

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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**Version 1.2  
January 29, 2018**

## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for G-Pen™ (glucagon injection). I have read the XSGP-303 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

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Signature of Investigator

---

Date

## PROCEDURES IN CASE OF EMERGENCY

**Table 1: Emergency Contact Information**

<b>Role in Study</b>	<b>Name &amp; Title</b>	<b>Email Address &amp; Telephone Number</b>
Sponsor's Study Leader & primary contact	Martin J. Cummins, VP, Drug Development	mcummins@xerispharma.com 512-498-2675 (direct) 806-282-2120 (cell)
Medical Monitor & 24-hour emergency contact	Dr. M. Khaled Junaidi, MD, Medical Director, Clinical Research	kjunaidi@xerispharma.com 312-517-1461 (direct) 815-593-2218 (cell)
Reporting of Investigational Product concerns, including device failures	Xeris Medical Affairs Department	safety303@xerispharma.com +1.630.915.5885 +1.815.593.2218

## 2. SYNOPSIS

<b>Protocol Number: XSGP-303</b>	
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-CENTER, RANDOMIZED, CONTROLLED, SINGLE-BLIND, 2-WAY CROSSOVER STUDY TO EVALUATE EFFICACY AND SAFETY.	
Principal Investigator:	Each participating clinical site will nominate a physician who, based on training and experience, will serve as Principal Investigator for that site.
IND:	115091
Project phase:	Phase 3b
Compound(s):	G-Pen™ (glucagon injection) Lilly Glucagon for Injection (rDNA origin)
Objectives:	<p>The primary objective of this study is to demonstrate the efficacy (return to plasma glucose &gt;70.0 mg/dL) of G-Pen 1 mg (test) to be non-inferior to Lilly Glucagon 1 mg (reference), in Type 1 diabetic (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 &gt; 70.0 mg/dL within 30 minutes of administration of glucagon.</p> <p>The secondary objectives of this study are:</p> <ol style="list-style-type: none"> <li>1. To demonstrate the efficacy (either return to plasma glucose &gt;70.0 mg/dL <i>or</i> an increase in plasma glucose <math>\geq</math> 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.</li> <li>2. To demonstrate the efficacy (return to plasma glucose &gt;70.0 mg/dL <i>or</i> 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.</li> <li>3. To compare the pharmacodynamic 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.</li> <li>4. To compare G-Pen (test) and Lilly Glucagon (reference) with regards to hypoglycemia symptom relief.</li> <li>5. 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.</li> </ol>

	6. To determine the safety and tolerability of G-Pen 1 mg (test) versus Lilly Glucagon 1 mg (reference) in T1D subjects in a state of induced hypoglycemia.
Study design:	This is a non-inferiority, multi-centered, randomized controlled, single-blind, two-way crossover efficacy and safety inpatient study in adult subjects with Type 1 diabetes mellitus (T1D). The study will involve two daytime clinical research center (CRC, or comparable setting) visits 7-28 days apart, with random assignment to receive G-Pen™ glucagon 1 mg during one period and Lilly Glucagon 1 mg during the other.
Study location:	Approximately 6 clinical research centers in North America.
Study duration:	The estimated duration of study participation for individual subjects is approximately 4 weeks. The estimated duration of the entire study is 4 months.
Sample size:	Approximately 200 subjects are anticipated to be screened for this study to achieve the goal of 85 subjects randomized and minimally 75 subjects who are evaluable for both periods.
Subjects:	The study will include male and female subjects with T1D between the ages of 18 and 75 years of age, inclusive, at Screening.
Inclusion Criteria:	<ol style="list-style-type: none"> <li>1. Males and females diagnosed with type 1 diabetes mellitus for at least 24 months.</li> <li>2. Current usage of daily insulin treatment that includes having an assigned “correction factor” for managing hyperglycemia.</li> <li>3. Age 18-75 years, inclusive.</li> <li>4. Random serum C-peptide concentration &lt; 0.5 ng/mL.</li> <li>5. Willingness to follow all study procedures, including attending all clinic visits.</li> <li>6. Subject has provided informed consent as evidenced by a signed/dated informed consent form completed before any trial-related activities occur.</li> </ol>
Exclusion Criteria:	<ol style="list-style-type: none"> <li>1. Pregnancy: For women of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception throughout the study and for 7 days after the last dose of study glucagon. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.</li> <li>2. Breastfeeding: Nursing mothers will be allowed into the study. However, breast feeding during the during in-patient study visits (Visit 2 &amp; Visit 3) and for 48 hours after each dose of study drug is not allowed.</li> <li>3. HbA1c &gt;9.0% at Screening.</li> <li>4. BMI &gt; 40 kg/m<sup>2</sup>.</li> <li>5. Renal insufficiency (serum creatinine greater than 3.0 mg/dL) or end-stage renal disease requiring renal replacement therapy.</li> <li>6. Serum ALT or AST equal to or greater than 3 times the upper limit of normal.</li> </ol>

7. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL.
8. Hematocrit  $\leq$  30%.
9. BP readings at Screening where SBP <90 or >150 mm Hg, and DBP <50 or >100 mm Hg.
10. Clinically significant ECG abnormalities.
11. Use of > 2.0 U/kg total insulin dose per day.
12. Inadequate venous access.
13. Congestive heart failure, NYHA class III or IV.
14. History of myocardial infarction, unstable angina, or revascularization within the past 6 months.
15. History of a cerebrovascular accident in past 6 months or with major neurological deficits.
16. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. Any history of breast cancer or malignant melanoma will be exclusionary.
17. Major surgical operation within 30 days prior to Screening.
18. Current seizure disorder (other than with suspect or documented hypoglycemia).
19. Current bleeding disorder, treatment with warfarin, or platelet count below  $50 \times 10^9$  per liter.
20. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
21. History of insulinoma.
22. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO & trehalose) in the investigational formulation.
23. History of glycogen storage disease.
24. Subject tests positive for HIV, HCV, or HBV infection (HBsAg+) at Screening.
25. Active substance or alcohol abuse (more than 21 drinks/wk for males or 14 drinks/wk for females). Subjects reporting active marijuana use or testing positive for tetrahydrocannabinol (THC) via rapid urine test will be allowed to participate in the study at the discretion of the Investigator.
26. Administration of glucagon within 28 days of Screening.
27. Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and during participation in the current study.
28. Any other reason the Investigator deems exclusionary.

Study Methods:	<p>Subjects will complete the screening procedures up to 30 days before dosing to determine eligibility before enrollment to the treatment period. Subjects not meeting eligibility criteria can be rescreened after a 30-day wait.</p> <p>The evening prior to each inpatient study visit, subjects with confirmed blood glucose not greater than 350 mg/dL will be admitted for an overnight stay between 6 and 8 pm and a CGM will be placed at the discretion of the Investigator. At investigator discretion, the subject may visit the clinic up to 5 days prior to the scheduled check-in for placement of the CGM. Subjects will be provided a standardized dinner and will continue their usual insulin regimen. At Investigator discretion, subjects may receive a standardized snack before midnight.</p> <p>Subjects will be instructed to fast after midnight. If site staffing allows for appropriate oversight, an intravenous catheter will be placed, and maintenance fluids administered. If not, the subject's own infusion pump will be used overnight if applicable. The subject's blood glucose will be monitored overnight, and glucose (IV or oral tablets) or insulin (IV or SC) will be administered as necessary to maintain blood glucose in a target range of 80-150 mg/dL.</p> <p>In the morning of the inpatient study visit, the subject's plasma glucose will be measured and verified to be not more than 270 mg/dL to be confirmed eligible for continuation into the insulin induction procedure. As another confirmation of eligibility for the induction procedure, overnight glucose data will be checked, and it will be verified that the subject did not have blood glucose &lt; 60 or greater than 270 mg/dL overnight.</p> <p>The subjects will continue fasting the morning of the procedure and will have an intravenous catheter for blood sampling inserted in the arm. The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow and achieve "arterialized" samples. The subject will be kept supine and covered under a blanket to maintain warmth.</p> <p>The subject will be eligible to begin the baseline euglycemic steady state period when the plasma glucose is confirmed to be within range of 70-270 mg/dL. IV insulin will be administered to maintain the plasma glucose within the range of 75-115 mg/dL for 30 minutes. If the plasma glucose has been maintained within the range of 75-115 mg/dL for at least 30 minutes, and the insulin infusion rate varies no more than +/- 20%, the induction procedure may commence.</p> <p>Eligible participants will enter a state of insulin-induced hypoglycemia in a gradual and controlled fashion, through a monitored, standardized induction protocol. Adherence to the protocol insulin dose adjustment algorithm will be facilitated by real time data entry on a pair of laptop computers. One will be for entry of glucose values as the measurements become available from the YSI glucose analyzer. The other laptop will display the induction procedure, glucose results, insulin bolus and insulin infusion rate data, and will provide information on glucose trajectory.</p> <p>Plasma glucose measurements will be taken every 10 minutes while glucose is &gt;80.0 mg/dL and at 5-minute intervals once plasma glucose is ≤ 80.0 mg/dL.</p> <p>Once the initial plasma glucose measurement &lt; 50.0 mg/dL is achieved, the IV insulin infusion will be stopped. A confirmatory plasma glucose reading will be taken 5 minutes later to confirm that a hypoglycemic steady state has been</p>
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	<p>reached, which is defined as two consecutive plasma glucose values between 43.0 and 49.9 mg/dL and an 8-minute linearly extrapolated value for plasma glucose is <math>\geq 42.0</math> mg/dL.</p> <p>When a state of stabilized insulin-induced hypoglycemia is verified, subjects will be administered the randomly assigned dose of either G-Pen™ glucagon 1 mg subcutaneously or Lilly glucagon 1 mg, via the subcutaneous route to the abdomen, around the umbilicus at a 90° angle to the skin.</p> <p>Study drug will not be prepared ahead of time. Rather, preparation of the IP will begin once the confirmatory plasma glucose reading is obtained, i.e., upon a “decision to dose.”</p> <ol style="list-style-type: none"> <li>1. As an assessment of the preparation time, the time between the decision to dose and injection of the randomized study drug to the abdomen will be measured.</li> <li>2. Following dosing, the plasma glucose will be monitored every 5 minutes until 90, and afterwards every 30 minutes until 180 minutes post-dosing.</li> <li>3. The induction procedure itself may elicit symptoms of hypoglycemia. Thus, subjects will complete a questionnaire regarding hypoglycemia symptoms at the start of the hypoglycemia induction period and periodically until either all symptoms abate or 180 minutes post-dosing with glucagon.</li> <li>4. After 180 minutes, the subject will resume insulin pump therapy, if applicable, and will be given a meal. The subject may be discharged after 180 mins with blood glucose <math>&gt; 100</math> mg/dL and if medically stable. At the Investigator’s discretion, the subject’s prescribed insulin regimen can be restarted, or the meal can be given sooner, but not earlier than 90 minutes post-glucagon, to prevent hyperglycemia or rebound hypoglycemia.</li> </ol> <p>After a wash-out period of 7 to 28 days, subjects will return to the clinic and the study procedures will be repeated with each subject crossed over to the other treatment. After study-related procedures are performed on each of the treatment days, subjects will be discharged. A follow-up visit will be conducted 2-7 days following administration of the final dose as a safety check.</p> <p>Tolerability will be assessed by comparing adverse event reports between the G-pen and Lilly Glucagon groups. In addition, at the end of each treatment period the subjects will complete questionnaires concerning injection site discomfort, and an Investigator will use modified Draize scales to evaluate the injection sites following each administration.</p>
<p>Data management and statistical analysis:</p>	<p>Data will be entered into an electronic Case Report Form by site personnel. Data will be monitored at on-site visits by Xeris personnel or by a CRO acting as Xeris’ agent. The primary endpoint will be assessed in both the per protocol (PP) and intent-to-treat (ITT) populations. The evaluable set for the PP population will be defined as all randomized patients who, during both study periods, successfully complete the insulin induction procedure, and fulfill the criteria for having achieved a hypoglycemic steady state, and successfully receive a dose of both study drugs (G-Pen followed Lilly Glucagon, or Lilly</p>

XSGP-303 Clinical Protocol  
G-Pen™ (glucagon injection)

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	Glucagon followed by G-Pen). PP and ITT analysis will also be applied to all secondary endpoints of the study.
Sample Size Determination:	<p>For the primary analysis, a failure is recorded if the subject's plasma glucose fails to rise above 70.0 mg/dL within 30 minutes of the administration of the dose of glucagon. Using this criterion, a sample size of 85 randomized subjects yields probabilities of G-Pen acceptance of 87.7% if the population failure rates of G-Pen and control are not more than 2%.</p> <p>Subjects will be recruited at approximately 6 clinical sites with a goal of no single center accounting for &gt; 20% of the total sample.</p>

### **3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES**

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 2: 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 <sub>max</sub>	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

## **5. STUDY OBJECTIVES AND ENDPOINTS**

### **5.1. 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.

### **5.2. 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  $\geq$  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 pharmacodynamic 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.

### **5.3. Endpoints**

#### **5.3.1. Primary Endpoint**

Treatment success in this study will be based on a primary endpoint of an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon.

#### **5.3.2. Secondary Endpoints**

The secondary endpoints for this study include:

- Return of plasma glucose to > 70 mg/dL or clearance of all neuroglycopenic symptoms within 30 minutes after receiving glucagon.

- Return of plasma glucose to  $> 70$  mg/dL or an increase in plasma glucose by  $\geq 20$  mg/dL within 30 minutes after receiving glucagon.
- Increase in plasma glucose by  $\geq 20.0$  mg/dL within 30 minutes after receiving glucagon.
- Relief within 30 minutes after receiving glucagon of all neuroglycopenic symptoms present immediately after the decision to dose.
- Pharmacodynamic characteristics, including: plasma glucose AUC, C<sub>max</sub>, and T<sub>max</sub>, time to achieve a 20.0 mg/dL increase, and time to reach  $>70.0$  mg/dL will be compared between the treatment groups both from time of glucagon administration and from time of the decision to dose.
- The total preparation time required to inject to the abdomen from a decision to treat will be compared between the treatment groups, as measured between the time of “decision to dose” and time of injection.
- Hypoglycemia symptom relief as measured using the hypoglycemia symptom questionnaire ([Appendix 1](#)), from just after the decision to dose to 180 minutes post-injection of glucagon.
- Safety-related parameters including:
  - Change in Vital signs from just prior to dosing to 180 minutes post-injection of glucagon
  - Changes in physical exam findings from Screening to Follow-up.
  - Changes in ECG findings from Screening to Follow-up.
  - Change in standard safety laboratory parameters (e.g., hematology and serum chemistry) from Screening to Follow-up.
  - 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 ([Appendix 2](#)).
  - Erythema and/or edema formation at site of injection assessed by an Investigator using the modified Draize scale (see [Appendix 3](#)).

## 6. BACKGROUND AND RATIONALE

### 6.1. Indication

The proposed indication is for the treatment of severe hypoglycemia.

#### 6.1.1. Background

The investigational product is glucagon. Glucagon is a 29 amino-acid polypeptide with a molecular weight of 3485 Daltons. The peptide is secreted by the alpha cells of the islets of Langerhan's in the pancreas, and functions as an anti-hypoglycemic agent and a gastrointestinal motility inhibitor. A single glucagon gene encodes a larger proglucagon biosynthetic precursor in mammals. Tissue-specific processing of proglucagon gives rise to glucagon, and to glicentin, oxyntomodulin, GLP-1, and GLP-2. As a natural (non-steroid) hormone synthesized in the pancreatic islet cells, it binds to glucagon receptors in the liver, causing liver cells to convert glycogen polymers into glucose molecules. The cloned glucagon receptor encodes a 485 amino acid protein with a predicted molecular weight of 54,962 Daltons [Jelinek], which signals through both adenylate cyclase and intracellular calcium with an EC50 of ~ 1 nM [Wakelam].

Historically glucagon is being used as rescue therapy for severe hypoglycemia. One of the main complications of diabetes treatment with insulin is the emergence of hypoglycemia, and the absolute or relative excess of therapeutic insulin is the determinant of risk. Hypoglycemia in diabetes is defined as “all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm” [ADA], and presents as diaphoresis, pallor, nausea, palpitations, tremors, and anxiety. If hypoglycemia becomes severe, symptoms may then include confusion, abnormal behavior, blurred vision, psychomotor abnormalities, loss of consciousness, seizures, and coma. [DCCT/EDIC) Study Research Group]. Recent reports have found that from 6% to 10% of deaths of patients with type 1 diabetes are attributable to hypoglycemia [Skrivarhaug, U.K. Hypoglycaemia Study Group]. The American Diabetes Association Workgroup recommends that patients with drug-treated diabetes (insulin secretagogue or insulin) become concerned about developing hypoglycemia at a plasma glucose concentration of  $\leq 70$  mg/dL (3.9 mmol/L) [ADA].

Therapy with insulin causes hypoglycemia during the course of established type 1 diabetes, and progressively more frequently over time in type 2 diabetes. The U.K. Hypoglycemia Study Group reported an incidence of 110 severe hypoglycemic episodes per 100 patient-years in patients with type 1 diabetes treated with insulin for  $<5$  years, and an incidence of 320 episodes per 100 patient-years in those with type 1 diabetes treated for  $>15$  years [U.K. Hypoglycaemia Study Group]. Type 1 diabetics suffer an average of two symptomatic hypoglycemic events per week – and a severe, temporarily disabling event approximately once a year [McLeod]. Insulin-using type 2 diabetics typically have several hypoglycemic episodes in a given year, 1-2 of these being severe episodes. There are currently approximately 1.4 million type 1 and 3.8 million insulin-using type 2 diabetics in the US alone [CDC]. On average, the total insulin-using patient population experiences about 3 million severe hypoglycemic events per year.

The American Diabetes Association [ADA], recommends that all insulin- and sulfonylurea-using diabetics carry glucagon emergency kits (GEKs) and use glucagon as first line therapy in the event of a severe hypoglycemic event. However, a recent survey indicates only about 30% of the insulin-using diabetics carry GEKs [Close Concerns]. The current standard of care for severe

hypoglycemia is an injection of glucagon. Administration of glucagon with current products (i.e. Lilly Glucagon for Injection, and Novo GlucaGen®) is a 9-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose [Glucagon, Glucagen].

### **6.1.2. Rationale**

Patients with diabetes frequently develop defective regulatory responses to hypoglycemia associated with reduced or absent glucagon responses. This is an important clinical problem, as current diabetes management with intensive insulin regimens usually increases the risk and frequency of severe hypoglycemic events that may require therapeutic intervention.

In response to the unmet medical need for a simple and ready-to-use glucagon for episodes of severe hypoglycemia, Xeris Pharmaceuticals is developing a glucagon rescue pen called the G-Pen™, which utilizes Xeris' biocompatible, non-aqueous peptide/protein reformulation technology. This technology has enabled Xeris to create a concentrated, low volume, stable glucagon formulation, pre-mixed and pre-loaded into a prefilled syringe and auto-injector pen. This creates a product with a number of advantageous features, including: a ready-to-use treatment with no reconstitution required, precise and rapid dosing, a hidden needle, and enhanced portability and availability due to room-temperature stability, to provide a superior alternative to currently marketed treatments.

## **6.2. Non-Clinical Pharmacology and Toxicology Experience with Glucagon**

Native glucagon for injection (bovine, porcine origin) was approved for use in humans in 1960 [FDA CDER #1]. The 29-amino acid sequence of pancreatic glucagon is identical in humans, cows, pigs, dogs, and rats, and is also conserved in biosynthetic versions of glucagon [Eistrup]. Glucagon for injection (rDNA origin) was approved in 1998, and is currently the drug substance identified in two approved NDAs ([NDA 20-928] and [NDA 20-918]). Complete NDA-required pharmacology and toxicology data have been reviewed and accepted by the FDA, as described in Lilly Glucagon [rDNA origin] for injection and Novo GlucaGen® (glucagon [rDNA origin] for injection) labeling [Glucagon, Glucagen]. As Xeris' drug product is produced by solid-phase peptide synthesis (SPPS), which also conserves the glucagon peptide sequence, the rDNA glucagon information is pertinent to the development of G-Pen for the treatment of severe hypoglycemia. A summary of this information can be found in Xeris' current Investigator's Brochure, which will be provided to each Investigator participating in this study.

### **6.2.1. Nonclinical Pharmacology and Toxicology of Xeris G-Pen™ (glucagon injection) Investigational Non-Aqueous, Synthetic Glucagon**

Information on the nonclinical pharmacology, pharmacokinetics, and toxicology of G-Pen™ (glucagon injection) is provided in Xeris' current Investigator's Brochure.

## **6.3. Description and Composition of Drug Product**

Synthetic glucagon is the drug substance in G-Pen. Glucagon cGMP grade is manufactured, packaged and released by Bachem AG (Bubendorf, Switzerland), conforms with USP standards and has a Type II DMF filed with the FDA. G-Pen is a sterile subcutaneous injectable non-

aqueous formulation for treatment of severe hypoglycemia. G-Pen delivers 1 mg of glucagon, with trehalose and DMSO as excipients. The drug product is stored at controlled room temperature (20-25°C) prior to use.

G-Pen is supplied in 1.0 mL long Crystal Zenith® pre-filled cyclic olefin polymer syringe with Flurotec® coated plunger. The pre-filled syringe is loaded into a Molly® single-use, disposable auto-injector from SHL Group, and is packaged in a sealed poly/foil pouch.

#### **6.4. Clinical Experience with Glucagon**

Glucagon has a long history of medical use in the US, and is currently marketed by Eli Lilly & Co. as Glucagon (Glucagon Injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both reference listed drugs (RLD) for treatment of severe hypoglycemia. Glucagon has a rapid onset of action and an extremely short half-life, and its safety, efficacy, and clinical pharmacology have been well established [[FDA CDER #2](#)]. The FDA first approved glucagon for use in humans in 1960.

On September 25, 2013, Xeris IND 115091 went into effect and Study No. XSGP-201 was completed in January 2014. This study examined safety, pharmacokinetics (PK), and efficacy of rescue doses (0.5 and 1.0 mg) of G-Pen as compared to Lilly Glucagon (1.0 mg) in healthy volunteers. Phase 3 studies in adult (XSGP-301) and pediatric (XSGP-302) subjects with type 1 diabetes were completed in August and June 2017, respectively. The results of these studies as well as a summary of clinical pharmacology, published studies, post-market surveillance data, and immunogenicity of Lilly Glucagon are provided in Xeris' current Investigator's Brochure.

## 7. STUDY DESIGN

### 7.1. Study Overview

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). The study involves two daytime clinical research center (CRC) visits 7-28 days apart, with random assignment to receive G-Pen™ glucagon 1 mg during one period and Lilly Glucagon 1 mg during the other. Each daytime visit will be preceded by an overnight stay in the CRC. Subjects will complete the screening procedures up to 30 days before Randomization to determine eligibility before enrollment to the treatment phase. Subjects not meeting eligibility criteria may be rescreened after a 30-day wait.

The evening prior to each in-patient study visit, subjects will be admitted for an overnight stay between 6 and 8 pm and at Investigator discretion a continuous glucose monitor (CGM) (Dexcom® G4 to be provided by Xeris) will be placed. At investigator discretion, the subject may visit the clinic up to 5 days prior to the scheduled check-in for placement of the CGM. Instead of placing a CGM, at Investigator discretion, blood glucose will be assessed periodically during the overnight stay via YSI model 2300 or 2900 or an FDA/Health Canada cleared blood glucose meter (hereafter, simply “glucose meter”). Subjects will be asked to refrain from consuming alcohol during the day prior to the overnight stay. Upon arrival in the evening, plasma glucose will be measured by blood glucose meter and confirmed to be  $\leq 350$  mg/dL, or the visit will be rescheduled.

In clinic, subjects will receive a standardized dinner meal as per the usual practices of the clinical site. Subjects should complete dinner before 9 pm. Subjects should follow their usual, prescribed insulin regimen at dinner time under the supervision of a study nurse, and will continue their usual, prescribed insulin regimen until midnight.

Subjects will be instructed to fast starting at midnight, at which point an intravenous catheter will be placed, and maintenance fluids administered. Blood glucose will be confirmed by glucose meter as necessary to calibrate the CGM, and blood glucose will be monitored overnight by CGM. At Investigator discretion, CGM glucose values may be confirmed by glucose meter or Yellow Springs Instrument (YSI) glucose analyzer.

After midnight, the Investigator should optimize blood glucose within a target range of 80.0-150.0 mg/dL through the administration of IV insulin and glucose. If operational considerations at a site preclude IV administration of insulin overnight, no catheter will be placed, and oral glucose tablets and the subject’s own insulin infusion pump or subcutaneous insulin will be used to optimize blood glucose within a target range of 80.0-150.0 mg/dL. This range is considered a target only, and values outside of this range will not be considered protocol deviations.

In the morning of the inpatient study visit, the subject’s plasma glucose will be measured and verified to be not more than 270 mg/dL to be confirmed eligible for continuation into the insulin induction procedure. As another confirmation of eligibility for the induction procedure, CGM data will be checked and it will be verified that the subject did not have blood glucose  $< 60$  or greater than 270 mg/dL overnight. If either of these criteria is not met, the visit will be rescheduled after a minimum 7-day wait.



The subject will continue fasting the morning of the procedure, and will have another intravenous catheter for blood sampling inserted in the contralateral arm. Ideally, the sampling IV catheter should be placed in a vein within the antecubital fossa. The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow to achieve “arterialized” samples. The subject will be kept supine and the abdomen and torso covered under a blanket to maintain warmth.

Baseline euglycemic steady state period will begin when the plasma glucose is confirmed to be within range of 70-270 mg/dL. IV insulin will be administered to maintain the plasma glucose within the range of 75-115 mg/dL for 30 minutes. If the plasma glucose has been maintained within the range of 75-115 mg/dL for at least 30 minutes and the insulin infusion rate varies no more than  $\pm 20\%$ , the induction procedure may commence.

During the induction procedure, the subject will enter a state of hypoglycemia through the administration of regular insulin diluted in normal saline (see Section 7.2), within a controlled and monitored setting. Adherence to the insulin dose adjustment algorithm will be facilitated by real time data capture on a pair of laptop computers. One laptop will be used for entry of glucose values as the measurements become available from the YSI glucose analyzer. The other laptop will display the induction procedure, glucose values, insulin bolus doses, and insulin infusion rate data, and will provide guidance on appropriate insulin dosing changes based on the subject’s glucose trajectory. The application will include a data entry form for the Investigator to either document concurrence or to provide reasoning for any deviations from the protocol algorithm.

Both laptops will be connected via either wireless or hard-wired secure internet connection to each other as well as a central database, allowing Sponsor personnel to monitor the induction procedures virtually in real time.

The combination of one or more IV bolus doses of insulin along with continuous IV infusion of insulin will be used to gradually decrease a subject’s plasma glucose to a target  $<50.0$  mg/dL. As per Section 11.2, all plasma glucose levels will be based on the average of two readings taken via YSI glucose analyzer at each time point. Plasma glucose measurements will be taken every  $10 \pm 5$  minutes while glucose is  $>80.0$  mg/dL and every  $5 \pm 2$  minutes once plasma glucose is  $\leq 80.0$  mg/dL.

The IV insulin infusion may be stopped when the plasma glucose first reaches  $<50$  mg/dL, or, as guided per the insulin dosing algorithm, when plasma glucose is  $> 50$  mg/dL. Five minutes after this first plasma glucose  $<50$  mg/dL, a confirmatory plasma glucose reading (plasma glucose  $<50.0$  mg/dL) will be verified. The Investigator will determine whether a hypoglycemic steady state has been achieved, which 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  $\geq 42.0$  mg/dL.

If plasma glucose is not in a steady state, the subject’s plasma glucose should be rechecked at a subsequent 5-minute interval. If this second confirmatory glucose is  $\geq 42.0$  mg/dL and a linearly extrapolated 8-minute later glucose value  $\geq 42.0$  mg/dL is obtained, the subject will be deemed to be within a hypoglycemic steady state.

If the second confirmatory plasma glucose measurement is  $< 42.0$  mg/dL, the subject should not be administered study glucagon, should be treated instead with IV glucose or oral carbohydrates at the Investigator’s discretion, verified to be euglycemic, and their visit rescheduled after a minimum 7-day wait.

After a hypoglycemic state is verified, the subject will be eligible to receive either G-Pen or Lilly Glucagon in one of the randomized treatment sequences shown in [Table 3](#). The time of this “decision to dose” on the part of the Investigator will be documented.

**Table 3: Randomized Treatment Sequence**

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

Plasma glucose levels will be monitored for 180 minutes post-dosing. It is believed that blood glucose <50 mg/dL will be low enough to generate neuroglycopenic and autonomic symptoms in most subjects, yet high enough (i.e., > 40 mg/dL) to avoid the impairment of consciousness. Consequently, subjects will complete a questionnaire about symptoms of hypoglycemia [[Nermoen](#)] during the hypoglycemia induction phase, and for 180 minutes after treatment with glucagon.

After a wash-out period of 7 to 28 days, subjects will return to the clinic and the procedure will be repeated with each subject crossed over to the other treatment.

After study-related procedures are performed on each of the treatment days, subjects will be discharged after receiving a meal as per each site’s usual practice. A follow-up visit as a safety check will be conducted 2-7 days following administration of the final dose of study drug.

## **7.2. Hypoglycemia Induction Procedure and Justification**

The most commonly used hypoglycemia insulin induction method cited in the literature [[Nermoen](#)] involves constant insulin infusion rates many-fold above normal basal infusion rates. As hepatic glucose production is determined by the glucagon to insulin ratio, this procedure may not create realistic circumstances for evaluating the effectiveness of glucagon in raising blood glucose. The predecessor study (XSGP-301), therefore, utilized a comparatively lower rate of insulin infusion at 1 to 2 times the normal basal rate, combined with intravenous push of a bolus dose of insulin derived from the subject’s own self-reported glucose correction factor. About 30% of the procedures performed in XSGP-301 study resulted in plasma glucose (PG) <40 mg/dL. To achieve more precision in achieving a steady state of PG below 50 mg/dL, individual procedure data from the XSGP-301 study were fitted to a model of insulin action allowing identification of opportunities for algorithm enhancements. The algorithm was modified accordingly and tested in the model of the procedures representing a broad spectrum of subjects, including the two extremes of insulin sensitivity that were associated with low PG in XSGP-303.

### **Hypoglycemia Induction Procedure**

Subjects will be admitted the evening prior, provided a standardized meal, use their regularly prescribed evening insulin regimen, and fast overnight. During the fast, subjects will be provided maintenance IV fluids and their glucose optimized, if site staffing permits. In morning of the procedure (prior to the baseline euglycemia steady state period), the subject’s plasma glucose will be verified to be not more than 270 mg/dL. CGM will be used to verify that subjects did not experience hypo- or hyperglycemia overnight (i.e., blood glucose < 60 mg/dl or > 270 mg/dl). During the baseline euglycemia steady state and hypoglycemia induction, subjects should be

hydrated using IV fluids. Once glucagon dosing has taken place, IV fluids may be discontinued at investigator discretion and replaced by oral intake of water.

After the overnight stay, subjects will have a second catheter placed for blood sampling, ideally located in a vein within the antecubital fossa. The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow and achieve “arterialized” samples. Use of the heated-hand box will follow the manufacturer’s printed instruction sheet.

### **Baseline Euglycemic Steady State**

Prior to starting the hypoglycemia induction procedure, the subject must have PG stable for at least 30 minutes at 95 +/- 20 mg/dL (75-115 mg/dL) and a stable IV insulin infusion rate varying no more than +/- 20% during which PG must be measured at least every 15 minutes.

### **Induction Start**

For the induction, the starting plasma glucose level will be determined as the average of three YSI measurements taken over the final 30 minutes of the baseline steady state period. The following procedures will then be undertaken:

1. Subjects will continue the IV insulin infusion at the final rate of the baseline euglycemic steady state.
2. Subjects then will be given an initial IV bolus push dose of regular insulin diluted in saline:
  - a. The dose will be calculated as 75% of the dose estimated to reduce plasma glucose from the subject’s starting plasma glucose level to 50 mg/dL based on the subject’s self-reported glucose correction factor. This dose will be referred to as “1 bolus (full bolus dose)” subsequently. The Investigator may use discretion to decrease the amount of the calculated bolus dose based upon the subject’s insulin sensitivity factor. However, the Investigator is not allowed to increase the amount of the bolus dose.
  - b. PG will be measured every 5 to 10 minutes, depending on the current PG value (see [Table 4](#)).
  - c. The first insulin adjustment will be made no earlier than 20 minutes after the initial bolus, but will otherwise follow the directions for insulin adjustments shown in [Table 4](#).

The Investigator may at discretion override the insulin dosing algorithm, but must document the reason for this decision.

**Table 4: Insulin Dose Adjustments**

PG (mg/dl)	PG (mM)	Measurement interval	Target Rate of PG decrease	Insulin Bolus Criteria	Insulin Basal Rate Adjustment Criteria
>80	>4.4	10 min.	>30 mg/(dl*hr) (>1.67 mM/hr)	If PG decrease < 9 mg/(dl*hr) (<0.5 mM/hr); give 1 bolus	If PG decrease <30 mg/dl*hr (<1.67 mM/hr); increase 20% (15 min)
61-80	3.4-4.4	5 min.	30 mg/(dl*hr) (1.67 mM/hr)	If PG decrease < 9 mg/(dl*hr) (<0.5 mM/hr); give 1/2 bolus	If PG decrease <30 mg/dl*hr (<1.67 mM/hr); increase 20% (15 min)
					If PG decrease >60 mg/dl*hr (>3.33 mM/hr); decrease 25% (15 min)
56-60	3.1-3.3	5 min.	15 mg/(dl*hr) (0.83 mM/hr)	Not allowed	If PG decrease <9 mg/dl*hr (<0.5 mM/hr); increase 20% (10 min), or set at 120% of previous rate if previously stopped or decreased by 50% (5 min)
					If PG decrease >30 mg/dl*hr (>1.67 mM/hr); decrease 50% (5 min)
					If PG decrease >60 mg/dl*hr (>3.33 mM/hr); Stop (5 min)
50-55	2.8-3.1	5 min.	15 mg/(dl*hr) (0.83 mM/hr)	Not allowed	If PG decrease <9 mg/dl*hr (<0.5 mM/hr); increase 20% (10 min), or set at 120% of previous rate if previously stopped or decreased by 50% (5 min)
					If PG decrease >30 mg/dl*hr (>1.67 mM/hr); Stop (5 min)
<50	<2.8	5 min.	0	Not allowed	Stop

**Note: mM = mmol/l**

When PG is > 60 mg/dL, insulin adjustments should not be made more frequently than every 15 minutes. When PG is ≤60 mg/dL, the minimum time between adjustments to decrease, terminate or re-start insulin is either 10 or 5 minutes, as indicated in [Table 4](#).

1. While PG is greater than 80 mg/dL (4.4 mM):
  - a. Measure PG at least every 10 minutes.
  - b. When 15 minutes have passed from the last insulin dose adjustment:
    - i. If the rate of PG decrease is less than 30 mg/dl\*hr ( $<1.67$  mM/hr), then the insulin infusion rate should be increased by 20%.
    - ii. If the rate of PG decrease is less than 9 mg/dl\*hr ( $<0.5$  mM/L\*hr), then the insulin infusion rate should be increased by 20%, plus an additional 1 bolus (full bolus dose) should be administered.
2. While PG is 61-80 mg/dL (3.4 – 4.4 mM):
  - a. Measure PG at least every 5 minutes.
  - b. When 15 minutes have passed from the last insulin dose adjustment:
    - i. If the rate of PG decrease is greater than 60 mg/dl\*hr ( $>3.33$  mM/hr), then the insulin infusion rate should be decreased by 25%.
    - ii. If the rate of PG decrease is less than 30 mg/dl\*hr ( $>1.67$  mM/hr), then the insulin infusion rate should be increased by 20%.
    - iii. If the rate of PG decrease is less than 9 mg/dl\*hr ( $<0.5$  mM/hr), then the insulin infusion rate should be increased by 20%, plus an additional 1/2 bolus dose (one-half of the “1 bolus”) should be administered.
3. While PG is 56-60 mg/dL (3.1 – 3.4 mM):
  - a. Measure PG at least every 5 minutes.
  - b. Bolus doses of insulin should not be given.
  - c. When 5 minutes have passed from last insulin adjustment:
    - i. If the rate of PG decrease is greater than 60 mg/dl\*hr ( $>3.33$  mM/hr), then stop the IV insulin infusion.
    - ii. If the rate of PG decrease is greater than 30 mg/dl\*hr ( $>1.67$  mM/hr), then the insulin infusion rate should be decreased by 50%.
    - iii. If the infusion was previously stopped or decreased by 50%, and the rate of PG decrease rate is less than 9 mg/dl\*hr ( $<0.5$  mM/hr), then the insulin infusion should be set at 120% of the previous rate.
  - d. When 10 minutes have passed from the last insulin dose adjustment:
    - i. If the rate of PG decrease rate is less than 9 mg/dl\*hr ( $<0.5$  mM/hr), then the insulin infusion rate should be increased by 20%.
4. While PG is 50-55 mg/dL (2.8 – 3.1 mM):
  - a. Measure PG at least every 5 minutes.
  - b. Bolus doses of insulin should not be given
  - c. When 5 minutes have passed from last insulin adjustment:

- i. If the rate of PG decrease is greater than 30 mg/dl\*hr ( $>1.67$  mM/hr), the IV insulin infusion should be stopped.
  - ii. If the infusion was previously stopped or decreased by 50%, and the rate of PG decrease rate is less than 9 mg/dl\*hr ( $<0.5$  mM/hr), then the insulin infusion should be set at 120% of the previous rate.
- d. When 10 minutes have passed from the last insulin dose adjustment:
  - i. If the rate of PG decrease is less than 9 mg/dl\*hr ( $<0.5$  mM/hr), then the insulin infusion rate should be increased by 20%.
- 5. If the PG is less than 50 mg/dL ( $<2.8$  mM), then the IV insulin infusion should be stopped.

### **7.3. Interruption and Termination of Dosing**

At any time during the induction procedure if there are two consecutive plasma glucose measurements taken 5 minutes apart that are  $< 42.0$  mg/dL, the procedure will be terminated and appropriate measures (oral or IV glucose) will be taken at the Investigator's discretion. If a subject exhibits signs of coma or convulsions, a 25-mL IV bolus dose of 50% dextrose will be given in lieu of study drug. Signs and symptoms should be monitored, and if the subject's condition fails to improve in a timely fashion, additional dextrose or other medical intervention may be given at the discretion of the Investigator.

Euglycemia will be confirmed and the subject should be medically stabilized per Investigator discretion before being released. The treatment visits should be rescheduled after a minimum 7-day wait.

The study procedure will end for any SAE that occurs during the induction procedure. Causality should be fully assessed by both the Investigator and the Sponsor.

Note: subjects will undergo a maximum of 4 hypoglycemia inductions in this study to achieve two successful procedures.

## **8. ELIGIBILITY CRITERIA AND STUDY ENROLLMENT**

Subject eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before a subject is included in the study. Subjects must meet the following inclusion and exclusion criteria to be eligible for enrollment into the study.

### **8.1. Inclusion Criteria**

1. Males and females diagnosed with type 1 diabetes mellitus for at least 24 months.
2. Current usage of daily insulin treatment that includes having an assigned "correction factor" for managing hyperglycemia.
3. Age 18-75 years, inclusive.
4. Random serum C-peptide concentration < 0.5 ng/mL.
5. Willingness to follow all study procedures, including attending all clinic visits.
6. Subject has provided informed consent as evidenced by a signed/dated informed consent form completed before any trial-related activities occur.

### **8.2. Exclusion Criteria**

1. Pregnancy: For women of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception throughout the study and for 7 days after the last dose of study glucagon. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Breastfeeding: Nursing mothers will be allowed into the study. However, breast feeding during the during inpatient study visits (Visit 2 & Visit 3) and for 48 hours after each dose of study drug is not allowed.
3. HbA1c >9.0% at Screening.
4. BMI > 40 kg/m<sup>2</sup>.
5. Renal insufficiency (serum creatinine greater than 3.0 mg/dL) or end-stage renal disease. requiring renal replacement therapy.
6. Serum ALT or AST equal to or greater than 3 times the upper limit of normal.
7. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL.
8. Hematocrit of less than or equal to 30%.
9. BP readings at Screening where SBP <90 or >150 mm Hg, and DBP <50 or >100 mm Hg.
10. Clinically significant ECG abnormalities.
11. Use of > 2.0 U/kg total insulin dose per day.
12. Inadequate venous access.

13. Congestive heart failure, NYHA class III or IV.
14. History of myocardial infarction, unstable angina, or revascularization within the past 6 months.
15. History of a cerebrovascular accident in past 6 months or with major neurological deficits.
16. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. History of breast cancer or malignant melanoma will be exclusionary.
17. Major surgical operation within 30 days prior to Screening.
18. Current seizure disorder (other than with suspect or documented hypoglycemia).
19. Current bleeding disorder, treatment with warfarin, or platelet count below  $50 \times 10^9$  per liter.
20. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
21. History of insulinoma.
22. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO & trehalose) in the investigational formulation.
23. History of glycogen storage disease.
24. Subject tests positive for HIV, HCV or HBV infection (HBsAg+) at Screening.
25. Active substance or alcohol abuse (more than 21 drinks/wk. for males or 14 drinks/wk. for females). Subjects reporting active marijuana use or testing positive for tetrahydrocannabinol (THC) via rapid urine test will be allowed to participate in the study at the discretion of the Investigator.
26. Administration of glucagon within 28 days of Screening.
27. Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and during participation in the current study.
28. Any reason the Investigator deems exclusionary.

### **8.3. Randomization**

Randomization will be carried out via the Vision™ electronic data capture (EDC) system, version 9.3. The just-in-time randomization algorithm is programmed as a calculation within the Vision software system. The calculation is triggered when 1) site staff complete the Eligibility form and the subject is found to be eligible based on the inclusion/exclusion answers, and 2) the user checks a box on the Randomization form indicating a decision to randomize. This triggers the randomization calculation that sets the treatment group on the Dose Administration form. When the calculation is triggered, Vision generates a treatment based on the remaining treatments left within the block. This randomization calculation uses the java cryptographically strong SecureRandom random number generator in the case that the treatment group is not



already determined by the previous assignments. The SecureRandom algorithm computes the SHA-1 hash over a true-random seed value concatenated with a 64-bit counter, which is incremented by 1 for each operation. From the 160-bit SHA-1 output, only 64 bits are used. As a result, there is no known computer analysis that is able to predict the next "toss" better than a random guess.

Subjects meeting all eligibility criteria and the following additional requirements will be randomized 1:1 by site in simple blocks to receive G-Pen™ glucagon or Lilly glucagon injection at the first treatment visit. Randomization at the first treatment visit (i.e., Day 0) should happen following the overnight stay and after the baseline euglycemia steady state has been achieved and the Investigator deems it is appropriate to begin the induction procedure (see Section 10.2).

A member of the study staff who has verified the above criteria have been met will randomize the subject using the Vision EDC system. Once a subject has been randomized, information regarding the glucagon (G-Pen or Lilly) to be administered to the subject at each of the treatment visits will be viewable by study staff in the Dose Administration form in the EDC system.

#### **8.4. Subject Numbers**

As each subject is added to the EDC system, they will be assigned a unique Screening number, which will consist of a unique 2-digit site code (starting with 01) and a 2-digit number (starting with 01 at each site) indicating the sequence at which the subject was screened for eligibility. Upon randomization on Treatment Day 0 (see 10.2.1), eligible subjects will be assigned a unique Subject ID number that will consist of the project number "XSGP-303," the Screening number and a 3-digit number (starting with 001 at each site) indicating the sequence at which the subject was randomized for treatment. For example, XSGP-303-05-10-007 would be the Subject ID assigned to the 10<sup>th</sup> subject screened and the 7<sup>th</sup> subject randomized at site number 5.

## **9. STUDY TREATMENTS**

### **9.1. Allocation to Treatment**

Subjects will be randomized to one of the two treatment groups to receive the appropriate sequence of blinded study medication (see [Table 3](#)). A total of 85 subjects will be randomized, with a goal of an approximately equal number of subjects being randomized to each treatment at both visits. If there are subjects who are randomized but fail to receive either study drug, compensatory enrollment may be utilized to achieve at least 85 subjects who receive at least one of the treatments. Each subject will receive a single subcutaneous injection to the abdomen on each of the two (2) treatment days, with a period of 7-28 days between doses.

### **9.2. Blinding**

For this study, the subject but not the Investigator will be blinded (single-blind design). The 1 mg G-Pen™ device makes a series of two audible clicks when the dose is administered. To help ensure blinding, the subject will wear headphones that play music to mask sound during dosing procedures. The subject's ability to see the injection equipment and procedure will be obstructed by use of a blindfold placed prior to dosing. The subject will be instructed not to talk with the study staff about their impression of which product he/she received at a visit.

Subjects for whom the treatment has been unblinded inadvertently will be noted, and allowed to continue further study treatments, as per protocol. The statistical analysis plan for the study will outline a separate subgroup analysis for these subjects.

### **9.3. Drug Supplies**

#### **9.3.1. Drug Product Formulation and Packaging**

G-Pen from Xeris Pharmaceuticals, Inc. is a non-aqueous, injectable liquid formulation of glucagon. The G-Pen™ drug product consists of 1 mg synthetic glucagon peptide dissolved in a primary DMSO solvent, with trehalose added as a stabilizing excipient. G-Pen drug product is filled into West Pharmaceutical's 1 mL long Crystal Zenith® cyclic olefin polymer (plastic) pre-filled syringe with a Flurotec® coated plunger. The pre-filled syringe is loaded into an SHL Molly® single-use, disposable auto-injector, and packaged in a sealed poly/foil pouch. The drug product is stored at controlled room temperature (20-25°C) prior to use.

The G-Pen drug product is manufactured under cGMP by Pyramid Laboratories, Inc. (Costa Mesa, CA), and packaged under cGMP by SHL Group (Deerfield Beach, FL), both Xeris Pharmaceuticals' contract manufacturers.

#### **9.3.2. Lilly Glucagon for Injection**

Lilly Glucagon will be purchased commercially and provided by Xeris. The glucagon will be stored at the research pharmacy according to labeled storage conditions.

#### **9.3.3. Preparation, Dispensing and Administration**

- G-Pen will be supplied as 0.2 mL of non-aqueous solution in a plastic Crystal Zenith (CZ) 1 mL long syringe loaded into a Molly™ disposable auto-injector.

Subcutaneous administration will be performed by a qualified site staff member who has read the written Instructions for Use provided by Xeris.

- In the case of Lilly Glucagon, a new vial of lyophilized glucagon will be fully reconstituted immediately prior to abdominal administration using 1 ml of sterile diluent provided in the commercial kit as per the label [[Glucagon](#)].

Study medications will be administered according to the randomization schedule accessed in the EDC system (see [8.3](#)). Randomization will occur at the start of the induction procedure, or about 2-3 hours prior to glucagon dosing. When the investigator believes the induction procedure is approximately 1 hour from completion, a member of the study team will deliver the correct IP for the visit to the clinic area, making sure to maintain blinding of the subject.

The study drugs will not be prepared ahead of time. Instead, preparation of the investigational product (IP) (i.e., re-constitution of Lilly Glucagon) will begin *after* the confirmatory plasma glucose reading is obtained that indicates that a hypoglycemic steady state has been achieved, i.e., upon a “decision to dose.”

G-Pen™ is being developed for subcutaneous (SC) injection. The marketed comparator is labeled for both SC and intramuscular (IM) injection. Both products will be administered via the subcutaneous route to the abdomen, around the umbilicus.

The G-Pen auto-injector is made to be pressed against the skin perpendicularly (i.e., at a 90-degree angle) to the injection site. The injection technique for G-Pen will follow printed instructions for use (IFU) provided by Xeris.

For Lilly Glucagon, the skin should be pinched to avoid an IM injection. The needle will be inserted into the loose tissue under the injection site at a 90° angle and the product injected smoothly over 1-3 seconds. Following injection, light pressure should be applied to the injection site, as the needle is withdrawn.

Prior to administration of the study drugs, the intended injection site should be sterilized with an alcohol wipe and examined to ensure it has a normal appearance and is free from signs of inflammation or injury. The site staff will document the administration act (i.e. location, study product/dose) in the Vision EDC system.

#### **9.3.4. Drug Storage and Drug Accountability**

Unless notified otherwise by the Sponsor, all supplied G-Pen auto-injectors and Lilly Glucagon kits are to be stored at controlled room temperature between 20°C to 25°C (68° to 77°F), and drug solution should be clear and of a water-like consistency at time of use.

The Investigator or an approved study staff will ensure that the study medications are stored in a secure area under recommended storage conditions and in accordance with applicable regulatory requirements.

The site will maintain appropriate documentation of continuous storage conditions and these records will be monitored in an on-going basis by the monitor. Any deviations in the storage conditions must be documented (including minimum and maximum temperature excursion as well as estimate of total duration of storage outside the recommended storage conditions). Such deviations must be communicated to the Sponsor as soon as identified by the site with

appropriate course of action taken regarding the future use of the study medications upon consultation with Xeris Pharmaceuticals.

After administration, used vials of Lilly Glucagon should be returned to the kit and stored for accountability, while the syringe is disposed as per each site's standard practice. Used G-Pens should be returned to the foil pouch, which will be sealed with tape, and stored for accountability. Any devices that fail to function should be handled similarly, but be identified on the pouch label as a failure. Disposal of the study products should occur away from the subject in a manner that ensures blinding.

The Investigator must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational drug products and supplies. Unused G-Pens and Lilly kits will be returned to Xeris. Used G-Pen auto-injectors will be returned to Xeris after accountability is performed during site close-out. Used Lilly kits and other used supplies, will be destroyed according to local regulation and applicable Xeris Pharmaceuticals SOPs, following accountability by Xeris Pharmaceuticals or its designee.

#### **9.4. Concomitant Medications**

All subjects must be questioned about concomitant medications at each visit. Medications taken within 4 weeks before Day 0 will be documented in the case report form (CRF). Any changes to a subject's concomitant medication regimen after the first treatment on Day 0 will also be documented in the CRF.

Except for those medications (e.g., warfarin) listed under the exclusion criteria (see Section 8.2) and other currently investigational agents which are absolutely proscribed, there are no medications that are specifically prohibited during participation in the study. Subjects should be on a stable dose of all concomitant medications for at least 30 days prior to Screening, and they will be encouraged to avoid making changes to their concomitant medication regimen during participation in the study. In addition, Investigators are encouraged to avoid adding to or changing a participant's medications during study participation unless deemed medically necessary.

## 10. STUDY PROCEDURES

A schedule of assessments for this study is provided below in [Table 5](#).

### 10.1. Visit 1 - Screening (Day -30 to -3)

Subjects will be screened to confirm they meet the inclusion/exclusion criteria for the study. Prior to completing any screening activities, the Investigator or study team member will obtain informed consent from each subject in accordance with the procedures described in [Section 16.3 - Subject Information and Consent](#). A copy of the consent/authorization form will be given to the subject. The original will be kept by the site for the source document.

Subjects will be instructed to complete a screening visit at least 3 days (to allow for receipt of blood test results), and no more than 30 days prior to the anticipated date of the first treatment visit (Day 0). The following evaluations will be completed during the Screening visit to confirm subjects meet eligibility criteria for this study:

1. Assessment of inclusion/exclusion criteria by a study investigator, including a review of the subject's medical history and medications.
2. Recording of the subject's insulin correction factor (i.e., the reduction in blood glucose in mg/dL per 1 unit of insulin taken).
3. Measurement of height and weight (no shoes, lightly clothed).
4. Physical examination, excluding breast, pelvic, and genitourinary exams.
5. Performance of a 12-lead ECG after subject has completed a 10-minute supine rest.
6. Assessment of vital signs, including measurement of BP, after a 5-minute seated rest.
7. Urine drug screen. Note: At Investigator discretion, subjects with a positive result for drugs other than THC will be allowed to participate if the subject reports use of a concomitant medication that explains the result (e.g., positive urine test for opiates in a subject reporting use of cough syrup containing Dextromethorphan).
8. Urine pregnancy test for women of childbearing potential and discussion about study requirements regarding contraception.
9. If applicable, a discussion about study requirements regarding breast feeding.
10. Collection of venous blood for the following tests as outlined in the Schedule of Activities: hemoglobin A1C, c-peptide, complete blood count (without differential), metabolic set (including creatinine, liver set, and electrolytes), and screening for HIV, HBV and HCV ([Table 7](#)).
11. Gold scale for hypoglycemia unawareness ([Appendix 4](#)). Note: this is being collected for informational purposes only; no scores are considered exclusionary.

Once laboratory results are obtained and a final determination of eligibility is made, subjects will be contacted to schedule the first treatment visit. While immediate re-testing of laboratory results is not allowed, subjects failing to meet laboratory-based eligibility criteria may be rescreened after a 30-day wait.

## **10.2. Treatment and Follow-Up Phase**

Subjects will be instructed to eat normal meals during the day but to refrain from alcohol, and to follow their usual insulin regimen prior to their evening clinic arrival. Subjects will be instructed to arrive at the clinic between 6 and 8 pm, having not had dinner.

### **10.2.1. Visit 2 - Treatment 1 (Day 0)**

The following procedures will be carried out at this visit.

#### **Clinic Arrival**

1. Blood glucose (via glucose meter) will be assessed. If the result is > 350.0 mg/dL, no further procedures should be performed, and the visit should be rescheduled after a minimum 24-hour wait.
2. The subject will be questioned, any changes in concomitant medications will be documented in the CRF, and it will be confirmed that the subject is not receiving a medication that is exclusionary.
3. Women of childbearing potential will receive a urine pregnancy test, which must be negative before further participation is allowed.
4. If it has been more than 30 days since Visit 1 (i.e., the visit is occurring out of window), venous blood will be collected for a repeat of baseline hematology and serum chemistry assessments. However, the visit may continue based on qualification at the Screening visit.
5. Full vital signs will be assessed after a 5-minute seated rest. It will be confirmed that the subject continues to meet eligibility requirements for SBP and DBP. Other assessments of vital signs will be made during the visit as specified in the footnote to [Table 5](#).
6. A continuous glucose monitor should be placed and allowed to calibrate according to site procedures, which will include the use of a glucose meter. At investigator discretion, the subject may visit the clinic up to 5 days prior to the scheduled check-in for placement of the CGM.

#### **Evening Meal in Clinic**

1. A standardized healthy meal will be provided to the subject (see Section [7.1](#)) with a goal of completion by 9 pm. The composition of the meal should be described in the source documents, and the approximate percentage of the meal consumed should be recorded in 10% increments, etc.).
2. The subject should follow their normal prescribed regimen for insulin, including meal-time correction, until midnight.

#### **Overnight Monitoring (starting at approximately midnight)**

1. Subjects will be instructed to fast, taking nothing but water and oral glucose tablets if necessary, starting at approximately midnight and will be monitored for compliance by site staff.

2. An intravenous catheter will be placed in one arm, maintenance fluids started, and the subject's insulin pump will be discontinued, if applicable. If use of an overnight IV is not possible due to site staffing considerations, use of the subject's own insulin infusion pump or subcutaneous insulin will be used overnight.
3. Blood glucose will be monitored overnight by CGM, YSI or glucose meter. At Investigator discretion, CGM values may be confirmed by glucose meter or YSI. IV glucose or oral glucose tablets will be given and/or insulin will be administered by IV or infusion pump as necessary to optimize the blood glucose within a target range of 80-150 mg/dL.
4. Ideally, about 1 hour prior to the start of the Morning Procedures outlined below, subjects will be transitioned from SC to IV administration of insulin, and any use of IV glucose will be discontinued.
5. Overnight, if a blood glucose of  $< 60$  or  $> 270$  mg/dL is confirmed, the visit will be rescheduled after a minimum 7-day wait. Otherwise, the subject will be eligible to begin the Morning Procedures.

Note: After the overnight stay, data from the Sponsor-supplied CGM will be uploaded to the IMD EDC system, if applicable. Otherwise, the site's source document for overnight YSI or BGM values will be scanned and uploaded to the Vision EDC system.

#### Morning Procedures (starting at approximately 6 am)

1. In the morning, plasma glucose (via YSI) will be assessed, and if  $> 270.0$  mg/dL, the visit will be rescheduled after a minimum 7-day wait. Otherwise, the subject will be administered IV insulin to induce a baseline euglycemic steady state.
2. If applicable, the CGM will be discontinued at this point and all further glucose measurement will be assessed via YSI.
3. If not already placed, an IV catheter will be placed for administration of insulin and maintenance fluids.
4. A second IV catheter will be placed for blood sampling, ideally located in a vein within the antecubital fossa.

The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow and achieve "arterialized" samples. Note: The subjects will remain non-caloric fasting the morning of the procedure.

#### Baseline Euglycemic Steady State (early morning)

Prior to starting the hypoglycemia induction procedure, the subject must have PG stable for at least 30 minutes at  $95 \pm 20$  mg/dL ( $75-115$  mg/dl) at a stable IV insulin infusion rate varying no more than  $\pm 20\%$  during which PG must have be measured at least every 15 minutes (i.e., at least 3 consecutive values in the target range at 0, 15 and 30 minutes).



## Hypoglycemia Induction Procedure (following baseline euglycemic steady state)

### Induction Start

For the induction, the starting plasma glucose level will be determined as the average of 3 measurements taken over the final 30 minutes of the baseline euglycemic steady state period. The following procedures will then be undertaken:

1. Subjects will continue the IV insulin infusion at the final rate of the euglycemic steady state.
2. Subjects will be given an initial IV bolus push dose of regular insulin diluted in saline:
  - a. The dose will be calculated as 75% of the dose estimated to reduce plasma glucose from the subject's starting plasma glucose level to 50 mg/dL based on the subject's self-reported glucose correction factor. This dose will be referred to as "1 bolus (full bolus dose)" subsequently.
  - b. PG will be measured no less frequently than every 10 minutes.

The first insulin adjustment will be no earlier than 20 minutes after the initial bolus, but will otherwise follow the directions for insulin adjustments shown in Section 7.2 (see also Table 4).

### Insulin Dose Adjustments

Insulin dose adjustments will be performed as outlined in Section 7.2 (see also Table 4).

### Randomization

Randomization will be performed after the baseline stabilization period has been successfully completed and the Investigator deems it is appropriate to begin the induction procedure. At this time, the subject will be randomized to receive either G-Pen or Lilly Glucagon in one of the treatment sequences shown in Table 3.

### Confirmation of Hypoglycemic Steady State.

1. Once an initial plasma glucose measurement < 50.0 mg/dL is achieved, the IV insulin infusion will be stopped. Note: The requirement is that the average of the readings from the two YSI leads be < 50.0 mg/dL, but it is not required that both readings be < 50.0 mg/dL.
2. After a minimum of 5 minutes, a confirmatory plasma glucose measurement will be performed.
  - a. If the confirmatory plasma glucose measurement is 43.0-49.9 mg/dL, the Investigator must confirm that a hypoglycemic steady state has been achieved as follows. A **hypoglycemic steady state** is defined as two consecutive plasma glucose values between 43.0 and 49.9 mg/dL, and the 8-minute linearly extrapolated future PG value is  $\geq 42.0$  mg/dL.
    - i. If the extrapolated 8-minute PG value is  $\geq 42.0$  mg/dL, the subject is eligible for dosing with glucagon (see Decision to Dose, below).
    - ii. If the extrapolated 8-minute PG value is < 42.0 mg/dL, re-check PG after 5 minutes. If this subsequent PG measurement is  $\geq 42.0$  mg/dL and the extrapolated 8-minute PG value is  $\geq 42.0$  mg/dL, the subject is eligible for glucagon dosing (see Decision to Dose, below); otherwise, the treatment visit will be terminated (see item d, below).



- b. If the confirmatory plasma glucose measurement is  $> 50.0$  mg/dL, then the IV insulin infusion will be re-started, and insulin adjustments made as per the induction procedure described above (Table 4), and the sequence will be repeated until there are two consecutive plasma glucose readings between 43.0-49.9 mg/dL. These two consecutive measurements should occur within 60 minutes of the initial plasma glucose measurement  $< 50.0$  mg/dL.
- c. If the confirmatory plasma glucose measurement is  $< 43.0$  mg/dL, then the subject's plasma glucose should be rechecked after 5 minutes. If the subsequent PG is  $\geq 42.0$  mg/dL, then the subject may be deemed to be within a hypoglycemic steady state.
- d. If the subsequent plasma glucose reading is  $< 42.0$  mg/dL, the treatment visit will be terminated. In this case:
  - i. Study drug should NOT be given.
  - ii. If appropriate, medical intervention to achieve euglycemia can be implemented at the Investigator's discretion. The subject can leave the clinic after glucose is confirmed to be above 100 mg/dL and the subject is deemed medically stable by the Investigator.
  - iii. The visit should be rescheduled after a 7-day minimum wash-out period.

### Decision to Dose

If the subject is deemed to be within a hypoglycemic steady state, then the subject is ready to be dosed (decision to dose) with study drug. At this time, the subject will be eligible to receive the randomized study drug.

### Preparation and Administration of Study Drug

1. Once the induction procedure has begun and glucose  $< 50$  mg/dL is predicted to occur within approximately 1 hour, the study staff member who will be performing the study drug injection should be notified that the induction procedure is reaching conclusion. At this time the staff member will bring the appropriate unopened test article (pouched G-Pen or Lilly Glucagon kit) to the bedside, as assigned by the EDC system.
2. 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.
3. At this point, the subject will receive the blindfold and headphones with music playing in order to maintain the blind.
4. A stop watch will be started, and the treatment administrator will then open the study drug container (kit or pouch) and begin preparation of the glucagon for administration following the applicable IFU. An Investigator should verify that the contents of the vial of lyophilized Lilly Glucagon have been fully reconstituted prior to administration.
5. Subcutaneous administration of the study drug will be made to the abdomen as per Section 9.3.3. Upon completion of the administration, the stop watch will be stopped and the elapsed time in minutes and seconds will be recorded in the source documents. After the study drug injection, the study product will be disposed in a location away from the patient in a manner that maintains the blind. After disposal, the blindfold and headphones will be removed from the subject.

6. Following study drug administration, plasma glucose will be measured every  $5\pm 2$  minutes until 90 minutes, and every  $30\pm 2$  minutes thereafter until 180 minutes post-dosing.
7. At 180 minutes post-dosing, the subject will resume insulin therapy and be given a meal as per the standard practice at each site. The subject can be discharged from the clinic if glucose  $>100$  mg/dL and the subject is deemed medically stable.
8. 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.

### **Hypoglycemia Symptom Assessments**

Subjects will complete a questionnaire regarding severity of hypoglycemia symptoms ([Appendix 1](#)) at the following time points:

1. Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure (baseline),
2. Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure,
3. Just before study drug is administered,
4. Every  $5\pm 2$  minutes after glucagon is administered until all symptoms have abated (i.e., all symptoms have score = 1) or 90 minutes post-dosing, whichever occurs first, and
5. Every 30 minutes (coinciding with plasma glucose measurements) between 90-180 minutes post study drug dosing, or until all symptoms have abated (i.e., all symptoms have score = 1).

### **Local Tolerability and Adverse Events**

Local tolerability and adverse events will be assessed as follows:

1. Subjects will complete a Visual Analog (VAS) questionnaire regarding injection site discomfort ([Appendix 2](#)) at  $10\pm 5$  and  $30\pm 5$  minutes post-dosing, and again at  $180\pm 5$  minutes post-dosing if VAS score reported at 30 minutes is  $> 0$  mm.
2. Subjects will complete an Injection Site Discomfort Description and Duration Questionnaire at  $10\pm 5$  minutes post-dosing. If discomfort is ongoing at 10 minutes post-dosing, the questionnaire will be updated before the subject leaves the clinic to document the final duration.

3. The Investigator will use the modified Draize scales ([Appendix 3](#)) to assess erythema and edema formation at the injection site at 10±5 and 30±5 minutes following administration. Any injection site with a score > 0 for either erythema or edema at 30 minutes post-dosing will be re-evaluated for both at 180±5 minutes post-dosing. If any scores remain > 1 at the 180-minute evaluation, the subject may leave the clinic but will be instructed to contact study staff if the condition fails to resolve.

Note: Ideally, the same investigator will assess the injection sites on the subject, during both treatment visits.

4. Adverse events reported by the subject or observed by an Investigator during the visit will be recorded in the CRF.

#### **10.2.2. Visit 3 - Treatment 2 (Day 7-28)**

The subject will return 7 to 28 days following the first treatment visit. The procedures to be repeated at this visit are as listed in Section [10.2.1](#). If it has been more than 28 days since Visit 2 (i.e., the visit is occurring out of window), venous blood will be collected for a repeat of hematology and serum chemistry assessments. However, the visit may continue based on qualification at the Screening visit. At Visit 3, the other study drug will be administered at the time of Decision to Dose, so that between the two dosing visits, each subject will have received both G-Pen once, and Lilly Glucagon once.

#### **10.2.3. Visit 4 - Follow-Up (Day 9-35)**

The subject will attend a follow-up visit within 2-7 days of completing the final dosing visit or premature discontinuation. This visit will include the following assessments:

1. Review of changes in concomitant medications.
2. Physical examination, excluding breast, pelvic and genitourinary exams. To include review of injection sites to document any residual inflammation, pain or induration.
3. Body weight (no shoes, lightly clothed).
4. 12-lead ECG after 10-minute supine rest.
5. Vital signs after 5-minute seated rest.
6. Urine pregnancy test (females of child-bearing potential).
7. Blood draws for complete metabolic count and complete blood count.
8. Adverse event questioning by asking the subjects to respond to a non-leading question such as “how do you feel?”

In case of any premature discontinuation of a subject from the study, the subject will, if possible, be scheduled for a final follow-up visit.

### **10.3. Subject Withdrawal**

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject to determine the reason(s) why the subject failed to return for the scheduled visit, and to reschedule the missed visit. This includes contacting subjects via email and telephone, including family members or emergency contacts. If such efforts fail, a certified letter should be sent to the subject's last known address requesting they contact study staff.

In all circumstances, every effort should be made to document subject outcome, per the follow-up. Information regarding the reason for not completing the study will be recorded in the CRF. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, and follow-up with the subject regarding any unresolved AEs. It will be documented whether or not each subject completed the study. Any subject who receives at least one treatment dose of study medication will be included in the safety analysis.

If a decision by the Investigator or Sponsor is made to withdraw a subject, a final visit should be scheduled soon after the decision to withdraw is made. The subject will be asked to return to site for the assessments listed in Section [10.2.3](#).

If the subject withdraws from the study and also withdraws consent, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

**Table 5: Schedule of Assessments**

Assessment	Visit 1	Visit 2	Visit 3*	Visit 4*
	Screening Day -30 to -3	Treatment 1 Day 0	Treatment 2 Day 7-28	Follow-up Day 9-35
Informed consent	x	—	—	—
Medical History & Demographics	x	—	—	—
Inclusion/exclusion review	x	—	—	—
Concomitant medications	x	x	x	x
Height, weight & physical exam <sup>a</sup>	x	—	—	x
12-lead ECG	x	—	—	x
Vital signs <sup>b</sup>	x	x <sup>b</sup>	x <sup>b</sup>	x
Urine pregnancy test	x	x	x	x
Urine drug screen	x	—	—	—
Hematology & clinical chemistry	x	(x)	(x)	x
HbA1c and C-peptide	x	—	—	—
HIV, HCV and HBV	x	—	—	—
Gold scale for hypoglycemia unawareness	x			
Evening admission, CGM placement**, dinner meal	—	x	x	—
Overnight fast and CGM monitoring from midnight	—	x	x	—
Hypoglycemia induction & confirmation of steady state	—	x	x	—
Randomization	—	x	—	—
Administration of study medication	—	x	x	—
Hypo. symptom questionnaire	—	x	x	—
Injection site discomfort scales	—	x	x	—

XSGP-303 Clinical Protocol  
G-Pen™ (glucagon injection)

Assessment	Visit 1	Visit 2	Visit 3*	Visit 4*
	Screening Day -30 to -3	Treatment 1 Day 0	Treatment 2 Day 7-28	Follow-up Day 9-35
Draize scales for erythema/edema	—	x	x	—
Venous blood glucose (PD) <sup>d</sup>	—	x <sup>c</sup>	x <sup>c</sup>	—
Review adverse events (AE)	—	x	x	x

<sup>a</sup> Excluding breast, pelvic and genitourinary exams. Note: height assessment is not required at Visit 4.

<sup>b</sup> Temperature, respiration, HR and BP (after >5 min seated rest) will be performed at all visits. Additionally, at visits 2 and 3, HR and BP will be repeated immediately prior to, and at 30, 60, 120 and 180 minutes post-dosing, with ±5 minutes for all procedures.

<sup>c</sup> If plasma glucose is > 350.0 mg/dL upon clinic arrival or if the plasma glucose the morning after the overnight stay is > 270.0 mg/dL the visit should be rescheduled.

<sup>d</sup> Via rapid glucose analyzer (YSI 2300 or 2900) before and during hypoglycemia induction, and every 5 minutes post study drug dose through 90 minutes, with ±2 minutes for all collections, and at 120, 150 and 180 minutes with ±5 minutes for collections.

(X) = repeat if the visit is occurring out of window (i.e., more than 28 or 30 days have passed since the prior visit).

\*Visit 3 should occur 7-28 days following Visit 2, and Visit 4 should occur 2-7 days following Visit 3.

\*\*At investigator discretion, the subject may visit the clinic for CGM placement up to 5 days prior to the check-in for treatment visits.

## 11. ASSESSMENTS

Every effort should be made to ensure that the required tests and procedures are completed as described. However, it is anticipated that there may be circumstances outside the control of the Investigator, who will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason(s) and any corrective and preventive actions taken to ensure that study processes are adhered to as soon as possible. The study team and the Sponsor will be informed of these incidents in a timely fashion.

For all blood and urine collections, an effort should be made to obtain these samples at roughly the same time of day (i.e., morning or afternoon) across all visits as well as at the time periods specified in the Schedule of Activities. In addition, visits to the site must occur within the pre-defined windows outlined in this protocol, otherwise they will be considered as protocol deviations.

### 11.1. Blood Volume

There will be approximately 40 PD samples of about 2 cc each drawn at each treatment visit for a total of about 80 cc of blood per visit. These two treatment visits will be 7 to 28 days apart. There will be a 10.5 cc sample at Screening and at the Follow-up Visit for a clinical chemistry panel and hematology, with an additional 10.5 cc sample at Screening for eligibility determination. A total of about 200 cc of blood will be drawn over the total study ([Table 6](#)).

**Table 6: Frequency and Volume of Blood Collections**

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Treatment Visits 1-2	Follow-Up Visit	
Clinical Chemistry	7.5	1	(X)	1	15
Hematology	3	1	(X)	1	6
HbA1c	3	1	-	-	3
C-peptide	2.5	1	-	-	2.5
Serology	5	1	-	-	5
Pharmacodynamics <sup>a</sup>	2	-	c. 40/visit	-	160
<b>Total</b>	2-7.5	5	c. 40/visit	2	191.5

<sup>a</sup> Plasma glucose measurements (1-2 mL ea.) at bedside via rapid glucose analyzer.

(X) Optional if visit occurs outside the prescribed window.

### 11.2. Clinical Laboratory Tests

The tests outlined in [Table 7](#) will be performed at the specified time points described in the Schedule of Activities.

**Table 7: Clinical and Safety Related Laboratory Tests**

Hematology	Chemistry	Urine	Laboratory
WBC count	Glucose	β-hCG <sup>a</sup>	HbA1c
RBC count	Creatinine	Drug screen <sup>b</sup>	C-peptide
Hemoglobin	Na <sup>+</sup>		HIVab
Hematocrit	K <sup>+</sup>		HCVab
Platelet count	Ca <sup>++</sup>		HBsAg
	Albumin		
	Alkaline Phosphatase		
	AST/SGOT		
	ALT/SGPT		

<sup>a</sup> Female participants of childbearing potential require a negative pregnancy test at Screening and prior to dosing for each of the 2 Treatment Visits. Pregnancy testing will be repeated as the Follow-up visit for safety reasons.

<sup>b</sup> Drug screening performed at Screening will include: cocaine, THC, opiates, amphetamines, methamphetamine, and phencyclidine. Analytes other than those listed above may be included in the test kits provided to the sites. Investigator will exercise discretion in allowing of excluding a subject from study participation based on a positive test for one of these additional analytes. Except as noted below, continuation in the study requires all tests to be negative with the exception of THC, which will be noted, but will not be considered exclusionary.

A central laboratory will be utilized for analysis of all blood variables with the exception of rapid plasma glucose measurements made during treatment visits. A procedures manual will be provided to each site by the central laboratory. This manual will cover procedures for the collection, processing and shipping of blood samples, along with the Clinical Laboratory Improvement Act (CLIA) certification and normal ranges for the central laboratory.

The central laboratory will provide sites with all supplies needed for collection, processing and shipping of all blood samples, as well as point-of-care urine pregnancy tests and rapid urine drug screen kits.

If a subject tests positive for drugs other than THC, the subject will normally be excluded from further study participation. However, if a subject reports use of a concomitant medication (prescription or OTC) that provides a reasonable explanation for a positive result other than THC, the subject may be allowed to participate in the study at the Investigator's discretion. If the subject is not able to provide a reasonable explanation but still refutes a positive finding, a urine sample will be sent to the central laboratory for confirmation. The result of this confirmatory test will be considered definitive. The remainder of the screening visit should still be completed in this case.

During treatment visits, PG levels will be measured using a bedside YSI rapid glucose analyzer model 2300 or 2900. At each time point specified in Section 10, the results of both the black and white leads to one decimal place will be recorded in the source documents, with the average of the two values rounded up to the nearest one decimal place accepted as the plasma glucose level for the time point as per the following examples.

Example #1: black lead = 50.1 and white lead = 49.8

Calculation:  $50.1 + 49.8 = 99.9 / 2 = 49.95 = 50.0$  mg/dL recorded result

Example #2: black lead = 74.4 and white lead = 74.5



Calculation:  $74.4 + 74.5 = 148.9/2 = 74.45 = 74.5$  mg/dL recorded result

The glucose analyzer will be set to auto-calibrate following the standard practice at each site. Before each subject visit, performance checks will be made as per the standard practice at each site, and sites will maintain a log of these results.

The EDC system implemented for this study will allow entry of plasma glucose values in either mg/dL or mmol/L. For reference, both units are provided in the written description and summary (Table 4) of the insulin dose adjustment algorithm. In the rest of the protocol, plasma glucose values are provided in mg/dL. For reference, Table 8 provides a conversion chart for key values of plasma glucose referenced throughout the protocol.

**Table 8: Conversion Table for Plasma Glucose Values**

mg/dL	mmol/L
42.0	2.34
43.0	2.39
49.9	2.77
50.0	2.78
70.0	3.89
80.0	4.44
85.0	4.72
100	5.55
115.0	6.38
150.0	8.33
270.0	15.0
350.0	19.44

### 11.3. Electrocardiogram (12-lead ECG)

Single, supine 12-lead ECGs will be obtained at the pre-defined time-points outlined in the Schedule of Activities as follows:

- 12-lead ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.
- 12-lead ECGs should be obtained before assessment of BP and heart rate, and prior to blood collections.

#### **11.4. Blood Pressure and Heart Rate**

The BP and heart rate will be measured at the times specified in the Schedule of Activities. Additional or changes to collection times, or collection of BP and heart rate using automated devices is permitted, as necessary, to ensure appropriate subject's safety.

BP and heart rate will be measured in the seated position with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. The subject should be rested for at least 5 min. before the BP is obtained. Measurements of both the BP and heart rate must be taken at least 2 min. apart and recorded in the CRF.

## **12. SAFETY AND ADVERSE EVENT (AE) REPORTING**

### **12.1. Definition of an Adverse Event**

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which is not necessarily required to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Examples of AEs include:

- Abnormal test findings.
- Clinically significant symptoms and signs.
- Changes in physical examination findings which are untoward and deemed clinically significant by the Investigator.
- Allergy/hypersensitivity.

The criteria for determining whether an abnormal objective test finding may be reported as an AE are as follows:

- Test result is associated with accompanying symptoms.
- Test result requires additional diagnostic testing or medical/surgical intervention.
- Test result leads to a change in study dosing or discontinuation from the study. significant additional concomitant drug treatment or other treatment.
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeat of a test based on an abnormal result in the absence of the above conditions does not constitute an AE. Any abnormal test result determined to be an error does not require reporting as an AE.

A treatment-emergent AE (TEAE) is an AE that either commenced following initiation of study treatment or was present prior to study treatment but increased in frequency or severity following initiation of study treatment.

Standard medical terminology should be used in describing AEs. Informal descriptions should be avoided.

### **12.2. Reporting Adverse Events**

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be reported with two exceptions. Since it is being experimentally induced in this study, hypoglycemia will not be considered an AE in this study unless the event meets one of the definitions of an SAE (see Section 12.4). Injection site reactions will not be considered an AE unless a skin reaction or pain requires medical intervention.

For all AEs, the Investigator must pursue and attempt to obtain information adequate to determine the outcome of the AE and to assess whether it meets the FDA criteria for classification as an SAE, requiring immediate notification to Xeris Pharmaceuticals.

For all AEs, follow-up by the Investigator is required until the event resolves or stabilizes at a level acceptable to the Investigator to consider it resolved. For unresolved AEs to be considered stable, the Xeris Medical Monitor must concur with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined to be serious (according to the FDA definitions of an SAE) will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

### **12.3. Reporting Period**

For all AEs, the reporting period to Xeris Pharmaceuticals begins from the subject providing informed consent, through the Follow-up Visit. All adverse events will be followed until resolution or the subject is medically stable.

### **12.4. Serious Adverse Events**

An SAE is any untoward medical occurrence at any dose which:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in determining whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions which do not result in hospitalization.

### **12.5. Severity Assessment**

On the AE case report forms (CRF), the Investigator will use the adjectives “mild,” “moderate,” or “severe” to describe the maximum intensity of the AE. These intensity grades are defined as follows in [Table 9](#) below.

**Table 9: AE Severity Assessment**

Mild	Does not interfere with subject's usual function.
Moderate	Interferes to some extent (<50%) with subject's usual function.
Severe	Interferes significantly (≥50%) with subject's usual function.

The terms “serious” and “severe” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event. The event itself, however, may be of relatively minor medical significance. This is not the same as “serious,” which is based on subject/event outcome or action criteria. Accordingly, a severe event is not necessarily a serious event.

## **12.6. Causality Assessment**

The Investigator will use the following question when assessing causality between an adverse event to the study drug, where an affirmative answer designates the event as a suspected adverse reaction: “Is there a reasonable possibility that the drug caused the event?” A “reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the adverse event. The Investigator’s assessment of causality must be provided for all AEs. The Investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable (Section 12.9).

## **12.7. Withdrawal Due to Adverse Events**

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, and recorded on the appropriate CRF. When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements (see Section 12.9).

## **12.8. Eliciting Adverse Event Information and Reporting**

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. Each study subject will be questioned about AEs. Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow the provisions of Section 12.9.

## **12.9. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Xeris Pharmaceuticals is to be notified within 24 hours of awareness of the event by the Investigator. In particular, if the SAE is fatal or life-threatening, notification to Xeris Pharmaceuticals must be made immediately, irrespective of the extent of available AE information. This time frame also applies to follow-up on previously forwarded SAE reports.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., a study subject initially seeks treatment elsewhere), the Investigator is to

report the event within 24 hours after learning of the event and document the time of first awareness of the AE.

A death occurring during the study, during the per-protocol follow-up period, or within 30 days after stopping treatment with test drug must be reported to Xeris Pharmaceuticals or its designee(s) immediately, whether or not it is considered treatment-related. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Telephone and e-mail reports must be confirmed promptly either by facsimile or by overnight courier or mail.

Under 21 CFR 312.32(c), Xeris Pharmaceuticals or its designee(s) is required to notify FDA and all participating Investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the safety information is received and a determination is made that the information qualifies for reporting.

### **12.10. Non-Serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of the SAE information.

### **12.11. AE Reporting Requirements to Regulatory Authorities**

AE reporting by the Sponsor, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable regulations.

The Investigator must notify the IRB/Ethics Committee of the occurrence of any SAE, in writing, as soon as is practicable and in accordance with local regulations. A copy of this notification must be provided to Xeris Pharmaceuticals or its designee.

In the event of an SAE that meets the criteria for expedited reporting, an SAE report will be prepared for submission to the FDA and any other applicable authorities by Xeris Pharmaceuticals or its designee.

### **12.12. Pregnancy**

The active pharmaceutical product in Xeris Pharmaceuticals' G-Pen is Glucagon, which is in Pregnancy Category B. Female subjects able to become pregnant will be tested (rapid, urine) for pregnancy at the Screening visit. Any subject found to be pregnant at the Screening visit (Visit 1) will not be randomized to treatment. At both treatment visits and at the follow-up visit (i.e., Visits 2, 3 and 4), pregnancy testing will be repeated. Any subject who is found to be pregnant at one of the treatment visits will be withdrawn from the study immediately and no further study treatments will be given. Pregnancy at the follow-up visit will be noted, but the visit will be completed. Any pregnancy in a subject who received at least one dose of study drug will be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy). Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

### **12.13. Subject Monitoring**

Subjects will be monitored for AEs throughout the study by the study unit staff. The principal Investigator or designated sub-Investigator will be on site for drug administration and until 3 hours after administration of study drug to the last subject. The principal Investigator or designated sub-Investigator will also be on call for the remainder of the treatment visit. If necessary, a physician, either at the study site or in a nearby hospital, will administer treatment for any AEs.

Safety parameters, including laboratory results and ECGs, will be assessed by the principal Investigator or his delegate using the site's criteria for clinical laboratory and ECG acceptance ranges as suggested guidelines in making the medical assessment.

Scheduled safety measurements will be repeated according to appropriate SOPs or upon request from a physician. Any abnormal repeated measurement will be evaluated by a physician and repeated if judged necessary. Further action may be taken on the physician's request.

Subjects will be advised to notify their health care professionals (e.g., physician, dentist, and/or pharmacist) that they are participating in a clinical research study of a drug called synthetic Glucagon Injection before taking any medicines or undergoing any medical procedure.

## **13. DATA ANALYSIS AND STATISTICAL METHODS**

### **13.1. General Approach**

Detailed methodology for descriptive and inferential statistical analyses of the data collected in the XSGP-303 study will be documented in the statistical analysis plan (SAP). The SAP will be prepared by the Sponsor's contract research organization (CRO) and agreed upon by the Sponsor. The SAP will be finalized and approved by signature and dates prior to locking the database. In addition to the SAP, other graphical representations of the results may be produced after review of the data (post hoc). Any major modifications of the definition of the Primary Endpoint or analysis will be reflected in a protocol amendment.

### **13.2. Efficacy**

This is a non-inferiority study in which the primary objective is to test whether the G-Pen is not unacceptably less efficacious in terms of hypoglycemia relief than the Lilly Glucagon for injection. The primary endpoint comparison will be performed using both the Intention to Treat (ITT) and the per-protocol (PP) populations. The evaluable set for the PP population will be 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).

For analysis of the primary endpoint, a failure for the study treatment (G-Pen or Lilly Glucagon) will be recorded if plasma glucose remains  $\leq 70.0$  mg/dL throughout the 0-30-minute period from a drug administration, while a success is defined as a return to plasma glucose  $>70.0$  mg/dL in subjects from a state of insulin-induced hypoglycemia within the 0-30-minute period from drug administration.

The following scoring system for the primary endpoint will be applied to all subjects in the PP cohort. If a G-Pen failure is observed, then the treatment failure score = 1; similarly, the Lilly Glucagon failure score = 1 if a control failure is observed. An observed plasma glucose rising above 70.0 mg/dL within 30 minutes study drug administration yields a failure score = 0, for either treatment.

For the ITT cohort, the following scoring system will be applied for analysis of the primary endpoint: If a G-Pen failure is observed, then the treatment failure score = 1; similarly, the Lilly Glucagon 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. An observed plasma glucose rising above 70.0 mg/dL within 30 minutes study drug administration yields a failure score = 0, for either treatment [Koch].

Secondarily, analysis of the primary endpoint will be repeated with success/failure evaluated at a time point of 30 minutes from a decision to dose (see Section 10.2.1). For this analysis, the 30-minute value will be determined by linear interpolation between the two adjacent time points.

#### **13.2.1. Primary Endpoint:**

The G-pen acceptance criterion will be based on the sample mean of the failure scores derived from each subject (treatment-control). If Dht is designated as the sample mean of the G-Pen



minus control failure difference, and SE is the estimated standard error of Dht (square root of the estimated G-Pen minus control variance divided by the sample size), then the G-Pen will be accepted provided:

$$\text{Dht} + 2.8 \text{ SE} \leq 0.1.$$

This criterion, including the value 2.8, came from Monte-Carlo simulations from selected scenarios where the population G-Pen failure rate exceeded the control rate by 0.1. Under these circumstances the rate of G-Pen acceptance was found to be within 0.025 using this criterion, with missing data rates within 15%. This bound of 0.025 on the type 1 error rate was observed for control failure rates up to 5%. Monte Carlo simulation rather than asymptotic normality is necessary because an observed failure from either G-Pen or control is expected to be low, less than 5%.

### **13.2.2. Sample Size Calculation:**

Using the above criterion for the primary endpoint assumptions under scoring described above (Koch), 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%.

The power and type 1 error bounds were obtained from a simulation model using a 3x3 table of outcomes for G-Pen and control. The three outcomes for each were Success, Failure, and Missing. Probabilities were assigned to each of the 9 cells for determining the probability of G-Pen acceptance, either the type 1 error probability or power depending on the scenario being simulated, with the missing outcome being stochastically independent of the Success and Failure outcome combinations. Also, the failure score difference, G-Pen minus control, was assigned to each of the nine cells. To simulate one replicate of the study, 85 independent draws were made from the multinomial distribution determined by the probabilities from the 9 cells, and the sample mean with its estimated standard error were computed. The G-pen acceptance criterion was applied and either a 0 (G-pen failed) or 1 (G-pen accepted) was recorded. This was repeated 10,000 times to obtain the estimated probability of G-pen acceptance under the conditions defined by the cell probabilities. The simulations were performed using R version 3.1.2 (2014-10-31).

It is expected that randomization of 85 subjects will achieve at least 75 evaluable subjects for PP analysis at approximately 6 clinical sites with a goal of no single center accounting for > 20% of the total randomization. Screening and enrollment will continue until at least 85 randomized subjects have received at least one dose of study drug (see Section 9.1).

## **13.3. Secondary Endpoints**

All secondary endpoints will be assessed in both the ITT and PP analysis populations.

### **13.3.1. Binary Responses**

The following secondary response endpoints will be assessed. For each endpoint, scoring will follow the methods described for the primary endpoint in Section 13.2.

1. Return of plasma glucose to > 70 mg/dL or neuroglycopenic symptomatic relief within 30 minutes after receiving glucagon.

2. Return of plasma glucose to  $> 70$  mg/dL or an increase in plasma glucose by  $\geq 20$  mg/dL within 30 minutes after receiving glucagon.
3. Increase in plasma glucose by  $\geq 20.0$  mg/dL within 30 minutes after receiving glucagon.
4. Neuroglycopenic symptomatic relief within 30 minutes after receiving glucagon.

Secondarily, analysis of these secondary endpoints will be repeated with success/failure evaluated at a time point of 30 minutes from a decision to dose (see Section 10.2.1 ). For this analysis, the 30-minute value will be determined by linear interpolation between the two adjacent time points.

### 13.3.2. Pharmacodynamic Analyses

The pharmacodynamic endpoints will be derived from the individual glucose profiles.

Time for plasma glucose to increase by at least 20 mg/dL, time for plasma glucose to reach  $>70.0$  mg/dL, AUC,  $C_{\max}$  and  $T_{\max}$  will be compared between the treatment groups using a mixed model with treatment, period and sequence as terms.

### 13.3.3. Hypoglycemia Symptoms:

Symptom relief will be analyzed as aggregate scores for the four autonomic, four neuroglycopenic symptoms and 8 total symptoms (see Appendix 1).

For analysis, “relief” will be defined as a return to a score no more than one unit above baseline symptoms during the euglycemic baseline period.

The time to the minimal score post baseline will be described and compared between the treatment groups using a mixed model with treatment, period and sequence as terms. Similarly, the time to first reporting of “no” for the global hypoglycemia question will be described and compared between the groups.

### 13.3.4. Glucagon Preparation Time:

The time between “decision to dose” and time of study drug administration to the abdomen will be measured and be called glucagon preparation time. This time measurement will be used for analysis of study end points. The total preparation time required to inject to the abdomen from a decision to treat will be compared between the treatment groups, as measured between the time of “decision to dose” and time of injection.

## 13.4. Safety Analysis

All safety analyses will be performed using the safety population, namely those subjects receiving at least one dose of the study treatment.

The following variables will be compared between the treatments for safety purposes:

- Adverse events and serious adverse events
- Laboratory safety variables (Screening to Final Visit)
- Physical examination (Screening to Final Visit)
- Vital signs

- Body weight (Screening to Final Visit)
- ECG (Screening to Final Visit)
- Local tolerability, including:
  - Subjective injection site discomfort as reported by subjects using a 100-mm VAS and ordinal pain scales ([Appendix 2](#)).
  - Erythema and or edema formation at site of injection assessed using the Draize scale ([Appendix 3](#)).

#### **13.4.1. Adverse Events**

All verbatim adverse event terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and study drug. AE collection will begin from the time of consent. Listings of all AEs (including non-TEAEs), serious TEAEs (SAEs), and TEAEs leading to study drug discontinuation will be provided by treatment group, site, subject, verbatim term, MedDRA SOC and Preferred Term, start and end dates, seriousness flag, severity, relationship to study drug, action taken with study treatment, frequency, and outcome.

AEs will be summarized overall by the number and percentage of subjects who experienced at least 1 AE of the following categories in each treatment group: any AE, any TEAE, any drug related TEAE (defined as possibly, probably, or definitely related to study drug), any severe or life-threatening TEAE, any serious TEAEs, any drug-related SAE, any SAE leading to death, any TEAE leading to premature discontinuation of study drug, and any SAE leading to premature study drug discontinuation.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and Preferred Term; by SOC, Preferred Term, and severity (mild, moderate, and severe/life-threatening/death); and by SOC, Preferred Term, and relationship (unrelated [defined as unrelated or unlikely related to study drug] or related [defined as possibly, probably, or definitely related] to study drug).

For all analyses of TEAEs, if the same AE (based on Preferred Term) was reported for the same subject more than once, then the AE was counted only once for that Preferred Term and at the highest severity and strongest relationship to study drug.

The numbers and percentages of subjects reporting an SAE or reporting a TEAE leading to premature discontinuation of study drug in each treatment group will be summarized by SOC and Preferred Term.

Subjects will be analyzed for safety according to the study treatment received.

#### **13.4.2. Laboratory Safety Assessments**

Laboratory values (biochemistry and hematology) will be flagged if outside the normal range. A listing of clinically significant abnormal values will be presented. The individual values will be listed indicating values outside normal range. Laboratory assessments will be summarized at Screening and at end of trial. Significant deviations/changes from the Screening Visit to the Final Visit will be documented as AEs if the Investigator judges these as being clinically significant.

#### **13.4.3. Physical examination**

Subjects with any findings in the physical examination evaluation at Screening will be listed. Changes to physical examination from Screening to end of trial will be recorded as AEs if the Investigator judges these as being clinically significant.

#### **13.4.4. Vital signs and body weight**

Vital signs will be summarized by descriptive statistics. Significant changes from pre- to post-dosing at treatment visits or from the Screening Visit to the Final Visit will be documented as AEs if the Investigator judges these as being clinically significant.

#### **13.4.5. ECG**

Any clinically significant ECG changes will be recorded and followed as appropriate. The Investigator's evaluations will be summarized in a data listing.

Significant deviations/changes from the Screening Visit to the Final Visit will be documented as AEs if the Investigator judges these as being clinically significant.

#### **13.4.6. Local Tolerability**

The incidence of any injection site discomfort (score >0 on the ordinal rating scale) will be analyzed descriptively. The incidences of erythema and edema will be analyzed in a similar manner. Descriptive statistics (only) will be provided for time of onset and duration (of discomfort) and discomfort description (i.e., pain, irritation, itching, etc.). Mean VAS scores will be compared between the treatments.

### **13.5. Subgroup Analysis**

Safety and efficacy by gender (male, female), age (18-64 years, 65 years and above), and race/ethnicity (i.e. Whites, Hispanics, and African-Americans) will be analyzed descriptively.

More specific details regarding the analyses will be provided in the Statistical Analysis Plan (SAP).

### **13.6. Demographics and Baseline Characteristics**

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

## **14. QUALITY CONTROL AND QUALITY ASSURANCE**

During study conduct, Xeris Pharmaceuticals or its agent will conduct periodic visits to ensure that the protocol and Good Clinical Practices are being followed. The monitor may review source documents to confirm that the data recorded on CRFs is accurate. The Investigator and institution will allow Xeris Pharmaceuticals' monitor or its designee, and appropriate regulatory authorities, direct access to source documents to perform this verification.

The study site may be subjected to review by the Institutional Review Board and/or to quality assurance audits performed by Xeris Pharmaceuticals or its designee, and/or to inspection by appropriate regulatory authorities. It is important that the Investigator and study staff are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **15. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS**

### **15.1. Case Report Forms/Electronic Data Record**

Data collection is the responsibility of the clinical study staff under the supervision of the Investigator. During the study, the Investigator will maintain complete and accurate documentation for the study.

As defined in the ICH Guidelines for Good Clinical Practice (E6(R2)), Section 1.52, source documents may include: original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

As used in this protocol, the term CRF is understood to refer to an electronic data record, i.e., an eCRF. An eCRF is required and should be completed for each individual subject. The completed original eCRFs are the property of Xeris Pharmaceuticals and should not be made available in any form to third parties, except for authorized representatives of Xeris Pharmaceuticals or appropriate regulatory authorities, without written permission from Xeris Pharmaceuticals.

Completion of eCRFs will be accomplished using two independent 21 CFR Part 11 compliant web-based EDC systems. As described in Section 7.1, one system will be used to enter glucose and insulin data during treatment visits via laptop computers provided to the sites by Xeris. Sites will use existing computers other than the Xeris-provided laptops to enter all other study-related data into a second EDC system.

The Investigator has the responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that these are accurate, authentic, attributable, complete, consistent, legible, contemporaneous, enduring and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained in the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary), and should not obscure the original entry.

In most cases, the source documents are the hospital's or physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at Xeris Pharmaceuticals and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses to eCRF queries.

## **15.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Xeris Pharmaceuticals, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to the International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain Xeris Pharmaceuticals' written permission before disposing of any records, even if retention requirements have been met.

## **15.3. Monitoring**

Monitoring and auditing procedures developed by Xeris Pharmaceuticals and/or its designee will be implemented to ensure compliance with FDA and ICH GCP and GLP guidelines.

The Xeris Pharmaceuticals' designated representative (the monitor or auditor) will contact the Investigator and conduct regular visits to the clinical site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/Ethics Committee review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The monitor/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve all questions raised, and difficulties detected by the monitor.

## **15.4. Audits and Inspections**

The Investigator understands that regulatory authorities, the IRB/Ethics Committee, and/or Xeris Pharmaceuticals or their designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

## **16. ETHICAL CONSIDERATIONS**

### **16.1. Conduct**

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), and 59th (Seoul, 2008) General Assemblies. The Investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IRB/Ethics Committee requirements relative to clinical studies.

Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual subject. The Investigator will also ensure thorough familiarity with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

### **16.2. Institutional Review Board and Ethics Committee**

The Ethics Committee/IRB must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated informed consent forms, and the informed consent procedures must be submitted to the IRB for review and approved before the enrollment of any subject into the trial. Study drug may not be shipped to the Investigator until Xeris Pharmaceuticals has received a copy of the letter or certificate of approval from the IRB/Ethics Committee for the protocol and any protocol amendments.

All types of subject recruitment or advertising information must be submitted to Xeris Pharmaceuticals or its designee and to the IRB/Ethics Committee for review and approval prior to implementation. IRB approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study subjects. In such cases, the chair of the IRB/Ethics Committee should be notified immediately and the amendment forwarded to the IRB/Ethics Committee for review and approval.

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements from the IRB/Ethics Committee. All correspondence with the IRB/Ethics Committee should be retained in the Investigator File. Copies of IRB/Ethics Committee approvals should be forwarded to Xeris Pharmaceuticals.

### **16.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures. Subject names, address, date of birth and other identifiable data will be replaced by a numerical code consisting of a



numbering system provided by Xeris Pharmaceuticals to de-identify the study subject. In the case of data transfer, Xeris Pharmaceuticals will maintain confidentiality and protection of subject personal data.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/Ethics Committee and Xeris Pharmaceuticals before use. The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a study staff designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The Investigator will retain the original of each subject's signed consent document. Receipt of written informed consent will be documented in each subject's or potential subject's CRF. The signed informed consent document must remain on file at the study site and be available for verification by the study monitors at all times.

#### **16.4. Subject Recruitment**

All types of subject recruitment or advertising information must be submitted to Xeris Pharmaceuticals or its designee and to the IRB/Ethics Committee for review and approval prior to implementation. Advertisements approved by the IRB/Ethics Committee may be used as recruitment procedures.

#### **16.5. Reporting of Safety Issues and Serious Breaches of the Protocol**

In the event of any prohibition or restriction imposed (i.e., clinical hold), or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Xeris Pharmaceuticals should be notified immediately. In addition, the Investigator will inform Xeris Pharmaceuticals immediately of any urgent safety measures taken by the Investigator to protect study subjects against any immediate hazard, and of any serious breaches of this protocol.

## **17. DEFINITION OF END OF TRIAL**

Last Subject Last Visit (LSLV) for each site is defined as the date the last subject completes the follow-up visit (Visit 4), with the understanding that final review by the Investigator may be delayed a few days to allow for receipt of final lab results.

## **18. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY**

### **18.1. Protocol Modifications and Deviations**

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

### **18.2. Study Termination**

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB/Ethics Committee, safety problems resulting in subject deaths, or at the discretion of Xeris Pharmaceuticals or the principal Investigator.

Circumstances that may warrant premature study termination include, but are not limited, to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects,
- Failure to enter subjects at an acceptable rate,
- Insufficient adherence to the requirements of the protocol,
- Insufficient provision of complete and evaluable data, or
- Plans to modify, suspend, or discontinue development of the study drug.

If the study is prematurely terminated or discontinued, Xeris Pharmaceuticals will promptly notify the Investigators and document the reason for study termination. Specific procedures for termination will be arranged by the Sponsor in coordination with the Investigators. After notification, the Investigators must contact all participating subjects within 7 days. All study materials must be collected and all CRFs completed to the greatest extent possible, and all study materials must be returned to Xeris Pharmaceuticals or its designee within an additional 28 days.

## **19. PUBLICATION OF STUDY RESULTS**

Publication of study results is discussed in the Clinical Study Agreement.

## 20. REFERENCES

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14. FDA CDER #2. rDNA Glucagon for Injection, Pharmacology and Toxicology Review. NDA No. 20-928. Eli Lilly and Company, Indianapolis, IN, April 16, 1998.
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## APPENDICES

### APPENDIX 1. HYPOGLYCEMIA SYMPTOM QUESTIONNAIRE

*Investigative Site Instructions:* The subject should complete the Hypoglycemia Symptom Questionnaire at the following time points:

- Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure.
- Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure.
- Just before study drug is administered.
- Every 5±2 minutes after glucagon is administered until all symptoms have abated (i.e., all symptoms have score = 1) or 90 minutes post-dosing, whichever occurs first.
- Every 30±5 minutes (coinciding with plasma glucose measurements) between 90-180 minutes post study drug dosing, or until all symptoms have abated (i.e., all symptoms have score = 1).

*Note:* If a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form.

*Subject Instructions:* Please rate the current intensity (severity) of each of the following symptoms on a scale of 1-6, with a minimum score of “1” meaning the symptom was absent and a maximum score of “6” meaning the symptom was severe. For the final question, please answer “yes” or “no.”

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?	

## APPENDIX 2. INJECTION SITE DISCOMFORT ASSESSMENT

### Visual Analog Scale (VAS) for Injection Site Discomfort

*Investigative Site Instructions:* The subject should complete the 100-mm Visual Analog Scale (VAS) for Injection Site Discomfort at both **10±5** minutes and **30±5** minutes following the injection of study drug, and again before the end of the clinic visit (i.e., at 180±5 minutes post-dosing) if the VAS score at **30±5** minutes is > 0 mm. The subject completes the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort according to the instructions below. The goal is for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion.

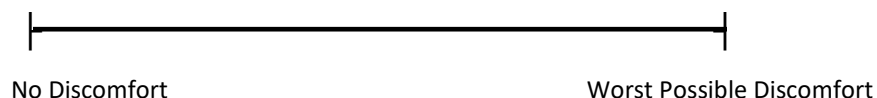
*Note:* If a subject is unable to physically complete the questionnaire, the subject will indicate the point on the VAS corresponding to their level of discomfort, and study staff will enter a vertical line at that point. Documentation will be provided on each completed questionnaire as to who completed the form.

**Please verify the length of the VAS line to be 100-mm before providing it to the subject.**

*Subject Instructions:* Ignoring any pain from insertion of the needle, please draw a single vertical line through the scale below that corresponds to the intensity (severity) of any discomfort you are feeling **right now** at the study drug injection site.

Discomfort could include stinging, burning, tingling, throbbing or pain. The further to the right you make your vertical mark, indicates the more intense discomfort you are feeling.

You should normally draw a straight line across the scale to indicate your current level of discomfort. However, if you are currently feeling no discomfort, you should circle the vertical line on the left end of scale (above the word “no”). If you are currently feeling the worst discomfort possible, you should circle the vertical line on the right end of the scale.





**Injection Site Discomfort Description and Duration Questionnaire**

*Study Personnel Instructions:* Question 1a should be should be completed by the subject at **10±5** minutes following the injection of study drug. Any subject reporting discomfort other than “none,” should complete question 1b. Any subject reporting duration of discomfort of “at least 10 minutes” should complete follow-up question 1c at the end of the study visit (i.e., at 180±5 minutes post-injection). The goal is for the subject to report the qualitative nature and duration of discomfort, if any, associated with injection of study drug, ignoring any transient pain associated with needle insertion.

*Note: If a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form.*

*Subject Instructions:* Please answer question 1a and, if applicable to you, questions 1b and 1c. In answering these questions, you should ignore any pain from insertion of the needle.

**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

### APPENDIX 3. DRAIZE SCALE

- *Study Personnel Instructions:* The modified Draize Scale as shown in the table below will be used for physical examination/rating of abnormalities at the injection site.
- The injection site should be examined for formation of both erythema and edema and results recorded in the Case Report Form. Evaluations of the injection site should be performed at  $10 \pm 5$  and  $30 \pm 5$  minutes post-treatment, and again at the end of the treatment visit (i.e., at  $180 \pm 5$  minutes post-dosing) if any scores  $> 0$  were noted at 30-minutes post-dosing.

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

## APPENDIX 4. GOLD SCALE

### Hypoglycemia Awareness

*Study Personnel Instructions:* The following question should be answered by the subject at the Screening visit. This score is being collected for information purposes only; there are no scores that are considered exclusionary.

*Subject Instructions:* Please respond to the following question using the scale of 1-7 below. A minimum score of “1” indicates that you are always aware of an onset of hypoglycemia. A maximum score of “7” indicates that you are never aware of an onset of hypoglycemia.

**To what extent are you aware of the onset of hypoglycemia?**

1	2	3	4	5	6	7
Always	Almost Always	Often	Sometimes	Seldom	Almost Never	Never

Your score: \_\_\_\_\_