Statistical Analysis Plan for:

Study No. XSGP-304

Title: G-Pen (glucagon injection) compared to Glucagen® HypoKit® (glucagon) for induced hypoglycemia rescue in adults with T1D: a Phase 3 multi-center, randomized, controlled, single blind, 2-way crossover study to evaluate efficacy and safety

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G-PEN (GLUCAGON INJECTION) COMPARED TO GLUCAGEN® HYPOKIT® (GLUCAGON) FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULTS WITH T1D: A PHASE 3 MULTI-CENTER, RANDOMIZED, CONTROLLED, SINGLE BLIND, 2-WAY CROSSOVER STUDY TO EVALUATE EFFICACY AND SAFETY

STATISTICAL ANALYSIS PLAN

Prepared for:
Xeris Pharmaceuticals

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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
C_{max}	Maximum Plasma Concentration
ECG	Electrocardiogram
GCP	Good Clinical Practice
CRO	Contract Research Organization
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
MedDRA	Medical Dictionary for Regulatory Activities
QTN	Quartesian LLC
PD	Pharmacodynamics
PGR	Positive Glucose Response
SAE	Serious Adverse Event
Tmax	Time to Maximum Plasma Concentration
T1D	Type 1 Diabetes Mellitus
VAS	Visual Analog Scale
WHO	World Health Organization

2 INTRODUCTION

This documentation describes the planned data analyses for clinical trial XSGP-304 sponsored by Xeris Pharmaceuticals, Inc.

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).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

The primary objective of this study is to demonstrate that G-Pen 1 mg (test) is not inferior to GlucaGen Hypokit 1 mg (reference), in Type 1 diabetic (T1D) subjects in a state of insulin-induced hypoglycemia.

3.2 Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of G-Pen 1 mg versus GlucaGen Hypokit 1 mg in the study population.

3.3 Endpoints

3.3.1 Primary Endpoint

For the primary endpoint, groups will be compared for rates of achieving a positive plasma glucose response (PGR), defined as either a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) or an increase in plasma glucose concentration > 20 mg/dL (> 1.11 mmol/L), within 30 minutes of study drug injection.

3.3.2 Secondary Endpoints

For the secondary endpoints, treatment groups will be compared based on each of the following:

1. Rate of achieving a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) within 30 minutes from injection of study drug.
2. Rate of achieving an increase in plasma glucose concentration > 20 mg/dL (> 1.11 mmol/L) within 30 minutes from injection of study drug.
3. Rates of positive symptomatic response, defined as relief of neuroglycopenic symptoms within 30 minutes from a decision to dose.
4. Rates of positive treatment response, defined as exhibiting either a positive plasma glucose response (within 30 minutes from injection of study drug) *or* a positive symptomatic response (within 30 minutes from a decision to dose).
5. Time to a positive plasma glucose response from injection of study drug.
6. Time to administer study drug from a decision to dose.

7. Pharmacodynamic (PD) characteristics of mean plasma glucose concentration (0 to 90 minutes post-dose), maximum observed concentration (C_{max}), time to maximum observed concentration (Tmax), area under the concentration versus time curve from time 0 to 90 minutes (AUC_{0-90}), and area under the concentration versus time curve from time 0 to 180 minutes (AUC_{0-180}).
8. Time to (a) initial relief and (b) complete resolution of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose.
9. Time to resolution of the overall feeling of hypoglycemia from a decision to dose.
10. Safety endpoints, including adverse event (AE)/serious adverse event (SAE) rates, and changes in vital signs, laboratory variables, and physical exam/electrocardiogram (ECG) findings.
11. Tolerability endpoints, including: Draize scale scores for injection site erythema and edema as assessed by the investigator, and injection site discomfort and duration as assessed by subject questionnaire responses.

4 STUDY DESIGN

4.1 General Design

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

Subjects will be randomized to one of two treatment sequences below and will receive one dose within each treatment period separated by a washout period.

Table 1: Randomized Treatment Sequence

Treatment Sequence	Treatment 1	Treatment 2
1	G-Pen 1 mg	GlucaGen Hypokit 1 mg
2	GlucaGen Hypokit 1 mg	G-Pen 1 mg

In each period subjects will be confined to clinic at Day -1 before dosing, will undergo the following procedures and will be discharged at Day 1.

Day -1: Clinic arrival, assessments specified by protocol, evening meal in clinic.

Day 1:

- **Overnight monitoring (starting approximately at midnight) and Morning Procedures (starting at approximately 6 AM)**.

  Subjects will be monitored by glucose and will be given glucose and/or insulin to optimize plasma glucose levels. In the morning, plasma glucose (via YSI) will be assessed, and if > 270.0 mg/dL (> 15.0 mmol/L), the visit will be rescheduled after a minimum 3-day wait. Otherwise, the subject will be administered IV insulin to induce a baseline euglycemic steady state.

- **Baseline Euglycemic Steady State (early morning).**

Prior to starting the hypoglycemia induction procedure, the subject must have stable plasma glucose for at least 30 minutes at 95±20 mg/dL (75 to 115 mg/dL [4.17 to 6.38 mmol/L]) at a stable IV insulin infusion rate varying no more than ±20% during which plasma glucose must be measured at least every 15±2 minutes (i.e., at least 3 consecutive values in the target range at 0, 15, and 30 minutes).

The starting plasma glucose level (SG) will be determined as the average of the last 3 measurements taken over the final 30 minutes of the baseline euglycemic steady state period.

- **Hypoglycemia Induction Procedure (following baseline euglycemic steady state).**

  Hypoglycemia will be induced by adding an initial IV bolus push dose of regular insulin diluted in normal saline until and further ***insulin dose adjustments*** specified in the protocol.

  Initial IV bolus push dose will be calculated as 75% of the dose estimated to reduce plasma glucose from the subject's starting plasma glucose level (SG) to desired glucose level 54 mg/dL (3.0 mmol/L) based on the subject's self-reported glucose correction factor. This dose will be referred to as "first bolus (full bolus dose)" (BD1) subsequently:

  $$\text{BD1 (mg/dL)} = [(\text{SG} - 54\ \text{mg/dL}) / \text{Correction factor})] \times 0.75.$$

- **Randomization.** Once the initial bolus dose of insulin has had time to take effect and the subject is observed to be in a controlled rate of glucose decline, the subject will be randomly assigned to one of the treatment sequences shown in Table 1.

- **Confirmation of Hypoglycemic Steady State.** Once the initial plasma glucose measurement < 54.0 mg/dL (< 3 mmol/L) is achieved, the IV insulin infusion will be returned to the rate established at the end of the baseline euglycemia steady state period. After 5 minutes, the IV insulin infusion will be stopped, and up to 3 confirmatory plasma glucose readings will be taken at subsequent 5-minute intervals to determine whether a hypoglycemic steady state has been reached.

  A ***hypoglycemic steady state*** is defined as a confirmatory plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L) and < 54 mg/dL (< 3 mmol/L), and an 8-minute linearly extrapolated future plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L).

- **Decision to Dose.** Once the hypoglycemic steady state is confirmed, the Investigator will confirm that it is appropriate to administer study drug to the subject. The clock time of this "Decision to Dose" will be captured in the source documents. Decision to dose time is entered on the Induction CRF for each visit and will be used in the analysis.

- **Preparation and Administration of Study Drug**. Following a decision to dose, subjects were administered a subcutaneous injection around the umbilicus with either 1 mg GlucaGen Hypokit or 1 mg G-Pen.

- **Post-dose assessments**. 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.

  Plasma glucose levels and assessments of neuroglycopenic symptoms will be censored after the time of drug administration. This censoring is applicable only if the insulin is

restarted prior to the 180 minutes timepoint as per the following language in the protocol:

"After study drug administration and before 180 minutes post-dosing, if rising glucose levels are observed and if deemed medically necessary, insulin therapy or other medical intervention may be initiated by the Investigator.

a. Such intervention is not recommended to occur before 90 minutes post-dosing of study drug.

b. Plasma glucose data and assessments of neuroglycopenic symptoms will be censored after the time of intervention, per the statistical analysis plan.

c These interventions (such as insulin, carbohydrates, or a meal) prior to 180 minutes post study drug administration should be captured in the source documents, and further glucose measurements may be performed at the discretion of the Investigator."

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

4.2 Sample Size Determination

For the primary objective, a failure is recorded if the subject's plasma glucose fails to rise above 70.0 mg/dL (3.88 mmol/L) and fails to increase by at least 20.0 mg/dL (1.11 mmol/L) within 30 minutes of the decision to administer the dose of glucagon.

In this study, it is expected that the recovery (cure rate) will be high and approaching 100%. Since this is a cross-over design and each subject will serve as his/her control, power is improved.

The sample size was derived for 80% power of detecting non-inferiority with respect to the Odds Ratio of subject recovery rates at an alpha of 0.025 under a cross-over design. Based on an underlying Odds Ratio of 1.0, and rates of 0.20 versus 0.25, 111 subjects are required for the study. With an anticipated 10% drop-out rate, the total sample size for the study is 122 randomized subjects.

If there are subjects who are enrolled, but fail to be randomized, compensatory enrollment may be utilized to achieve at least 122 subjects who are randomized for the study. Once a subject is randomized, the subject will be analyzed for the study.

4.3 Randomization

Subjects who meet all eligibility criteria, who reach the baseline euglycemia steady state, and who the Investigator deems appropriate to begin the induction procedure at the first treatment visit will be randomized for the study.

The randomization schedule will be produced by the Study statistician a priori for loading and implementing in the Interactive Web-based Randomization System (IWRS). Using a permuted random block assignment, stratified by site, subjects will be randomly assigned to receive either Treatment Sequence 1 (G-Pen → GlucaGen Hypokit) or Treatment Sequence 2 (GlucaGen Hypokit → G-Pen).

4.4 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 unblinding requirements needed for the study.

In the event that a subject is inadvertently unblinded during one or both of the treatment sequences, the investigator will note the event as a protocol violation, and the subject will be allowed to continue further study treatments as per the protocol.

At the end of the study, the subjects will be asked to guess what their first treatment was, and what their second treatment was from the choices of "Xeris Glucagon, G-Pen, administered by auto-injector" or "Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe". The subject's responses will be recorded in the electronic Case Report Form (eCRF) for the Subject Study Drug Assignment Questionnaire.

4.5 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this statistical analysis plan.

5 STATISTICAL AND ANALYTICAL PROCEDURES

5.1 Analysis Populations and Treatment Groups

The following populations will be considered for the study:

5.1.1 Intent-to-Treat Population (ITT)

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. ITT population will be used for all summaries except safety/tolerability and disposition (where Enrolled population will be used). Primary endpoint comparison and secondary efficacy analysis will be performed for ITT, mITT and PP populations.

5.1.2 Modified Intent-to-Treat Population (mITT)

The Modified Intent-to-Treat (mITT) population is defined as all ITT subjects and received at least one dose of study drug. The actual treatment received will be used for analysis.

5.1.3 Per-Protocol Population (PP)

The Per-Protocol (PP) population is defined as all randomized patients who during both study periods successfully receive a dose of both study drugs (G-Pen followed by GlucaGen Hypokit or GlucaGen Hypokit followed by G-Pen) and have no any major protocol deviations. The actual treatment received will be used for analysis.

Primary endpoint comparison and secondary efficacy analyses will be performed for ITT, mITT and PP populations.

5.1.4 Safety Population

The safety population is defined as all subjects randomized that received at least one dose of study drug. The actual treatment received will be used for analysis. The safety population will be used for all safety analyses and endpoints.

5.1.5 Treatment groups

For summary statistics, subjects will be presented in two different ways, as applicable to the type of analysis:

- by planned treatment sequence of randomized subjects (GlucaGen Hypokit – G-Pen and G-Pen – GlucaGen Hypokit). This presentation and analysis will be used optionally

for descriptive outputs, but generally will not be used for analysis of the primary objective.

- by planned/actual treatment of subject in each treatment period (GlucaGen Hypokit and G-Pen). This presentation and analysis will be used for all primary and secondary endpoints, and optionally for descriptive outputs (disposition, demographics, etc.).

Planned treatment will be used for ITT population analyses and actual treatment received (by Period) will be used for mITT, PP and Safety population analyses.

5.2 Reference Dates, Analysis Periods, Analysis Visits, and Baseline

There will be two treatment periods defined and analyzed, which starts from study drug administration and the associated clinical phases associated, related with the pre-dose study procedure:

SCREENING/BASELINE, RUN-IN (1 and 2), TREATMENT PERIOD (1 and 2).

- SCREENING/BASELINE: analysis phase starts with Informed Consent, includes Day -1 check-in before first drug administration.

  Baseline will be defined as the last assessment within this phase and used as the reference point for safety assessments across the study to each of the visits (laboratory data, ECG, physical examination, weight, temperature and respiratory rate).

- PRE-TREATMENT PERIOD 1: analysis phase will be assigned only if subject failed to achieve hypoglycemic steady state and study drug was not administered at the first treatment visit. It will start from first overnight monitoring to last check-in before first drug administration inclusively.

  Baseline 1 will be defined as last assessment at Day -1 of Treatment 1 and will be used as the reference point for safety assessments within Treatment Period 1(HR and BP).

- RUN-IN 1: analysis phase starts from Day 1 of Treatment 1 study procedures prior to first drug administration and continues until the first drug administration or study discontinuation, whichever comes first.

- TREATMENT PERIOD 1: analysis phase/period starts from first drug administration to check-in of the next treatment visit or study discontinuation, whichever comes first.

- PRE-TREATMENT PERIOD 2: analysis phase will be assigned only if subject failed to achieve hypoglycemic steady state and the subject's second study drug was not injected at the first treatment visit after the end of Treatment Period 1. The period will start from first overnight monitoring after the end of Treatment Period 1 to last check-in before second drug administration inclusively.

  Baseline 2 will be defined as last assessment at Day -1 before Treatment 2 and used as reference point for safety assessments within Treatment Period 2 (HR and BP).

- RUN-IN 2: analysis phase starts from Day 1 of Treatment 2 study procedures prior to second drug administration and continues until the second drug administration or study discontinuation, whichever comes first.
- TREATMENT PERIOD 2: analysis period/phase starts from second dose administration to the end of study.

RUN-IN 1 and RUN-IN 2 analysis phases will include all interventions before dose injections, thereof:

- EUGLYCEMIC BASELINE 1 / 2.

  The Euglycemic Baseline phase will be determined as time interval which starts from last 30 minutes of the baseline euglycemic steady state period, covering at least 3 scheduled consecutive plasma measurements in the target range at 0, 15, and 30 minutes used to confirm euglycemic steady state; and stops just before hypoglycemia induction with IV bolus push dose.

  Euglycemic Baseline (1 and 2): to determine for the Hypoglycemia Symptoms Assessment scheduled at the end of this phase just before the IV bolus push dose of insulin, will serve as baseline to determine hypoglycemia symptoms relief and/or resolution within Treatment Period (1 and 2). If more than one assessment is performed in this time interval, then the last assessment of each hypoglycemia symptom or score will be selected for use as the baseline.

- HYPOGLYCEMIA INDUCTION (1 and 2). During the induction procedure the subject will enter a state of hypoglycemia through the administration of regular insulin diluted in normal saline within a controlled and monitored setting.

  Hypoglycemic steady state (1 and 2): for Treatment Period (1 and 2) is confirmed if:

  - penultimate plasma glucose measurement during hypoglycemia induction is < 54.0 mg/dL (< 2.78 mmol/L);
  - last plasma glucose measurement during hypoglycemia induction is ≥ 42 mg/dL (≥2.33 mmol/L) and < 54 mg/dL (< 2.78 mmol/L); and
  - 8-minute linearly extrapolated value from two last measurements of plasma glucose is ≥ 42 mg/dL (≥ 2.33 mmol/L).

  Hypoglycemic Baseline (1 and 2). If the subject achieved hypoglycemic steady state then from the last of the last two plasma glucose readings during hypoglycemia induction to time of study drug administration will be defined as Hypoglycemic Baseline for the corresponding treatment period and will serve as baseline for the Primary Endpoint and Secondary Endpoints related to pharmacokinetic and pharmacodynamic characteristics within Treatment Period (1 and 2).

Assessments and Adverse Events with onset in TREATMENT PERIOD 1 or TREATMENT PERIOD 2 will be attributed to the actual treatment and analyzed respectively. Adverse

Events which started at RUN-IN (1 and 2) phase, will be treated as TEAE, but not attributed to forthcoming treatment. They will be attributed to the previous treatment period (or prior to first treatment administration and not categorized as treatment emergent).

Visit 2 and Visit 3 will be differentiated to Day -1 and Day 1 according to protocol and schedule of assessments. Analysis periods, visits, and baseline are summarized in the table below.

Table 3 - Analysis Periods and Visits

Analysis Phase/ Period	Analysis Subperiod (optional)	Analysis Visit	Protocol Visit/ Period	Baseline for period?
SCREENING - BASELINE	Screening	Screening, Baseline*	Visit 1	Overall
	Check-In 1 (CRC Admission)	Treatment 1 Day -1, Baseline 1*/Baseline*	Visit 2	Period 1, Overall
RUN-IN 1	Overnight monitoring	Treatment 1 Day 1	Visit 2	
	Euglycemic Baseline 1	Treatment 1 Day 1, Euglycemic Baseline 1*	Visit 2	Period 1
	Hypoglycemia Induction 1	Treatment 1 Day 1 (pre-dose measurements), Hypoglycemic Baseline 1*	Visit 2	Period 1
TREATMENT PERIOD 1 / TREATMENT PERIOD 1	Post treatment 1 measurements/ CRC discharge	Treatment 1 Day 1 (post-dose measurements)	Visit 2	
	Outclinic 1			
	Follow-Up (optionally)	Follow-Up (optionally)		
	Check-In 2 (CRC Admission)	Treatment 2 Day -1, Baseline 2*	Visit 3	Period 2
RUN-IN 2	Overnight monitoring	Treatment 2 Day 1	Visit 3	
	Euglycemic Baseline 2	Treatment 2 Day 1, Euglycemic Baseline 2*	Visit 3	Period 2
	Hypoglycemia Induction 2	Treatment 2 Day 1 (pre-dose measurements), Hypoglycemic Baseline 2*	Visit 3	Period 2
TREATMENT PERIOD 2 / TREATMENT PERIOD 2	Post treatment 2 measurements/ CRC discharge	Treatment 2 Day 1 (post-dose measurements)	Visit 3	
	Outclinic 2			
	Follow-Up	Follow-Up	Visit 4	

* Derived visit.

5.3 Analysis Variables

5.3.1 Subject's Disposition and Analysis Sets

Disposition will be summarized descriptively using counts and percentages for Enrolled Population by treatment sequence, and for the ITT Population by planned treatment.

The number and percentage of subjects screened, screen failures, entered the study, randomized, and completed the study will be presented, together with number and percentage of subjects who prematurely discontinued from the study along with reasons for study discontinuation by treatment sequence and overall.

A listing of the subject's disposition status will be provided. The number of subjects in each analysis set will be summarized descriptively by treatment with counts and percentages. A listing of subject's inclusion to analysis sets will be provided. A subject's eligibility with inclusion/exclusion criteria completions or deviations will be listed.

5.3.2 Demographics and Baseline Characteristics

Demographic data will include gender (male, female), age, age group (>=18 to <65 and >=65 years), race, ethnic origin and treatment group.

Baseline characteristics will include:

- body weight, height, BMI;
- Gold Scale of Hypoglycemia Unawareness;
- average correction factor per unit of insulin (mg/dL);
- duration of Type 1 diabetes calculated in years.

Subjects who:

- were diagnosed with Type 1 diabetes by a health care practitioner;
- were taking daily insulin treatment;
- has assigned correction for managing their hypoglycemia, and average correction factor per unit of insulin (mg/dL) for subjects with assigned correction factor.

Demographics and baseline characteristics will be summarized for all subjects overall and by treatment. Summary statistics (e.g., number of subjects, mean and standard deviation, median and range) will be generated for all continuous variables (i.e., age and weight,) and the number and percentage of subjects within each category will be presented for all categorical variables (i.e., gender, race, ethnicity,). The summary results will be based on the ITT population.

5.3.3 Medical History

Medical history will consist of two parts:

1) **General Medical History.** This data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version), listed and summarized with descriptive statistics by System Organ Class (SOC) and Preferred Term (PT).
2) **Diabetes History** will include information about date of diagnosis of Type 1 Diabetes diagnosis, current daily insulin treatment and correction factor for managing hypoglycemia. This data will be listed separately as part of demographics and baseline characteristics.

Duration of T1D in years will be calculated using date of informed consent and date of diagnosis as integer part of

[<Date of Informed Consent> - <Date of Diagnosis> + 1]/365.25.

If day of diagnosis is unknown, then day will be imputed as '01' (first day of the month).

If month of diagnosis is unknown, then month will be imputed as '01' (Jan of year of diagnosis).

Duration of T1D will be listed and analyzed with descriptive statistics as Baseline characteristics.

5.3.4 Pregnancy and Childbearing Potential

For female subjects, pregnancy test and/or childbearing potential will be listed.

5.3.5 Prior and Concomitant Medications

Medications will be coded with the latest version of the WHO drug dictionary, listed and presented by ATC Class 2 and Preferred Term.

If a medication cannot be coded by WHO dictionary, it will be coded as "WHO Code Not Defined".

Each medication will be classified as prior, concomitant, or both.

Any medication taken within 4 weeks before Day 1 will be considered as prior.

Any medication taken on or after the drug administration (Day 1) will be considered as concomitant.

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

- If there is reasonable possibility that medication was taken within 4 weeks (28 days) before study drug administration, the medication will be considered as prior;
- If there is no evidence that medication was taken before the drug administration, medication will not be classified as prior;
- If there is reasonable possibility that medication was taken on or after study drug administration and there is no evidence that medication intake was stopped before first drug administration, then the medication will be classified as concomitant.

If dates of medications are incomplete, missing, or medication is ongoing, the medication will be considered as concomitant if there is no evidence that the 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.

Prior and Concomitant medication will be summarized and listed with ATC Class 2 and preferred term (PT) by treatment sequence and overall for the Safety population.

Concomitant medication which started or changed with dosing/regimen after study drug administration, will be attributed to Treatment Period 1 or 2 by start date and analyzed descriptively by treatment received 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.

5.3.6 Efficacy Variables

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

5.3.6.1 Primary Endpoint

Positive Plasma Glucose Response 1 (PGR1)

Positive Plasma Glucose Response 1 (PGR1) is defined as reaching a plasma glucose concentration ≥70 mg/dL (≥ 3.88 mmol/L) within 30 minutes of study drug injection (actual time).(The baseline plasma glucose is the blood glucose reading immediately before study drug dosing.)

Positive Plasma Glucose Response 2 (PGR2)

Positive Plasma Glucose Response 2 (PGR2) is defined as reaching an increase in plasma glucose concentration ≥ 20 mg/dL (≥ 1.11 mmol/L) within 30 minutes of study drug injection (actual time).

Positive Plasma Glucose Response (PGR)

For the primary endpoint, Positive Plasma Glucose Response (PGR) is defined as reaching Positive Plasma Glucose Response 1 (PGR1) **or** Positive Plasma Glucose Response 2 (PGR2).

For the primary endpoint, treatment groups will be compared for rates of achieving a positive plasma glucose response. The comparison will be performed using Intention to Treat (ITT), Modified Intent-to-Treat (mITT) and the Per-Protocol (PP) populations. Risk difference in rates of failing to achieve Positive Plasma Glucose Response (PGR) will be assessed for G-Pen versus GlucaGen Hypokit used as reference and the associated 95% CIs presented.

5.3.6.2 Secondary Endpoints

5.3.6.2.1 Pharmacodynamic (PD) Parameters

The PD endpoints will be derived from the individual glucose profiles. Pharmacodynamic characteristics, including:

- $AUC_{0\text{-}90}$ and $AUC_{0\text{-}180}$: plasma glucose area under the concentration versus time curve for 90 and 180 mins from glucagon administration;
- C_{max}: Maximum concentration of glucose in plasma;
- T_{max}: time (in mins) when Glucose C_{max} is reached;

The following rules will be used for incomplete data:

- AUC: If there are missing data points before the last observed value, they will be extrapolated using the last two data points;
- AUC: If there are missing data points after the last observed value, they will not be imputed, and the AUC will be treated as not defined;
- If insulin starts after receiving glucagon, the glucose values post insulin start will be censored out and considered as missing. This is also considered a major protocol deviation.

Comparison between the treatments will be performed using a mixed model with treatment, period and treatment*period as fixed factors and subject as a random factor.

5.3.6.2.2 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	
Tremor	
Palpitations	
Feeling of nervousness	
Overall Assessment of Hypoglycemia	Yes/No
Do you currently feel hypoglycemic?	

The following three mean scores will be calculated for each subject at each of the measurement time points:

1. **Average Neuroglycopenic Symptom Score (ANS) :**

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

2. **Average Autonomic Symptom Score (AAS):**

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

3. **Average Total Symptom Score (ATS):**

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

Overall Assessment of Hypoglycemia:

- this will be treated as a categorical variable and analyzed with descriptive statistics by timepoints;
- additional descriptive summary will be done for overall assessment of hypoglycemia as number and percentage of subjects who: answered “Yes” at baseline, answered “Yes” at baseline and never answered “No” post-baseline, answered “No” at baseline,

answered "No" at baseline and at least once answered "Yes" post-baseline.

This parameter will be analyzed from a decision to dose.

5.3.6.2.3 Time-to-Event Efficacy Endpoints

Symptom relief will be analyzed as aggregate scores for the four autonomic symptoms, four neuroglycopenic symptoms, and 8 total (autonomic and neuroglycopenic) symptoms.

Symptom relief of hypoglycemia is defined as a return to a score (ANS, AAS, and ATS) no more than one unit above euglycemic baseline (1 / 2). Only subjects with baseline score at least 2 or more (for ANS, AAS, or ATS) will be evaluable for this analysis.

Complete resolution of hypoglycemia symptoms is defined as all symptoms in the domain (ANS, AAS, or ATS) have a score of 1 after receiving glucagon.

The time to resolution of the overall feeling of hypoglycemia is defined as first reporting of "No" for the global hypoglycemia question. 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 to decision of glucagon dosing.

Glucagon Preparation Time is defined as time to administer study drug from a decision to dose.

The following timing parameters will be calculated for analysis:

1. Time to a Positive Plasma Glucose Response (PGR) from injection of study drug.
2. Glucagon Preparation Time.
3. Time to symptom relief of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose. That include:
    - time to symptom relief of neuroglycopenic symptoms (ANS) from a decision to dose;
    - time to symptom relief of autonomic symptoms (AAS) from a decision to dose;
    - time to symptom relief of autonomic and neuroglycopenic symptoms (ATS) from a decision to dose;
4. Time to complete resolution of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose. That include:
    - time to complete resolution of neuroglycopenic symptoms (ANS) from a decision to dose;
    - time to complete resolution of autonomic symptoms (AAS) from a decision to dose;
    - time to complete resolution of autonomic and neuroglycopenic symptoms (ATS) from a decision to dose;
5. Time to minimal score of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose. That includes:
    - time to minimal score of neuroglycopenic symptoms (ANS) from a decision to dose;

- time to minimal score of autonomic symptoms (AAS) from a decision to dose;
- time to minimal score of autonomic and neuroglycopenic symptoms (ATS) from a decision to dose;

6. Time to resolution of the overall feeling of hypoglycemia from a decision to dose. The following rules will be applied:
   - only subjects who answered "Yes" at baseline will be evaluable for this analysis;
   - in very rare cases, if subject answers "Yes" all the way to the last time point, the total time to the last assessment will be recorded.

Actual Time will be used for calculations.

5.3.6.2.4 Binary Responses

For secondary response endpoints the following parameters will be defined:

Positive Symptomatic Response

Positive Symptomatic Response is defined as relief of neuroglycopenic symptoms (ANS) within 30 minutes from a decision to dose.

Positive Treatment Response

Positive Treatment Response is defined as exhibiting either a positive plasma glucose response (PGR) or a positive symptomatic response.

The following secondary response endpoints will be assessed.

1. Rate of failing to achieve a Positive Plasma Glucose Response 1 (PGR1).
2. Rate of failing to achieve a Positive Plasma Glucose Response 2 (PGR2).
3. Rate of failing to achieve a Positive Symptomatic Response.
4. Rate of failing to achieve a Positive Treatment Response.

For these secondary endpoints, analysis will be the same that for primary endpoint (PGR) described above in section 5.3.6.1. Actual time will be used for calculations.

5.3.6.3 Safety Variables

All Safety and Tolerability assessments will be performed using the Safety Population.

5.3.6.3.1.1 Adverse Events (AE)

All verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version) and summarized by System Organ Class (SOC) and Preferred Term (PT). AE collection will begin from the time of informed consent.

Time periods for Adverse Events

Adverse Events will be attributed to analysis phases and periods by time of onset.

Treatment Emergent Adverse Events (TEAEs) will be defined as AEs not present prior to the start of study procedures, or AEs present before study medication that worsened after starting of study procedures at Day 1 prior to first dose administration. If a partially missing date or time of onset allows the possibility that an AE may be a TEAE it will be assumed that it is a TEAE.

TEAEs will be analyzed by treatment and in overall. TEAEs will be attributed to study treatment which was administered before the AE onset within the respective Treatment Period 1 or 2.

Each TEAE will be attributed to Treatment Period 1 or 2. If TEAE started at the time of Day 1 Pre-dosing procedures of second dose, it will not be attributed to Treatment Period 1, but will be counted in the Overall TEAE summary.

AEs will be summarized by treatment, period and in overall by the number and percentage of subjects who experienced at least one AE of the following categories in each treatment group: any AE, any AE from CRC admission to the time of induction, any AE from time of induction to treatment, any TEAE, any drug related TEAE, any severe or life-threatening TEAE, any serious TEAEs, any drug-related SAE, any SAE leading to death, any TEAE leading to study discontinuation, and any SAE leading to study discontinuation.

AEs will be tabulated by SOC and PT in each category.

TEAEs will be summarized by highest relationship to study drug (Not Related, Related) and maximum severity (Mild, Moderate, Severe). If severity of AE is missing, then the AE will be analyzed as 'Severe'. If relationship to study drug for the AE is unknown, then the TEAEs will be classified as Related, and non-TEAEs will be classified as Not Related.

AEs will be analyzed for safety according to the study treatment received in corresponding treatment period and overall. All AEs will be summarized by actual treatment sequence, treatment period (Treatment Period 1 / Treatment Period 2) and overall. Subjects will be counted only once in the Overall analysis.

Listings of all AEs, SAEs, and TEAEs leading to study drug discontinuation will be provided with treatment group, site, subject, then in chronological order displaying treatment period, verbatim term, MedDRA SOC and PT, start and end dates, seriousness flag and category, severity, relationship to study drug, action taken, contributing factors, and outcome.

5.3.6.3.2 Laboratory safety assessments

Laboratory values (chemistry and hematology) will be flagged if outside the normal range and a listing of clinically significant abnormal values will be presented.

Normality ranges and evaluation should be consistent across the study.

Laboratory measurements will be summarized with descriptive statistics for actual value and change from baseline.

Baseline will be defined as last assessment before the first dose administration. Summaries will be presented by actual treatment received.

5.3.6.3.3 Physical Examination

Subjects with any findings in the physical examination evaluation at Screening will be listed.

5.3.6.3.4 Body Weight

Body weight and change from baseline to end of study will be summarized with descriptive statistics. Baseline is defined as last assessment before first drug administration.

5.3.6.3.5 Vital signs

Vital signs (temperature, respiration, heart rate and BP after >5 mins seated rest) will be summarized for actual values and change from baseline with descriptive statistics by scheduled timepoints.

Temperature and respiration will be analysed by treatment sequence and by actual treatment received with baseline defined as last assessment before first drug administration.

Change from baseline will be assessed within period only. Summaries will be presented by treatment sequence and by actual treatment received.

5.3.6.3.6 Electrocardiogram (ECG)

ECG assessment and Investigator's evaluations will be displayed in a data listing.

5.3.6.3.7 Local Tolerability

Summaries for tolerability will be presented by treatment and tabulated by scheduled timepoints. Worst post-baseline cases or scores will be determined for each subject and analyzed, which will include all scheduled and unscheduled assessments, if any.

5.3.6.3.7.1 Injection Site Discomfort

The incidence of any injection site discomfort reported by the subject will be analysed descriptively with counts and percentages for all scheduled time points.

- None
- Any injection site discomfort (including 'Other');
- Pain;
- Itching;
- Tingling, twitching or numbness;
- Irritation.

The following descriptive statistics will be provided for all timing variables for subjects reporting at least one injection site discomfort:

- Counts and percentages of time of onset from study drug injection (0-<1 min, 1-2 mins, 3-5 mins, 6-9 mins, >=10 mins);
- Total duration of discomfort will be analysed with descriptive statistics for continuous variables.

5.3.6.3.7.2 Draize Scale (Erythema and Edema)

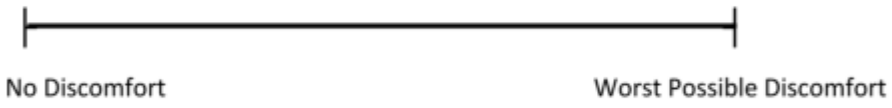
The incidence of erythema and edema will be analysed descriptively with counts and percentages by scheduled timepoints, worst post-baseline score, and by the categories indicated below:

Erythema Formation		**Edema Formation**	
Description	Score	Description	Score
No erythema	0	No edema	0
Erythema	1-4	**Edema**	1-4
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. 1mm*	3
Severe erythema: *Beet redness to slight eschar formation*	4	Severe edema: *raised more than 1mm and beyond exposure area*	4

Subject will be counted only once per actual treatment and timepoint and once for worst post-baseline score or erythema/edema occurrence.

5.3.6.3.7.3 VAS

VAS is reported using a 100-mm scale.



VAS scores will be summarized by all timepoints and worst post-baseline score.

Mean VAS scores will be compared between the treatments. Comparison between the treatments will be performed using a mixed model with treatment, period and treatment*period as fixed factors and subject as a random factor. This analysis will be performed on the Safety population.

6 STATISTICAL METHODS

6.1 General Considerations

The statistical analyses will be performed using SAS Version 9.4 (or higher). All tables, figures and listings will be produced in landscape format.

Data will be presented at each scheduled timepoint (nominal time), where applicable. However, time-related endpoints (time to event) will be summarized using actual time.

For actual time, two reference points will be used: (a) decision to dose and/or (b) injection of study drug, which are specified in the primary and secondary endpoint analyses.

The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables.

All study data will be included in the study data listings. Listings will be displayed by subject in chronological order, if not stated otherwise.

For tabulated safety summaries, only the scheduled timepoints will be included in the summary tables. Unscheduled assessments will be listed and used for evaluation of worst post-baseline value in categorical assessments, where applicable.

Sample codes and calculations for the efficacy analysis are provided in Appendix 2: Code Fragments. Actual code or procedure usage can differ from these samples, based on the model and conditions that correspond to those pre-specified in the SAP. Additional analysis may be performed for the cases not specified in SAP and will be described in CSR.

6.1.1 General guideline for descriptive summaries

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

Additionally, coefficient of variation, geometric mean and geometric coefficient of variation will be calculated for: $C_{max,}$, AUC_{0-90} and AUC_{0-180}.

For categorical variables, count and percent of subjects/counts in each treatment group and category will be presented. Percentages will be based on number of subjects with non-missing values, if not specified otherwise.

6.2 Euglycemic Baseline

Prior to starting the hypoglycemia induction procedure, the subject must have stable plasma glucose for at least 30 minutes at 95 ± 20 mg/dL (75 to 115 mg/dL [4.17 to 6.38 mmol/L]) at a stable IV insulin infusion rate varying no more than ±20% during which plasma glucose must be measured at least every 15 ± 2 minutes (i.e., at least 3 consecutive values in the target range at 0, 15, and 30 minutes).

For Hypoglycemia Symptoms Assessment scheduled at the end of the Euglycemic Baseline phase just before the IV bolus push dose of insulin, will serve as baseline to determine hypoglycemia symptoms relief and/or resolution. If more than one assessment performed in this time interval, then the last assessment of each hypoglycemia symptom or score will be selected for baseline.

6.3 Hypoglycemic Baseline

Hypoglycemic steady state is defined as a confirmatory plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L) and < 54 mg/dL (< 3 mmol/L), and an 8-minute linearly extrapolated future plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L).

To determine whether a hypoglycemic steady state has been achieved, confirmatory plasma glucose measurements will be taken as necessary at 5, 10 and 15 minutes after an initial plasma glucose < 54 mg/dL (< 3 mmol/L). Depending on the outcome, the following procedures will be followed.

1. If any of the confirmatory measurements meets the criteria for hypoglycemic steady state, the subject will be eligible to receive study glucagon, and further confirmatory plasma glucose measurement are not required.
2. If the final confirmatory plasma glucose value is < 42 mg/dL (< 2.33 mmol/L), the procedure will be terminated, study glucagon will NOT be administered, and the visit will be rescheduled after a minimum 3-day wait. At the Investigator's discretion, the subject should be treated with IV glucose or oral carbohydrates, it should be verified that the subject achieved a euglycemic state and is medially stable prior to discharge.
3. If any of the confirmatory plasma glucose measurements are > 54 mg/dL (> 3 mmol/L), then the IV insulin infusion will be re-started, and insulin adjustments will be made as per the induction procedure. Once another initial plasma < 54 mg/dL (< 3 mmol/L) is obtained, the sequence of up to 3 confirmatory plasma glucose readings will repeated.

If the subject achieved hypoglycemic steady state their linearly extrapolated plasma glucose value from the last two readings of hypoglycemia induction to time of study drug administration will be defined as Hypoglycemic Baseline for corresponding treatment period and will serve as baseline for the Primary Endpoint and Secondary Endpoints related to pharmacokinetic and pharmacodynamic characteristics within Treatment Period 1 / 2.

6.4 General guideline for define the protocol time

Protocol time is needed to find the 30-minute glucose value as well as to generate most 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 (receiving glucagon):
  - 5, 10,15,20,25,30,35,40,45,50,55,60,65,70,75,80,85,90;
  - 120,150, and180.
- 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.

Several analyses will be conducted using both the protocol time based on study drug administration and the one based on decision to dose. These analyses will be noted in each of the corresponding sections.

6.5 Analysis of Primary Endpoint

The primary endpoint analysis will be based on the risk difference in rates of failing to achieve Positive Plasma Glucose Response (PGR) of G-Pen versus GlucaGen Hypokit and a 95% CI will be calculated. Non-inferiority will be declared if the upper limit of the 95% confidence interval for the difference in failure rates is ≤ 5%; where the absolute failure rate of G-Pen treatment is ≤ 5%. This analysis will be repeated for ITT, mITT and PP populations.

Subjects who are missing the primary endpoint for a study treatment will be considered as having a failure in the primary analysis for that treatment administration. This imputation will be conducted for both the ITT and the mITT populations. If a subject received the same two treatment administrations for both periods (Period 1 and Period 2), only the visit with the planned treatment received will be included in the primary analysis and the subject will be considered a failure in the primary analysis for the for unreceived treatment administration (ITT, mITT). For all other analyses, data will be included for only the planned treatment received in those analyses.

A sensitivity analysis will be performed for where all missing data will be considered a success and the same analysis as above completed.

6.6 Secondary Endpoints

6.6.1 Binary Responses

The same test as described in the previous section 6.5, will be applied to each of the binary responses (no sensitivity analyses will be performed).

Note that all these analyses will be repeated for ITT, mITT and PP population.

6.6.2 Pharmacodynamics Analyses

All PD parameters will be presented descriptively.

A mixed model with treatment, period and treatment*period as fixed factors and subject as a random 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 95% 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 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 conducted based on the mITT population only.

6.6.3 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 for each treatment group. A LOCF imputation will be used for post-baseline assessments to 90 minutes inclusively. Additionally, this will also be presented graphically.

Analysis will be conducted for the mITT population only and will use time from decision to dose.

6.6.4 Time-to-Event Analyses

All the Time-to-Event Efficacy parameters will be presented descriptively.

A survival analysis will be conducted for comparing the difference between treatments. Survival curves will be provided to compare both treatments graphically. Two-sided log-rank p-value for the difference will be reported.

This analysis will be repeated for ITT, mITT and PP population.

6.6.5 Study Drug Assignment Questionnaire

After study procedures at Visit 3, the subject will be asked to guess what their first treatment was, and what their second treatment was from the choices of “Xeris Glucagon, G-Pen, administered by auto-injector”, and “Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe”.

This data will be analyzed descriptively with counts and percentages by treatment. Percentage of guessing will be compared against 50% using binomial proportion for each treatment.

This will be conducted based on the PP population only.

6.7 Subgroup Analysis

Analysis of subgroups will not be performed in this study.

6.8 Interim Analysis

Interim analysis will not be performed in this study.

7 DATA HANDLING CONVENTIONS

7.1 Missing Data

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

7.2 Repeated and Unscheduled Visits

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. Worst post-baseline assessments will be defined using all visits, including unscheduled.

7.3 Conversion of Plasma Glucose Values

For measurements of plasma glucose standard units will be considered as mg/dL. All measurements in mmol/L will be converted into mg/dL with next rule applied:

1 mmol/L = 18.0182 mg/dL

8 PLANNED LISTINGS, TABLES AND FIGURES

Please see the Appendix 1.

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

9 SOFTWARE REQUIREMENTS

SAS – Version 9.4 or higher.

WinNonlin - Professional Version 5.2 or higher.

Excel - Microsoft Excel 2007 or higher.

10 DEVIATIONS FROM PLANNED ANALYSIS

For timing parameters mixed model analysis was replaced by time-to-event analysis.

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APPENDIX 2: CODE FRAGMENTS

Risk difference test for binary response

```
Proc Freq data = <Data> order=data;
      weight Count / ZEROS;
      tables <Treatment>*<Response> / riskdiff;
      output out = <Out> riskdiff;
run;
```

Mixed model

```
ods output lsmeans(match_all) = <Out_LSmean>
           Diffs(match_all) = <Out_Diffs>;
Proc Mixed data=<Data>;
      class <Treatment> <Period> <Subject>;
      model <Value> = <Treatment> <Period> <Treatment>*<Period>;
      random <Subject> / Type = un;
      lsmeans <Treatment> / cl DIFF;
run;
```

Time-to-Event

```
ods output means=<Out_Means> HomTests=<Out_Test>;
proc lifetest data=<Data>;
      time <Time>;
      strata <Treatment>;
run;
```

Study Drug Assignment

```
proc freq data=<Data>;
      tables <Treatment>/ BINOMIAL (p=0.50) alpha=0.05;
      output out=<Out> Binominal;
      weight count;
run;
```