Statistical Analysis Plan for:

PROTOCOL XSGP-303

G-PEN™ (GLUCAGON INJECTION) COMPARED TO LILLY

GLUCAGON (GLUCAGON FOR INJECTION [RDNA ORIGIN])

FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULTS WITH

T1D: A PHASE 3B MULTI-CENTERED, RANDOMIZED,

CONTROLLED, SINGLE BLIND, 2-WAY CROSSOVER STUDY

TO EVALUATE EFFICACY AND SAFETY

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STATISTICAL ANALYSIS PLAN

G-PEN™ (GLUCAGON INJECTION) PROTOCOL XSGP-303 V2.0

G-PEN™ (GLUCAGON INJECTION) COMPARED TO LILLY GLUCAGON (GLUCAGON FOR INJECTION [RDNA ORIGIN]) FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULTS WITH T1D: A PHASE 3B MULTI-CENTERED, RANDOMIZED, CONTROLLED, SINGLE BLIND, 2-WAY CROSSOVER STUDY TO EVALUATE EFFICACY AND SAFETY

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Approval: _____ _____ _____
          Sponsor/Name   Signature   Date

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Abbreviations and Specialist Terms

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRC	Clinical Research Center
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DMSO	Dimethyl sulfoxide
ECG	Electrocardiogram
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Im	Intramuscular

IRB	Institutional Review Board
IUD	Intra-uterine device
Iv	Intravenous
Kg	Kilogram
L	Liters
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
min	Minute
mmHg	Millimeters Mercury
mM	Millimoles per Liter
NOAEL	No Observed Adverse Effect Level
PG	Plasma Glucose
PD	Pharmacodynamics
PK	Pharmacokinetic
RBC	Red blood cells
rDNA	Recombinant
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
Sc	Subcutaneous
THC	Tetrahydrocannabinol
Tmax	Time to Maximum Plasma Concentration
T1D	Type 1 Diabetes Mellitus
ULN	Upper Limit of Normal

VAS	Visual Analog Scale
WHO	World Health Organization
YSI	Yellow Springs Instrument

1 OVERVIEW

1.1 INTRODUCTION

This documentation describes the planed data analyses for clinical trial XSGP-303 sponsored by Xeris Pharmaceuticals, Inc.

1.2 OBJECTIVES

1.2.1 Primary Objective

The primary objective of this study is to demonstrate the efficacy (return to plasma glucose >70.0 mg/dL) of G-Pen 1 mg (test) to be non-inferior to Lilly Glucagon 1 mg (reference), in T1D subjects in a state of insulin-induced hypoglycemia. This will be assessed by the comparison of failure rates of plasma glucose to have a measured value > 70.0 mg/dL within 30 minutes of administration of glucagon.

1.2.2 Secondary Objectives

The secondary objectives of this study are:

- To demonstrate the efficacy (either return to plasma glucose >70.0 mg/dL or an increase in plasma glucose ≥ 20 mg/dL within 30 minutes post study drug injection) of G-Pen 1 mg (test) to be non-inferior to Lilly Glucagon 1 mg (reference), in T1D subjects in a state of insulin-induced hypoglycemia.

- To demonstrate the efficacy (return to plasma glucose >70.0 mg/dL or alleviation of all neuroglycopenic symptoms at 30 minutes post study drug injection) of G-Pen 1 mg (test) to be non-inferior to Lilly Glucagon 1 mg (reference), in T1D subjects in a state of insulin-induced hypoglycemia.

- To compare the pharmacodynamics characteristics of G-Pen 1 mg (test) versus Lilly Glucagon 1 mg (reference) in T1D subjects who are in a state of insulin-induced hypoglycemia.

- To compare G-Pen (test) and Lilly Glucagon (reference) with regards to hypoglycemia symptom relief.

- To compare G-Pen (test) and Lilly Glucagon (reference) with regards to the preparation time required to inject to the abdomen from a decision to treat.

- To compare the safety and tolerability of G-Pen 1 mg (test) versus Lilly Glucagon 1 mg (reference) in T1D subjects who are in a state of insulin-induced hypoglycemia.

1.3 ANALYSIS SOFTWARE

SAS 9.1.3 or newer (Windows)

1.4 MODIFICATIONS FROM THE STATISTICAL SECTION IN THE PROTOCOL

None

2 INVESTIGATIONAL PLAN

2.1 STUDY DESIGN AND RANDOMIZATION

2.1.1 Study Design

This is a non-inferiority, multi-centered, randomized, controlled, single-blind, two-way crossover efficacy and safety in-patient study in subjects with Type 1 diabetes mellitus (T1D).

Table 2-1:   Randomized treatment sequence

Group	Dose 1	Dose 2
1	G-Pen™ 1 mg	Lilly 1 mg
2	Lilly 1 mg	G-Pen™ 1 mg

The procedure consists of:

1. Inducing hypoglycemia by IV administration of regular insulin diluted in normal saline until the subjects reach a verified stable hypoglycemic state.

2. Treating subcutaneously with either 1 mg Lilly Glucagon or 1 mg G-Pen™ (glucagon injection).

Blood glucose levels will be monitored for up to 180 minutes post-dosing. Subjects will also complete a questionnaire about symptoms of hypoglycemia during the hypoglycemia induction phase and for up to 180 minutes after treatment with glucagon.

The specific hypoglycemia induction procedures and justification, and rules for interruption and termination of dosing are listed in the protocol.

2.1.2 Sample Size

For the primary objective, a failure is recorded if the subject's plasma glucose fails to rise above 70.0 mg/dL within 30 minutes of administration of the dose of glucagon. Using this criterion, a sample size of 85 randomized subjects yields probabilities of G-Pen acceptance of 88% if the population failure rate differences of G-Pen and control are within 2%, and the rate of missing observations is within 5%.

Subjects will be recruited at approximately 6 clinical sites with a goal of no single center accounting for > 20% of the total sample.

2.1.3 Randomization

Randomization will be carried out via the Vision™ electronic data capture (EDC) system, version 9.3. Subjects meeting all eligibility criteria and achieving a baseline euglycemic steady state at the first treatment visit as described in the protocol, completing the baseline will be randomized 1:1 by site in simple blocks to receive G-Pen™ glucagon or Lilly glucagon injection at the first treatment visit.

2.1.4 Unblinding

This is a single-blind study. Only the subjects are blinded for treatment. The investigator and clinical staff will be aware of the treatment. Thus, there is no unbinding needed.

3 STATISTICAL AND ANALYTICAL PROCEDURES

3.1 ANALYSIS POPULATIONS

3.1.1 Intent-to-Treat (ITT) population

The intent-to treat (ITT) population is defined as all subjects randomized. A subject's randomized treatment will be used for analysis regardless of the actual treatment received.

3.1.2 Per-protocol (PP) Population

The Per-protocol (PP) population is defined as all randomized patients who, during both study periods, successfully complete the insulin induction procedure, fulfill the criteria for having achieved a hypoglycemic steady state, and successfully receive a dose of both study drugs (G-Pen followed by Lilly Glucagon, or Lilly Glucagon followed by G-Pen).

3.1.3 Safety Population

The safety population is defined as all subjects randomized. However, the actual treatment received will be used for analysis. Safety population will be used for all safety analyses (section 3.3.4).

3.2 ANALYSIS VARIABLES

3.2.1 Handling of Hypoglycemia Induction Procedure Data

Specific rules were applied to creation of the analysis dataset for the hypoglycemia induction procedure data (Appendix 3).

3.2.2 General guideline for define the protocol time

Protocol time is needed to find the 30-minute glucose value as well as to generate some of the glucose or hypoglycemia score curves.

Protocol time will be developed based on the following procedures:

- Protocol time zero will be based on either receiving glucagon or decision to dose:

- Receiving glucagon: T0 = actual time stamp of glucagon injection
- Decision to dose: T0 = actual time stamp when dose decision is made
- Subsequent protocol times are calculated by the following minutes plus T0:
  - 5, 10,15,20,25,30,35,40,45,50,55,60,65,70,75,80,85,90
  - 120,150,180
- For any continuous (number) variable, the value at the protocol time will be determined by linear interpolation between the two adjacent time points.
- For any categorical (text) variable, the value at the protocol time will be determined using the nearest value:
  - Protocol time 5 – 85 : -2 minute to +3 minute
  - Protocol time 90: -2 minute to 15 minute
  - Protocol time 120, 150, 180:   -15 minute to +15 minute
  - If multiple values are attributed to a single protocol time, then the last value will be used

Many analyses will be done using both the protocol time based on receiving glucagon and the one based on decision to dose. These analyses will be noted in each of the corresponding sections.

3.2.3 For categorical variables, the last entered value will be used

3.2.4 Demographics

3.2.4.1 Age

Age in years will be calculated as follows:

Age = (date of screening - Date of birth) / 365.24

3.2.4.2 Gender, Race and Ethnicity

These variables will be imported directly from the EDC. The Race and Ethnicity category will be combined (i.e. Whites, Hispanics, and African-Americans) for subgroup analysis.

3.2.4.3 Medical History

Medical History data will be imported directly from the EDC. No coding is planned.

3.2.4.4 Prior and Concomitant Medications

Medications will be imported directly from the EDC. It will be coded with the latest version of the WHO drug dictionary.

- If a medication cannot be found in WHO dictionary, it will be coded as "Who Code Not Defined"

3.2.5 Efficacy Variables

The following efficacy variables will be considered in the efficacy analyses.

3.2.5.1 *Primary Endpoint: Sample Mean of Failure Scores*

The primary endpoint of the study is the failure score, where a failure is defined as the event when plasma glucose of a subject remains ≤ 70 mg/dL throughout the 0-30-minute period from the administration of study drug. The 30 minutes referenced in this section will be based on the protocol time. If the value to be analyzed was not collected at exactly 30 minutes, the value will be determined by linear interpolation between the two adjacent time points as mentioned in section 3.2.1.

The following scoring system will be applied to determine the failure score.

- If a G-Pen failure is observed then the treatment failure score = 1; similarly the control failure score = 1 if a control failure is observed.

- If the G-Pen treatment outcome is missing then the treatment failure score = 0.2. A missing control outcome yields a control failure score = 0.1. Note that for PP population, this will not apply since PP subjects always have both treatments outcomes.

- An observed successful plasma glucose rising above 70 mg/dL within 30 minutes yields a failure score = 0, for either treatment.

The following variables will be derived from the failure score.

- For each subject, derived score is the G-Pen minus Lilly failure score (Dht).

- Then from an analysis population, the sample Mean (Dht) and Standard Error SE (Dht) (SE = Standard Deviation of Dht/square root of N) will be obtained.

Secondarily, this will be repeated with success/failure evaluated at a time point of 30 minutes from a decision to dose.

3.2.5.2 Secondary Endpoints

3.2.5.2.1 Binary Responses

The following secondary response endpoints will be assessed. Mean (Dht) and SE (Dht)) corresponding to these conditions will be evaluated based on the same system defined in section 3.2.5.1. The 30 minutes reference in this section will be the protocol time.

1. Return of plasma glucose to > 70 mg/dL or neuroglycopenic symptomatic relief within 30 minutes after receiving glucagon. The Baseline Glucose will be the last glucose measurement prior to time 0.

2. Return of plasma glucose to > 70 mg/dL or an increase in plasma glucose by ≥20 mg/dL within 30 minutes after receiving glucagon. The Baseline Glucose will be the last glucose measurement prior to time 0.

3. Increase in plasma glucose by ≥ 20.0 mg/dL within 30 minutes after receiving glucagon. The Baseline Glucose will be the last glucose measurement prior to time 0.

4. Neuroglycopenic symptomatic relief within 30 minutes after receiving glucagon.

Secondarily, this will be repeated with success/failure evaluated at a time point of 30 minutes from a decision to dose.

3.2.5.2.2 Number of subjects having glucose >70 mg/dL within 30 minutes of receiving glucagon

This will be the raw count of subjects at protocol time points: 5, 10,15, 20, 25, and 30 minutes.

This analysis will be done both based on time from receiving glucagon and from a decision to dose.

3.2.5.2.3 Pharmacodynamics (PD) Parameters

The PD endpoints will be derived from the individual glucose profiles. The Baseline Glucose will be the last glucose measurement prior to time 0.

Actual Time will be used to the calculation of the following variables.

If insulin starts after receiving glucagon, the glucose values post insulin start will be censored out and considered as missing.

- Cmax : Maximum concentration of Glucose

- TMax : Time (in mins) when Glucose CMax is reached

- AUC_{0-30}: Area under the curve of Glucose from 0 to 30 minutes

- o AUC$_{0-30}$ of Glucose will be calculated as the sum of areas of trapezoids, which are composed of adjacent Glucose values. The following rules will be considered:

- o If there are missing data points before the last observed value, they will be imputed as described in section 3.2.1

- o If there are missing data points after the last observed value, they will not be extrapolated and the AUC will be treated as undefined.

- AUC$_{0-180}$: Area under the curve of Glucose from 0 to 180 minutes

  - o AUC$_{0-180}$ of Glucose will be calculated as the sum of areas of trapezoids, which are composed of adjacent Glucose values. The following rules will be considered:

  - o If there are missing data points before the last observed value, they will be imputed as described in section 3.2.1.

  - o If there are missing data points after the last observed value, they will not be extrapolated and the AUC will be treated as undefined.

- Time for plasma glucose to reach >70.0 mg/dL from receiving of glucagon.
  - o The time stamp for 70.0 mg/dL will be imputed using linear interpolation between the two adjacent time points

- Time for plasma glucose to increase by at least 20 mg/dL from receiving of glucagon.

  - o The time stamp for 20 mg/dL increase will be imputed using linear interpolation between the two adjacent time points

These PD parameters will be done based on both receiving glucagon and decision to dose.

3.2.5.2.4 Hypoglycemia Symptom Mean Scores

Symptoms of hypoglycemia are captured using the following questionnaire:

Neuroglycopenic Symptoms	Severity Score (1-6)
Dizziness	
Blurred vision	
Difficulty in thinking	
Faintness	
Autonomic Symptoms	Severity Score (1-6)
Sweating	

Neuroglycopenic Symptoms	Severity Score (1-6)
Tremor	
Palpitations	
Feeling of nervousness	
Overall Assessment of Hypoglycemia	**Yes/No**
Do you currently feel hypoglycemic?	

The following 3 Mean Scores will be calculated for each subject at each of the measurement time points:

1. Average Neuroglycopenic Symptom Score (ANS) :

$$\frac{Dizziness + Blurred\ vision + Difficulty\ in\ thinking + Faintness}{4}$$

2. Average Autonomic Symptom Score (AAS):

$$\frac{Sweating + Tremor + Palpitations + Feeling\ of\ nervousness}{4}$$

3. Average Total Symptom Score (ATS):

$$\frac{Sum\ of\ all\ symptoms}{8}$$

Overall Assessment of Hypoglycemia:

- This will be treated as a categorical variable, so no means will be calculated.

This parameter will be analyzed both on time from receiving glucagon and from a decision to dose.

3.2.5.2.5 Symptom relief

Symptom relief of hypoglycemia is defined as a return to a score (ANS, AAS and ATS) no more than one unit above baseline symptoms during the euglycemic baseline period, where the baseline symptom is the minimal values of score (ANS, AAS and ATS) prior to receiving glucagon (T0).

The time (min) to Symptom relief will be derived for analysis purpose. Actual Time will be used in calculation.

This parameter will be done based on both receiving glucagon and decision to dose.

3.2.5.2.6 The time to the minimal score post dose

This will be calculated for sub-scales ANS, AAS and ATS as the difference (in mins) between the actual time when the minimal number is observed and the time of receiving glucagon. Actual Time will be used to the calculation of the following variables.

- Subjects who never develop symptoms will be assumed to have a value of 0.

This parameter will be analyzed both on time from receiving glucagon and from a decision to dose.

3.2.5.2.7 The time to first reporting of "no" for the global hypoglycemia question will be defined as below:

This will be calculated as the difference (in mins) between the actual time when the first "no" for "Overall Assessment of Hypoglycemia" is observed and the time receiving glucagon. Actual Time will be used to the calculation of the following variables.

- Subjects who never develop symptoms (never answers No) will be assumed to have a value of 0.
- In very rare cases, if subject answers Yes all the way to the last time point, the total time will be recorded. (And it will be analyzed based survival model.)

This parameter will be analyzed both on time from receiving glucagon and from a decision to dose.

3.2.5.2.8 The Glucagon Preparation Time:

Glucagon preparation time (min) is defined as the time between "decision to dose"

and time of study drug administration to the abdomen. Actual Time will be used to calculate this variable.

3.2.6 Safety Variables

3.2.6.1 Adverse Events (AE)

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the study drug will be recorded in the eCRF. This information will be imported directly from the EDC.

For all safety variables, if there is need of protocol time, it will be done based on time of receiving glucagon only.

3.2.6.2 Laboratory safety assessments

Laboratory values (biochemistry and hematology) will be imported via a web portal from a database maintained by the central laboratory.

3.2.6.3 Physical examination and ECG

Physical examination evaluations will be imported directly from EDC. Note that only abnormal ECG values will be reported, and these are reported as a sub category on the Physical examination CRF.

3.2.6.4 Vital signs and body weight

Vital sign variables and body weight will be imported directly from EDC.

3.2.6.5 Local Tolerability: Visual Analog Scale (VAS), Injection Site Discomfort and DRAIZE SCALE

Local Tolerability includes the VAS, Injection Site Discomfort and Draize scales. These data will be imported directly from the EDC. The questionnaires used to capture these variables are illustrated briefly below; further details are available in the protocol.

3.2.6.5.1 <u>VAS</u>

VAS is reported using a 100-mm scale.

No Discomfort   Worst Possible Discomfort
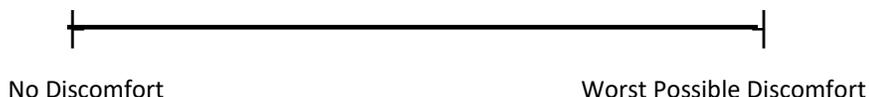
3.2.6.5.2 <u>Injection Site Discomfort</u>

The following variable is derived based on the questionnaire:

- The first question (1a) will derive a category value for discomfort description.
- Question 1b and 1c will be combined to generate the duration of discomfort:
    - If 1c is answered, then Duration of discomfort = answer in 1c.
    - Otherwise:
        - Duration of discomfort = 0.5 (if less than 1 minute checked)
        - Duration of discomfort = 1.5 (if 1-2 minute checked)

- Duration of discomfort = 4 (if 3-5 minute checked)
- Duration of discomfort = 7.5 (if 6-9 minute checked)

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*1a. How would you describe any discomfort you felt from the study drug? (Check **all** that apply):*

_____None (**Please ignore question 1b.**)

_____Pain (e.g., throbbing, soreness, muscle ache)

_____Itching

_____Tingling, twitching or numbness

_____Irritation (e.g., burning, stinging)

Other or additional
comments:_____

1b. About how long did the discomfort last after the injection? (Check one):

_____Less than 1 minute

_____1-2 minutes

_____3-5 minutes

_____6-9 minutes

_____at least 10 minutes (**Please complete question 1c before leaving the clinic.**)

1c. In total, how long did the discomfort last after the injection? (Please enter a number below):

_____ Minutes

3.2.6.5.3 Draize (Erythema and or edema)

Erythema and edema formation at the site of injection is assessed using the Draize scale shown below:

Erythema Formation		Edema Formation	
Description	**Score**	**Description**	**Score**
No erythema	0	**No edema**	0
Very slight erythema Barely perceptible	1	**Very slight edema** Barely perceptible	1
Well defined erythema	2	**Well defined edema**	2

Moderate erythema	3	Moderate edema Raised approx. 1 mm	3
Severe erythema Beet redness to slight eschar formation	4	Severe edema Raised more than 1 mm and beyond exposure area	4

3.3 STATISTICAL METHODS

3.3.1 General guideline for descriptive summaries

For continuous variables, mean, standard deviation, minimum, and maximum will be presented for each treatment group.

For categorical variables, count and % of subjects/counts in each treatment group will be presented.

3.3.2 Baseline Characteristics

3.3.2.1 Demographics

The demographics variables of age, sex, race and ethnicity will be presented descriptively.

3.3.2.2 Subject disposition

Subject disposition will be summarized for treatment group, population and study completions.

3.3.2.3 Medical History

Medical History will be summarized by body system.

3.3.2.1 Prior and Concomitant Medications

All Medications will be separated as prior and concomitant medication based on ending date and randomization date. It will be summarized descriptively.

3.3.3 Efficacy Analysis

3.3.3.1 Primary Endpoint analysis

The primary endpoint analysis will be based on the sample mean and SE of (D_{ht}, as defined in section 3.2.5.1). Descriptive summary will be presented for each treatment group.

> H0: G-Pen is inferior to control (population mean failure score difference (G-Pen - Control) exceeds 0.1
>
> Ha: not H0

Inferential analysis will be based on the following criterion:

> Reject H0, if D_{ht} + 2.8 SE ≤ 0.1, (Establish non-inferiority)

Where SE is the estimated standard error as defined in section 3.2.5.1

This analysis will be repeated for ITT and PP populations and also time based on both "receiving glucagon" and "decision to dose" time. In total, four groups of summary tables will be presented.

3.3.3.2 Secondary Endpoints

3.3.3.2.1 <u>Binary Responses</u>

The same test as described in previous section 3.2.5.1 will be applied to each of the binary responses defined in section 3.2.5.2.1.

Note that all of these analyses will be repeated for ITT and PP population as well as time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.2 <u>Number of subjects having glucose >70 mg/dL within 30 minutes of receiving glucagon.</u>

The number of subjects having glucose >70 mg/dL within 30 minutes of receiving glucagon will be presented descriptively.

This will be done in the ITT population only, and will be done for time based on both "receiving glucagon" and "decision to dose".

Note that subgroup analysis is needed for this (section 3.3.5.1)

3.3.3.2.3 Pharmacodynamics Analyses

All of the PD parameters (as defined in section 3.2.5.2.2) will be presented descriptively.

A mixed model with treatment, period and sequence as fixed factors and subject as a repeated factor will be applied to compare the least square mean differences. Log transformation will be applied if skewness is observed. Unstructured covariance matrix will be used for the covariance matrix unless the model failed. In such case, structured covariance matrix will be selected based on the one given the smallest AIC (Akaike Information).

P-value for the difference test and 90% confidence for non-inferior test will be reported.

Additionally, mean glucose curve from 0 to 180 minutes post receiving glucagon will be presented graphically for each treatment. For this group of figures, the protocol defined time (section 3.2.1) will be used.

The mean glucose curve during hypoglycemia induction time will also be presented for each treatment. Since there is no protocol time for hypoglycemia induction stage, the mean glucose will be summarized for every 5 minutes based on the glucagon injection time.

This will be done based on the ITT population only, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.4 Neuroglycopenic, Autonomic and Total Symptom scores

The average Neuroglycopenic, Autonomic and Total Symptom scores (ANS, AAS, and ATS) will be summarized descriptively at each of the protocol defined time points (section 3.2.1) for each treatment group.

Additionally, this will also be presented graphically.

This will be done for ITT population, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.5 Symptom relief of hypoglycemia

The time to symptom relief will be presented descriptively.

A survival analysis will be done to comparing the difference between treatment groups. P-value for the difference will be reported.

This will be done for ITT population only, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.6 The time to the minimal score post baseline

The time to the minimal score will be summarized descriptively for each treatment.

A survival analysis will be done to comparing the difference between treatment groups. P-value for the difference will be reported.

This will be done for ITT population only, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.7 The time to first reporting of "no" for the global hypoglycemia question

The time to first reporting of "no" for the global hypoglycemia question will be summarized descriptively for each treatment. In rare cases if a subject does not answer "no," the total time of 180 minutes will be used in the summary, but noted in the footnote.

A survival analysis will be done to compare the difference between treatment groups. P-value for the difference will be reported. Again, if a subject does not answer "no," the total time of 180 minutes will be used, but noted as a censored value in the analysis model.

This will be done for ITT population only, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.3.2.8 The Glucagon Preparation Time

The glucagon preparation time will be summarized descriptively for each treatment.

A mixed model with treatment, period and sequence as fixed factors and subject as a repeated factor will be applied to compare the least square mean differences. Log transformation will be applied if skewness is observed. Unstructured structure will be used for the covariance matrix unless model failed. In such case, structured covariance matrix will be selected based on the one given the smallest AIC (Akaike Information).

This will be done for both the ITT and PP populations.

3.3.4 Safety Analysis

All safety analyses will be performed using the safety population. Note, actual received treatment will be used. Analyses will be based on time of receiving glucagon if protocol time is involved.

3.3.4.1 Adverse Events (AE)

All AEs will be coded using the latest Medical Dictionary for Regulatory Activities and summarized descriptively by system organ class and study drug. A summary table indicating the number and the percentage of exposed subjects having at least one AE will be made. A similar table will provide a breakdown of AEs (all and related) by intensity level (mild, moderate, severe).

Note that subgroup analysis is needed for this (section 3.3.5.1)

3.3.4.1 Laboratory safety assessments

Laboratory test results will be presented descriptively for screening visit and follow-up visit.

3.3.4.1 Physical examination and ECG

Physical exam including ECG results will be presented descriptively for screening visit and follow-up visit.

3.3.4.2 Vital signs and body weight

Height, weight, heart rate and blood pressure will be summarized by descriptive statistics.

3.3.4.3 Local Tolerability

3.3.4.3.1 <u>Subjective injection site discomfort from VAS</u>

VAS will be summarized descriptively for each treatment at each protocol defined time point. VAS will be treated as a continuous variable, so mean, sd, median, minimum, maximum. will be presented.

Additionally, number and % of subjects with score >0 for each treatment at each protocol defined time point will also be presented descriptively.

If there are enough data (i.e., data with score >0), a mixed model will also be applied to comparing the difference between treatment group. Since we may expect few data with score >0, the choice of model will be based on the actual data.

3.3.4.3.2 <u>Injection site discomfort from ordinal pain scales</u>

The discomfort description and duration of discomfort (section 3.2.6.5.2) will be summarized descriptively.

3.3.4.3.3 <u>Erythema and edema</u>

Erythema formation score and edema formation score will be summarized descriptively. These scores will be treated as continuous variables.

3.3.5 Other statistical Analysis

3.3.5.1 Subgroup Analysis

The following safety and efficacy variables will be summarized descriptively by gender (male, female), age (18.0 – 64.9 years, 65.0 years and above), and race (non-Hispanic Whites, Hispanics, and African-Americans):

- AE (Any)
- Time (min) to glucose >70 mg/dL within 30 minutes of receiving glucagon

This will be done in the ITT population only, and will be done with time based on both "receiving glucagon" and "decision to dose".

3.3.5.2 Interim Analysis

Interim analysis will not be performed in this study.

4   Data Handling Conventions

4.1 Missing Data

Unless specified in any of the previous sections, no missing data will be imputed.

4.2 REPEATED AND UNSCHEDULED VISIT

Unless specified in any of the previous sections, the principle of 'last observation priority' will be used to handle the situation of a repeated visit.

4.3 PROTOCOL VIOLATIONS

Potential protocol violations are incorporated into the definition of Per Protocol Population (see 3.1.2). This definition excludes from PP analysis any subject who has one of the following 4 major protocol violations:

1. Fails to meet all eligibility criteria.
2. Fails to meet the definition of hypoglycemia steady state prior to dosing at either treatment visit. A steady state of hypoglycemia is defined as two consecutive plasma glucose values between 43.0 and 49.9 mg/dL, and a linearly extrapolated 8-minute later glucose value ≥ 42.0 mg/dL.
3. Fails to complete both treatment visits.
4. Fails to receive a dose of both test articles during the study (G-Pen and Lilly Glucagon).

5 PLANED LISTING, TABLE AND FIGURES

Please see the Appendix 1.

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

6 SOFTWARE DOCUMENTATION

PC SAS – Windows version 9.1.3 or higher.
PC R - Windows version 12.0 or higher.
WinNonlin - Professional Version 5.2 or higher.

Excel - Microsoft Excel 2007 or higher.

7 APPENDIX

1. Statistical Analysis Plan V2 - Appendix 1 Table of contents V2.xlsx
2. Protocol XSGP-303 v1.2, 29 Jan 2018
3. Protocol XSGP-303 Analytical Data Conventions for Hypoglycemia Induction Procedure, 02 May 2018
4. Protocol XSGP-303 Analysis Populations and Protocol Violations, 03 May 2018