG <50 mg/dl - Per Protocol Population	14.2.2.3.1
14.2.2.4.1*	Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones During Induced Hypoglycemia with PG <50 mg/dl – ANOVA - Intent-to-Treat Population	
14.2.2.4.2*	Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones During Induced Hypoglycemia with PG <50 mg/dl – ANOVA - Per Protocol Population	14.2.2.4.1
14.2.2.5.1	Summary of Cumulative Glucose Infusion Rate (GIR) Required to Maintain Insulin-Induced Hypoglycemia Intent-to-Treat Population	
14.2.2.5.2	Summary of Cumulative Glucose Infusion Rate (GIR) Required to Maintain Insulin-Induced Hypoglycemia Per Protocol Population	14.2.2.5.1
14.2.2.6.1	Summary of Cumulative Insulin Infusion Rate Required to Maintain Insulin-Induced Hypoglycemia Intent-to-Treat Population	14.2.2.5.1
14.2.2.6.2	Summary of Cumulative Insulin Infusion Rate Required to Maintain Insulin-Induced Hypoglycemia Per Protocol Population	14.2.2.5.1
14.2.2.7.1.1	Change from Induction 1 (Baseline visit) in Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <70 mg/dl Intent-to-Treat Population	
14.2.2.7.1.2	Change from Induction 1 (Baseline visit) in Average Neuroglycopenic Scores (ANS), Average Autonomic	14.2.2.7.1.1

Table Number	Table Title	Shell Number (if repeat)
	Scores (AAS) and Average Total Scores (ATS) with PG <70 mg/dl Per Protocol Population	
14.2.2.7.2.1*	Change from Induction 1 (Baseline visit) in Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <50 mg/dl Intent-to-Treat Population	14.2.2.7.1.1
14.2.2.7.2.2*	Change from Induction 1 (Baseline visit) in Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <50 mg/dl Per Protocol Population	14.2.2.7.1.1
14.2.2.8.1.1	Summary of Overall Assessment of Hypoglycemia with PG <70 mg/dl Intent-to-Treat Population	
14.2.2.8.1.2	Summary of Overall Assessment of Hypoglycemia with PG <70 mg/dl Per Protocol Population	14.2.2.8.1.1
14.2.2.8.2.1	Summary of Overall Assessment of Hypoglycemia with PG <50 mg/dl Intent-to-Treat Population	14.2.2.8.1.1
14.2.2.8.2.2	Summary of Overall Assessment of Hypoglycemia with PG <50 mg/dl Per Protocol Population	14.2.2.8.1.1
14.2.2.9.1.1	Change from Baseline in CGM-Derived Hypoglycemia Parameters by Day - Intent-to-Treat Population	
14.2.2.9.1.2	Change from Baseline in CGM-Derived Hypoglycemia Parameters by Day - Per Protocol Population	14.2.2.9.1.1
14.2.2.9.2.1	Change from Baseline in CGM-Derived Hypoglycemia Parameters by Week - Intent-to-Treat Population	14.2.2.9.1.1
14.2.2.9.2.2	Change from Baseline in CGM-Derived Hypoglycemia Parameters by Week - Per Protocol Population	14.2.2.9.1.1
14.2.2.10.1*	Change from Induction 1 (Baseline visit) in Gold Scale Assessment of Hypoglycemia Unawareness - Intent-to-Treat Population	
14.2.2.10.2*	Change from Induction 1 (Baseline visit) in Gold Scale Assessment of Hypoglycemia Unawareness - Per Protocol Population	14.2.2.10.1
14.3.1.1*	Overview of Adverse Events - Safety Population	
14.3.1.2*	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term - Safety Population	
14.3.1.3	Summary of Treatment-related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term - Safety Population	14.3.1.2
14.3.1.4*	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term - Safety Population	14.3.1.2
14.3.1.5	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class, Preferred Term - Safety Population	14.3.1.2

Table Number	Table Title	Shell Number (if repeat)
14.3.1.6	Summary of Serious Adverse Events Leading to Death by System Organ Class, Preferred Term - Safety Population	14.3.1.2
14.3.1.7	Summary of Serious Adverse Events Leading to Study Discontinuation by System Organ Class, Preferred Term - Safety Population	14.3.1.2
14.3.1.8.1	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity - Safety Population	
14.3.1.8.2	Summary of Treatment-related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity - Safety Population	14.3.1.8.1
14.3.1.9*	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Relationship to Study Drug - Safety Population	
14.3.2.1	Summary of Deaths - Safety Population	
14.3.2.2*	Summary of Serious Adverse Events - Safety Population	
14.3.2.3	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation - Safety Population	
14.3.4.1.1	Summary of Clinical Chemistry Results - Safety Population	
14.3.4.2.1	Summary of Clinical Hematology Results - Safety Population	14.3.4.1.1
14.3.4.1.2	Summary of Clinical Chemistry Results: Shift from Baseline - Safety Population	
14.3.4.2.2	Summary of Clinical Hematology Results: Shift from Baseline Safety Population	14.3.4.1.2
14.3.5.1	Summary of Treatment Exposure Safety Population	
14.3.6.1	Summary of Vital Signs - Safety Population	
14.3.7.1.1	Summary of Overall ECG Interpretation - Safety Population	
14.3.7.1.2	Summary of Overall ECG Interpretation: Shift from Baseline - Safety Population	
14.3.7.2.1	Summary of Local Tolerability – Injection Site VAS Discomfort Score - Safety Population	
14.3.7.2.2	Summary of Local Tolerability – Injection Site Discomfort at 10 Minutes Following the Injection of Study Drug - Safety Population	
14.3.7.2.3	Summary of Local Tolerability – Draize Scale - Safety Population	
14.3.7.2.4	Summary of Local Tolerability – Draize Scale: Shifts from Week 1 - Safety Population	
14.3.8.1	Summary of Prior Medications - Safety Population	

Table Number	Table Title	Shell Number (if repeat)
14.3.8.2*	Summary of Concomitant Medications - Safety Population	14.3.8.1

Figure Number	Figure Title	Shell Number (if repeat)
14.2.2.1*	Observed Values and Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones Over Time - Intent-to-Treat Population	
14.2.1.2*	Observed Values and Change from Induction 1 (Baseline visit) in Counter Regulatory Hormones Over Time Per Protocol Population	14.2.2.1
14.2.2.1	Cumulative Glucose Infusion Rate (GIR) Required to Maintain Insulin-Induced Hypoglycemia Over Time - Intent-to-Treat Population	
14.2.2.2	Cumulative Glucose Infusion Rate (GIR) Required to Maintain Insulin-Induced Hypoglycemia Over Time - Per Protocol Population	14.2.2.1
14.2.3.1	Cumulative Insulin Infusion Rate Required to Maintain Insulin-Induced Hypoglycemia Over Time - Intent-to-Treat Population	14.2.2.1
14.2.3.2	Cumulative Insulin Infusion Rate Required to Maintain Insulin-Induced Hypoglycemia Over Time - Per Protocol Population	14.2.2.1
14.2.4.1.1	Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <70 mg/dl Over Time - Intent-to-Treat Population	
14.2.4.1.2	Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <70 mg/dl Over Time - Per Protocol Population	14.2.4.1.1
14.2.4.2.1*	Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <50 mg/dl Over Time - Intent-to-Treat Population	14.2.4.1.1
14.2.4.2.2*	Average Neuroglycopenic Scores (ANS), Average Autonomic Scores (AAS) and Average Total Scores (ATS) with PG <50 mg/dl Over Time - Per Protocol Population	14.2.4.1.1
14.2.5.1.1	CGM-Derived Hypoglycemia Parameters by Day - Intent-to-Treat Population	
14.2.5.1.2	CGM-Derived Hypoglycemia Parameters by Day - Per Protocol Population	14.2.5.1.1

Figure Number	Figure Title	Shell Number (if repeat)
14.2.5.2.1	CGM-Derived Hypoglycemia Parameters by Week - Intent-to-Treat Population	14.2.5.1.1
14.2.5.2.2	CGM-Derived Hypoglycemia Parameters by Week - Per Protocol Population	14.2.5.1.1
14.2.6.1	Gold Scale Assessment of Hypoglycemia Unawareness Over Time - Intent-to-Treat Population	
14.2.6.2	Gold Scale Assessment of Hypoglycemia Unawareness Over Time - Per Protocol Population	14.2.6.1

Listing Number	Listing Title	Shell Number (if repeat)
16.1.7*	Randomization of Subjects Intent-to-Treat Population	
16.2.1.1*	Subject Disposition All Subjects	
16.2.1.2*	Subject Eligibility and Inclusion/Exclusion Criteria Assessment All Subjects	
16.2.2.1*	Protocol Deviations All Subjects	
16.2.2.2	Major Protocol Deviations All Subjects	
16.2.3*	Analysis Populations All Randomized Subjects	
16.2.4.1*	Subject Demographic and Baseline Characteristics Intent-to-Treat Population	
16.2.4.2*	Medical History Intent-to-Treat Population	
16.2.4.3*	Prior and Concomitant Medications Safety Population	
16.2.5.1	Study Drug Administration Intent-to-Treat Population	
16.2.5.2	Euglycemic Baseline and Hypoglycemia Induction Intent-to-Treat Population	
16.2.5.3*	Plasma Blood Glucose during Euglycemic Maintenance, Hypoglycemia Induction and Stabilization, and Normalization to Euglycemia All Subjects	
16.2.5.4	Plasma Blood Glucose Levels from Plasma Glucose Screener Intent-to-Treat Population	
16.2.6.1	Subject Insulin Diary Safety Population	
16.2.6.2.1	Interstitial Glucose Parameters During CGM Monitoring All Subjects	
16.2.6.3.1	Average Glucose Infusion Rate to Maintain Glucose at 50 mg/dL for the first 30 minutes after 50 mg/dL Achieved during Hypoglycemia Stabilization All Subjects	
16.2.6.3.2	Cumulative Glucose Infusion to Maintain Glucose at 50 mg/dL for the first 30 minutes after 50 mg/dL Achieved during Hypoglycemia Stabilization All Subjects	
16.2.6.4.1.1	Hypoglycemia Symptom Questionnaire Responses After Achieving Plasma Glucose of < 70 mg/dL All Subjects	
16.2.6.4.1.2*	Hypoglycemia Symptom Questionnaire Responses After Achieving Plasma Glucose of < 50 mg/dL All Subjects	

Listing Number	Listing Title	Shell Number (if repeat)
16.2.6.4.2.1	Average Neuroglycopenic, Autonomic and Total Symptom Scores After Achieving Plasma Glucose of < 70 mg/dL All Subjects	
16.2.6.4.2.2*	Average Neuroglycopenic, Autonomic and Total Symptom Scores After Achieving Plasma Glucose of < 50 mg/dL All Subjects	
16.2.6.4.3.1	Overall Assessment of Hypoglycemia After Achieving Plasma Glucose of < 70 mg/dL All Subjects	
16.2.6.4.3.2	Overall Assessment of Hypoglycemia After Achieving Plasma Glucose of < 50 mg/dL All Subjects	
16.2.6.4.4	Gold Scale of Hypoglycemia Unawareness All Subjects	
16.2.7*	Adverse Events All Patients	
16.2.8.1*	Hormones and Counter Regulatory Hormone Response All Patients	
16.2.8.2	Serum Concentration of Glucagon during CSGI Treatment All Patients	
16.2.8.3	Serum and Plasma Concentration of Glucagon Antibodies All Patients	
16.2.8.4	Clinical Laboratory Results: Hematology All Patients	
16.2.8.5	Laboratory Results: Chemistry, Complete Metabolic Panel Safety Population	
16.2.8.6	Laboratory Results: Drug Screen All Patients	
16.2.8.7	Listing of Laboratory Results: Serology Intent-to-Treat Population	
16.2.8.8	Urine Pregnancy Test Results All Patients	
16.2.9.1	Injection Site Discomfort - Visual Analog Scale (VAS) Safety Population	
16.2.9.2	Injection Site Discomfort - Injection Site Discomfort Description and Duration Questionnaire Safety Population	
16.2.9.3	Injection Site Reactions - Draize Scale Safety Population	
16.2.9.4	Vital Signs and Weight Safety Population	
16.2.9.5	12-Lead Electrocardiogram (ECG) Interpretation Safety Population	
16.2.9.6	Physical Examinations Safety Population	
16.2.10	Comments All Patients	