G-PEN™ (GLUCAGON INJECTION)
PROTOCOL XSGP-301

G-PEN™ (GLUCAGON INJECTION) COMPARED TO LILLY GLUCAGON (GLUCAGON FOR INJECTION [RDNA ORIGIN]) FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULT PATIENTS WITH T1D: A PHASE 3, RANDOMIZED, BLINDED, 2-WAY CROSSOVER STUDY TO EVALUATE EFFICACY AND SAFETY

Version 1.6

March 16, 2017

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for G-Pen™ (glucagon injection). I have read the XSGP-301 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name & Title	Email Address & Telephone Number
Sponsor's Study Leader & primary contact	Martin J. Cummins, VP, Drug Development	mcummins@xerispharma.com 512-498-2675 or 806-282-2120
Medical Monitor & 24-hour emergency contact	Dr. Poul Strange, Medical Director	Pstrange@imdcro.com 609-897-0505 x 213, fax 609-897-0555
Reporting of Investigational Product concerns, including device failure and randomization issues	Integrated Medical Development Help Desk	helpdesk@IMDCRO.com 609-897-0505 ext. 151.

2. SYNOPSIS

Protocol Number: XSGP-301	
G-PEN™ (GLUCAGON INJECTION) COMPARED TO LILLY GLUCAGON (GLUCAGON FOR INJECTION [RDNA ORIGIN]) FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULT PATIENTS WITH T1DM: A PHASE 3, MULTI-CENTER, RANDOMIZED, BLINDED, 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 3
Compound(s):	G-Pen™ (glucagon injection) Lilly Glucagon for Injection (rDNA origin)
Objectives:	1. To demonstrate the efficacy (return to plasma glucose >70.0 mg/dL) of G-Pen™ (glucagon injection) 1 mg (test) to be non-inferior to Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference), in TID patients in a state of insulin-induced hypoglycemia. 2. To compare the pharmacodynamic characteristics of G-Pen™ (glucagon injection) 1 mg (test) versus Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference) in T1D patients who are in a state of insulin-induced hypoglycemia. 3. To describe and compare the hypoglycemia symptom relief of the two treatments. 4. To determine the safety and tolerability of G-Pen™ (glucagon injection) 1 mg (test) versus Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference) in TID patients in a state of induced hypoglycemia 5. To determine G-Pen™ (glucagon injection) 1 mg pharmacokinetics in the major ethnicities and races in the US: non-Hispanic Whites, Hispanics, and African-Americans.
Study design:	This is a randomized, blinded, two-way crossover comparative efficacy and safety inpatient study in patients 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 session and Lilly Glucagon 1 mg during the other.
Study location:	Approximately 8 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 5 months.

Sample size:	Approximately 150 subjects are anticipated to be screened for this study to achieve the goal of 75 subjects completing the study with evaluable results for at least one treatment period. To allow for possible drop-outs, approximately 80 subjects may be randomized. Enrollment may be constrained based on ethnicity and race to achieve approximately 12 subjects in each of the following groups: non-Hispanic Whites, Hispanics, and African-Americans.
Subjects:	The study will include male or female patients with T1D between the ages of 18 and 75 years of age, inclusive, at Screening.
Inclusion Criteria:	1. Males or 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.
Exclusion Criteria:	1. Pregnant and/ or Nursing: For women of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study, and for at least 1 month after the last does of study drug. 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. HbA1c >9.0% at Screening. 3. Renal insufficiency (serum creatinine greater than 3.0 mg/dL). 4. Serum ALT or AST equal to or greater than 3 times the upper limit of normal 5. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL; or serum bilirubin of over 2.0 mg/dL. 6. Hematocrit of less than or equal to 30%. 7. Mean of triplicate BP readings at Screening where SBP <90 or >140 mm Hg, and DBP <50 or >90 mm Hg. 8. Clinically significant ECG abnormalities. 9. Use of > 2.0 U/kg total insulin dose per day. 10. Inadequate bilateral venous access in both arms. 11. Congestive heart failure, NYHA class II, III or IV. 12. 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. 13. Major surgical operation within 30 days prior to Screening. 14. Current seizure disorder. 15. Current bleeding disorder, treatment with warfarin, or platelet count below 50,000.

16. Personal history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
17. History of insulinoma.
18. 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.
19. History of glycogen storage disease.
20. Subject tests positive for HIV, HCV or active HBV infection (HBsAg+) at Screening
21. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
22. Whole blood donation of 1 pint (500 mL) within 8 weeks prior to Screening. Donations of plasma, packed RBCs, platelets or quantities less than 500 mL are allowed at investigator discretion.
23. 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 THC via rapid urine test will be allowed to participate in the study at the discretion of the investigator.
24. Administration of glucagon within 28 days of Screening.
25. 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.
26. Any reason the investigator deems exclusionary.

Brief outline of treatments:

Subjects will complete the screening procedures up to 60 days before dosing to determine eligibility before enrollment to the treatment phase. Subjects will be instructed to fast from midnight prior to study visits and to dose with insulin as per their usual practice.

Eligible participants will undergo two episodes of insulin-induced hypoglycemia, and in random order will receive G-Pen™ glucagon 1 mg subcutaneously during one episode and Lilly glucagon 1 mg subcutaneously during the other episode. The procedure to evaluate the efficacy of the G-Pen™ glucagon consists of inducing hypoglycemia by an IV infusion of regular insulin diluted in normal saline.

For treatment visits, subjects will check into the clinical research center in the morning still fasting except for water.

Subjects will be randomized to receive either G-Pen™ (glucagon injection) or Lilly Glucagon blinded study medication to the following treatment sequence:

Group	Dose 1	Dose 2
1	G-Pen™ 1.0 mg	Lilly 1.0 mg
2	Lilly 1.0 mg	G-Pen™ 1.0 mg

Note: The following is a summary only. Please see section 7.2 for a detailed description of the hypoglycemia induction procedures and see Section 10.2.1 for a detailed description of the treatment visit procedures.

Subjects will have a catheter for IV insulin infusion inserted in one arm and another catheter for blood sampling inserted in the other. The arm used for blood sampling will be kept warm by use of a heating pad or similar device to increase blood flow to achieve "arterialized" samples.

Starting plasma glucose level will be determined by taking three measurements over 30 minutes. After 30 minutes:

1. Subjects will be given an initial IV bolus push dose of regular insulin:
   a. Dose will be calculated based on the starting plasma glucose level and the subject's self-reported glucose correction factor.
   b. Additional bolus doses of insulin may be given as guided by the investigator's experience if the trajectory of plasma glucose after 30 minutes is > 60 mg/dL. Late bolus doses (i.e., within 20 minutes of dosing) should be avoided.
2. Subjects will be given an IV infusion of regular insulin. The starting IV infusion rate will be based on a subject's current use of insulin:
   a. For subjects on insulin pump, the pump will be discontinued and IV insulin infusion will be started at 1.5x the recorded basal rate.
   b. For subjects on long-acting injected insulin:
      i. If the subject took their normal evening or morning dose before the visit, IV insulin infusion will be started at 1x the basal rate.*
      ii. If the subject did not take their normal evening or morning dose before the visit, IV insulin infusion will be started at 2x the basal rate.*
   c. Guided by experience, the investigator may adjust the IV insulin infusion rate at his discretion if the rate of glucose change after 30 minutes is < 1

	mg/dL/min. * For injected insulin uses, the basal rate will be calculated by dividing the daily dose by 24 to calculate the amount of insulin on board in units/hour. Plasma glucose measurements will be taken every 15 minutes while glucose is >80.0 mg/dL and at 5-minute intervals once plasma glucose is ≤ 80.0 mg/dL. Once the initial plasma glucose measurement < 50.0 mg/dL is achieved, the IV insulin infusion will be stopped. During the 5-minute period after the IV insulin infusion has stopped, the glucose level is expected to continue to decrease by approximately 5 mg/dL due to the delayed effect of insulin. Once the confirmatory plasma glucose reading < 50.0 mg/dL is achieved 5 minutes later, subjects will be administered blinded study drug via the subcutaneous route in the upper arm, leg or abdomen. Following dosing, plasma glucose will be monitored every 5 minutes until 90 minutes post-dosing. Additional blood samples will be collected at -5, 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes and stored at -70C for determination of plasma glucagon and potentially insulin levels. After this, the subject will resume insulin pump therapy, if applicable, and will be given a meal. The subject can then leave the clinic after glucose concentration is confirmed to be between 70 and 180 mg/dL. Subjects will complete a questionnaire regarding hypoglycemia symptoms at the start of the hypoglycemia induction period and periodically until 30 minutes post-treatment with glucagon. The hypoglycemia induction procedure is expected to elicit symptoms of a hypoglycemic response. However, the procedure is not expected to be of sufficient duration, or to generate such a low glucose concentration in the CNS that it will impair consciousness characteristic of severe hypoglycemia. 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 3-14 days following administration of the final dose as a safety check. Tolerability will be assessed by comparing adverse event reports between the groups. In addition, subjects will complete questionnaires concerning injection site discomfort. An investigator will use modified Draize scales to evaluate the injection sites following each administration.
Data management and statistical analysis:	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 comparison will be performed using the intent-to treat (ITT) cohort defined as all subjects randomized to one of the two sequence groups: G-Pen followed by control, or control followed by G-Pen. A failure is recorded if the subject's plasma glucose fails to rise above 70.0 mg/dL within 30 minutes of the start of therapy. The following scoring system will be applied to all subjects in the ITT cohort. If a G-Pen failure is observed then the treatment failure score = 1. Similarly, the failure score = 1 if a control failure is observed. If the treatment outcome is missing, then the treatment failure score = 0.2. A missing control outcome yields a control failure score = 0.1. An observed success for both groups yields

	a failure score = 0. The G-Pen acceptance criterion will be based on the sample mean of the treatment minus control failure scores from each subject in the ITT population. If Dht is the sample mean and SE is the estimated standard error of the subject treatment minus control failure scores, then the G-Pen will be accepted provided: Dht + 2.6 SE is less than or equal to 0.1. This criterion, particularly the value 2.6, 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. The acceptance criterion for the G-Pen in this study will be that the total difference in failures, G-Pen minus Control (i.e., Lilly Comparator), shall not exceed 3 and the total number of failures for the G-Pen shall not exceed 4, after the 75th evaluable subject completes both treatment periods. If the total number of subjects with criterion failures (counted in a blinded fashion) exceeds 4, a monitoring statistician not otherwise involved with study conduct may provide an unblinded determination of the distribution by treatment group for futility only, and communicate a finding of futility (or continue to conclusion) to Xeris' upper management for further decisions, while the study team remains blinded. Success will not be tested and no penalty for this futility only check is planned.
Sample Size Determination:	Using the above criterion, a sample size of 75 subjects yields probabilities of G-Pen acceptance of over 90% if the population failure rates of G-Pen and control are equal, and the rate of missing observations is within 15%. These results were obtained using Monte Carlo simulations with G-Pen and control total failure rates up to 5%, and with G-Pen success Control failure, or G-Pen failure Control success within 1%. Patients may be recruited at approximately 8 clinical sites with a goal of no single center accounting for > 20% of the total sample.

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

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LIST OF TABLES

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_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRC	Clinical Research Center
CRO	Contract Research Organization
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
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetic
RBC	Red blood cells
rDNA	Recombinant
RLD	Reference Listed Drug
SAE	Serious Adverse Event
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 (blood glucose) of G-Pen™ (glucagon injection) 1 mg (test) to be non-inferior to Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference) in T1D patients who are in a state of insulin-induced hypoglycemia as assessed by the failure rate of plasma glucose to have a measured value >70.0 mg/dL within 30 minutes of administration of treatment.

5.2. Secondary Objectives

The secondary objectives of this study are:

- To compare the pharmacodynamic characteristics of G-Pen™ (glucagon injection) 1 mg (test) versus Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference) in T1D patients who are in a state of insulin-induced hypoglycemia,
- To describe and compare hypoglycemia symptom relief of the two treatments,
- To describe G-Pen™ (glucagon injection) 1 mg pharmacokinetics in the major ethnicities and races in the US: non-Hispanic Whites, Hispanics, and African-Americans; and
- To compare the safety and tolerability of G-Pen™ (glucagon injection) 1 mg (test) versus Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg (reference) in T1D patients 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:

- Pharmacodynamic characteristics, including: plasma glucose AUC, Cmax, Tmax and time to reach >70.0 mg/dL will be compared between the treatment groups.
- Symptoms of hypoglycemia (if present) as documented using the hypoglycemia symptom questionnaire (Appendix 1) which is completed every time blood is sampled for determination of plasma glucose during the hypoglycemia induction procedure, at baseline immediately before injection and every 5 minutes until 45 minutes following administration of glucagon.
- Pharmacokinetic parameters include: descriptive analysis of AUC, C_{max} and Tmax of the different ethnicities.

- Safety-related parameters including:
  - Vital signs
  - Physical exam
  - ECG
  - Standard safety laboratory parameters
  - Incidence of adverse events (AEs) and serious adverse events (SAEs)
  - Subjective injection site discomfort as reported by subjects using a 100-mm VAS and other questionnaires (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

One of the main complications of glycemic control 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 manifests clinically as diaphoresis, pallor, nausea, palpitations, tremor, anxiety, cognitive impairment, behavioral changes and psychomotor abnormalities, and loss of consciousness, seizure, and coma in severe hypoglycemia [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 ≤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 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 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 nine-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose [Glucagon, Glucagen].

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].

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 hypoglycemic events.

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 subject of 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™ (glucagon injection) 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™ (glucacon injection) is referenced to Xeris' current Investigator's Brochure.

6.3. Description and Composition of Drug Product

Synthetic glucagon is the drug substance in G-Pen™ (glucagon injection). 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™ (glucagon injection) is a sterile subcutaneous injectable non-aqueous formulation for treatment of severe hypoglycemia. G-Pen™ (glucagon injection) 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™ (glucagon injection) 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 RLDs 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 Agency first approved glucagon for use in humans in 1960.

As of September 25, 2013, IND 115091 went into effect and Study No. XSGP-201 was completed in January 2014. This study examined safety, PK, and efficacy of rescue doses (0.5 and 1.0 mg) of G-Pen™ (glucagon injection) as compared to Lilly Glucagon (1.0 mg) in healthy volunteers. The results of this study 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 randomized, blinded, two-way crossover comparative efficacy and safety study in patients with T1D. The study involves two daytime CRC or comparable setting visits 7-28 days apart, with random assignment to receive G-Pen™ glucagon 1 mg during one session and Lilly Glucagon 1 mg during the other. Patients will complete the screening procedures up to 60 days before Randomization to determine eligibility before enrollment to the treatment phase (Table 3).

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

The procedure to evaluate the efficacy of the G-Pen™ (glucagon injection) consists essentially of inducing hypoglycemia by IV administration of regular insulin diluted in normal saline. Each participant will undergo two episodes of insulin-induced hypoglycemia in random order and receive 1 mg G-Pen™ (glucagon injection) during one episode and 1 mg Lilly Glucagon during the other episode. A combination of one or more IV bolus doses of insulin along an IV infusion of insulin will be used to decrease a subject's plasma glucose to a target <50.0 mg/dL. The IV insulin infusion will be stopped once the plasma glucose is <50.0 mg/dL. As per Section 11.2, all plasma glucose levels will be based on the average of two readings taken at each time point.

After a confirmatory plasma glucose of <50.0 mg/dL is obtained at least 5 minutes after the initial reading < 50.0 mg/dL, the subject will be treated subcutaneously in the upper arm, leg or abdomen with either 1 mg Lilly Glucagon or 1 mg G-Pen™ (glucagon injection).

Blood glucose levels will be monitored for 90 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 to avoid impairment of consciousness. Consequently, subjects will complete a questionnaire about symptoms of hypoglycemia [Nermoen] during the hypoglycemia induction phase, and for 45 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 3-14 days following administration of the final dose.

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 present study, therefore, utilizes a comparatively lower rate of insulin infusion at one to two 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.

Hypoglycemia Induction Procedure

Starting plasma glucose level will be determined by taking 3 measurements over 30 minutes upon the subject's arrival at the CRC (i.e., at 0, 15 and 30 minutes). After the third measurement at 30 minutes:

1. Subjects will be given an initial IV bolus push dose of regular insulin diluted in saline:
    a. Dose will be calculated 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.
    b. Guided by experience and the subject's HbA1c value at Screening, the investigator may adjust the starting bolus dose at his discretion. As a guideline, increasing the insulin dose by 20% should be considered for subjects with an HbA1c > 8.0%.
    c. An additional bolus dose of insulin may be given as guided by the investigator's experience if the trajectory of plasma glucose after 30 minutes is > 60 mg/dL. However, late bolus doses (i.e., within 20 minutes of dosing) should be avoided.
2. Subjects will be given an IV infusion of regular insulin diluted in saline. The starting IV infusion rate will be based on a subject's current use of insulin as follows:
    a. For subjects on insulin pump, the current basal rate will be recorded, the pump will be discontinued and IV insulin infusion will be started at 1.5x the recorded basal rate.
    b. For subjects on long-acting injected insulin:
        i. If the subject took their normal evening or morning dose before the visit, IV insulin infusion will be started at 1x the basal rate.*
        ii. If the subject did not take their normal evening or morning dose before the visit, IV insulin infusion will be started at 2x the basal rate.*
    c. Guided by experience and the subject's HbA1c value at Screening, the investigator may adjust the starting basal rate at his discretion. As a guideline, increasing the basal rate by 25% should be considered for subjects with an HbA1c > 8.0%.
    d. Guided by experience, the investigator may adjust the IV insulin infusion rate at his discretion if the rate of glucose change after 30 minutes is < 1 mg/dL/min.

    * For injected insulin uses, the basal rate will be calculated by dividing the daily dose by 24 to calculate the amount of insulin on board in units/hour.

7.3. Interruption and Termination of Dosing

Dosing will be paused for any SAE that occurs in a subject receiving treatment until causality is fully assessed by the Investigator. Dosing will cease if the SAE is determined to be either drug-related or unknown, and may resume if the SAE is determined to be not drug-related by the investigator and the Sponsor is in agreement.

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 or 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. C-peptide level < 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 or Nursing: For women of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study and for at least 1 month after the last dose of study drug. 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. HbA1c >9.0% at Screening.
3. Renal insufficiency (serum creatinine greater than 3.0 mg/dL).
4. Serum ALT or AST equal to or greater than 3 times the upper limit of normal.
5. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL; or serum bilirubin of over 2.0 mg/dL.
6. Hematocrit of less than or equal to 30%.
7. Mean of triplicate BP readings at Screening where SBP <90 or >140 mm Hg, and DBP <50 or >90 mm Hg.
8. Clinically significant ECG abnormalities.
9. Use of > 2.0 U/kg total insulin dose per day.
10. Inadequate bilateral venous access in both arms.
11. Congestive heart failure, NYHA class II, III or IV.
12. 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.

13. Major surgical operation within 30 days prior to Screening.
14. Current seizure disorder.
15. Current bleeding disorder, treatment with warfarin, or platelet count below 50,000.
16. Personal history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
17. History of insulinoma.
18. 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.
19. History of glycogen storage disease.
20. Subject tests positive for HIV, HCV or active HBV infection (HBsAg+) at Screening.
21. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
22. Whole blood donation of 1 pint (500 mL) within 8 weeks prior to Screening. Donations of plasma, packed RBCs, platelets or quantities less than 500 mL are allowed at the investigator's discretion.
23. 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 THC (rapid urine test) will be allowed to participate in the study at the discretion of the investigator.
24. Administration of glucagon within 28 days of Screening.
25. 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.
26. Any reason the investigator deems exclusionary.

8.3. Randomization

Randomization will be carried out via an EDC system. 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, eligible subjects will be assigned a unique Patient ID number that will consist of the project number "XSGP-301," 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-301-05-10-007 would be the Patient ID assigned to the 10th subject screened and the 7th subject randomized at site number 5. Subjects will be randomized 1:1 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 after confirmation that the subject remains eligible for the study (see Section 10.2).

To facilitate evaluation of PK results, enrollment may be constrained based on ethnicity and race to achieve approximately 12 subjects in each of the following groups: non-Hispanic Whites, Hispanics, and African-Americans.

9. STUDY TREATMENTS

9.1. Allocation to Treatment

Subjects will be randomized to one of the 2 treatment groups to receive the appropriate sequence of blinded study medication (see Table 3). Approximately 80 patients will be randomized with a goal of completing 75 patients, or roughly 37-38 patients per group. If there are a large number of subjects who are randomized but fail to receive either study drug, compensatory enrollment will be utilized to achieve at least 75 evaluable subjects. Each subject will receive a single subcutaneous injection on each of the two (2) treatment days, with a period of 7-28 days between doses.

9.2. Blinding

For this study, both subject and investigator will be blinded. The only unblinded study staff will be a pharmacist and depending on operational procedures at each site, one or more additional trained study staff member whose only role will be to administer the glucagon. (i.e., the unblinded staff administers the dose then leaves the room and does not participate in any other study procedures). The subject's ability to see the injection equipment and procedure will be obstructed and the subject will be instructed not to talk with the study staff about their impression of which product he/she received at a particular visit. G-Pen™ is being developed for subcutaneous (sc) injection. The marketed comparator is labeled for both sc and intramuscular (im) injection. To help maintain blinding, both drugs will be administered via the sc route in this study.

The 1 mg G-Pen™ device makes a series of two audible clicks when the dose is administered. To help ensure blinding, the clinical staff will move to an adjoining room during the process of drug administration by the unblinded staff. If operational considerations preclude leaving the room, the clinical staff will look away and will use means (e.g., headphones, fingers in ears and humming, etc.) to mask sound during dosing procedures.

Blinding should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult the Sponsor prior to breaking the blind. When the blinding is broken, the reason must be fully documented and entered in the CRF. Subjects for whom the treatment has been unblinded will be withdrawn from further study treatments, but will still complete a follow-up visit if practical (see Section 10.2.3).

9.3. Drug Supplies

9.3.1. Drug Product Formulation and Packaging

G-Pen™ (glucagon injection) 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™ (glucagon injection) 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 Instructions for Use (Appendix 4).
- In the case of Lilly Glucagon, a new vial of Glucagon will be reconstituted using 1 ml of sterile diluent immediately (i.e., within 2 hours) prior to use and subcutaneous administration will be performed as per the label [Glucagon] using the administrations sites specified below.

Study medications will be prepared and dispensed by an unblinded site pharmacist according to the randomization schedule accessed in the EDC system.

Study medications will be administered by an unblinded member of the study staff who will not be involved in collection or interpretation of study results. Prior to administration, the intended injection site should be examined to ensure it has a normal appearance and is free from signs of inflammation or injury. The staff member administering the injection will document the administration act in the EDC.

The injection site for a particular subject will remain fixed between the two treatment visits (i.e., arm, leg or abdomen) but will be varied between the left and right upper arm, leg or abdominal quadrant for the first and second dose of study medication. The injection site for each subject will be assigned as part of the randomization in the EDC.

9.3.4. Drug Storage and Drug Accountability

Unless notified otherwise by the Sponsor, all supplied G-Pen™ (glucagon injection) auto-injectors 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.

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

After administration, used vials of Lilly Glucagon should be returned to the kit and stored under blinded conditions 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 under blinded conditions for accountability. Any devices that fail to function should be handled similarly, but be identified on the pouch label as a failure.

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 CRF. Any changes to a subject's concomitant medication regimen after the first Treatment on Day 0 will also be documented in the CRF.

With the exception of 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 absolutely medically necessary.

10. STUDY PROCEDURES

A schedule of assessments for this study is provided below in Table 5.

10.1. Visit 1 - Screening (Day -60 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 site visit at least 3 days (to allow for receipt of blood test results), and no more than 60 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.
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 triplicate measurements of BP, after a 5-minute seated rest.
7. Urine drug screen. Note: At investigator discretion, subjects with a positive result for 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.
9. 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).

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 1-month wait.

Subjects will be instructed to fast, taking nothing but water by mouth from midnight prior to the next visit. Subjects will be instructed to take their long-acting insulin in the morning, if that is

their usual practice, and that they should also take any corrective insulin as they would normally do.

10.2. Treatment and Follow-Up Phase

The subject will arrive to the clinic in the morning having fasted (i.e., with nothing by mouth except for water) for at least 6 hours for the two treatment visits only (i.e., Visits 2 and 3), at which time the following procedures will be completed:

10.2.1. Visit 2 - Treatment 1 (Day 0)

The following procedures will be carried out at this visit.

1. Plasma glucose (via YSI) will be assessed. If the result is > 270.0 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, 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, including triplicate BP 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.
    a. Heart rate and single BP will be repeated immediately prior to dosing and at 30, 60, 120 and 240 minutes post-dosing with ± 5 minutes for all collections.
6. **Important: at this point, the subject may be randomized via the EDC system.**
7. Hypoglycemia induction (see Section 7.2), PD/PK determinations and study treatment will be performed as follows:
    a. Subjects will have a catheter for IV insulin infusion inserted in one arm and another catheter for blood sampling inserted in the other. The arm used for blood sampling will be kept warm by use of a heating pad or similar device to increase blood flow in order to achieve “arterialized” samples.
    b. Three measurements of plasma glucose concentration will be made over 30 minutes, approximately every 15 minutes to determine the starting plasma glucose level. Thereafter, plasma glucose will be determined every 15±5 minutes while the concentration is > 80.0 mg/dL and every 5±2 minutes once it is ≤ 80.0 mg/dL. Note: once the confirmatory glucose < 50.0 mg/dL is obtained, the next plasma glucose to be collected will be at 5 minutes post-dosing with glucagon, at which point the schedule of collecting plasma glucose every 5 minutes will resume.

c. Within 5 minutes of determining of the starting plasma glucose level, , subjects will be given an initial IV bolus push dose of regular insulin diluted in saline:

   i. Insulin dose will be calculated to reduce plasma glucose from the subject's starting plasma glucose level to a target of 50 mg/dL based on the subject's self-reported glucose correction factor.

   ii. For example, if the subject's starting BG is determined to be 130 mg/dL and the subject's reported correction factor is 40 mg/dL per unit of insulin, the IV bolus push dose would be calculated as: 130-50 = 80/40 = 2.0 units of insulin.

   iii. Guided by experience and the subject's HbA1c value at Screening, the investigator may adjust the starting bolus dose at his discretion.

   iv. As a guideline, the investigator should consider increasing the bolus dose of insulin by 20% for subjects with an A1c level > 8.0% at Screening. Using the above example, the bolus dose would be increased as follows: 2.0 units x 1.2 = 2.4 units of insulin.

An IV infusion of regular insulin diluted in saline will be started. The starting IV infusion rate will be based on a subject's current use of insulin (i.e., continuous infusion pump vs. daily long-acting injections) and daily basal dose of insulin as shown below in Table 4.

Table 4: Calculation of Starting IV Insulin Infusion Rate

<table>
<tr><th>Subjects on Insulin Pump</th><th colspan="2">Subjects on Long-Acting Injected Insulin</th></tr>
<tr><td>1. Discontinue the pump</td><td colspan="2">1. Calculate the basal rate in units / hr.
(i.e., cumulative basal dose / 24 hrs.)</td></tr>
<tr><td rowspan="3">2. Start IV insulin infusion at 1.5x the current basal rate</td><td colspan="2">2. Did the subject take their normal daily dose either the evening before or the morning before the visit?</td></tr>
<tr><td>YES</td><td>NO</td></tr>
<tr><td>3. Start IV insulin infusion at 1x the calculated basal rate</td><td>3. Start IV insulin infusion at 2x the calculated basal rate</td></tr>
</table>

d. Guided by experience and the subject's HbA1c value at Screening, the investigator may adjust the starting basal rate at his discretion. As a guideline, increasing the basal rate by 25% should be considered for subjects with an A1c > 8.0%. For example, if the subject's current basal rate is 0.8 units/hour, it would be increased as follows: 0.8 units/hour x 1.25 = 1.0 units/hour.

e. Guided by experience, the investigator may adjust the IV insulin infusion rate at his discretion if the rate of glucose change after 30 minutes is < 1 mg/dL/min.

f. 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 2 YSI leads be < 50.0 mg/dL, but it is not required that both readings be < 50.0 mg/dL.

i. A first baseline PK blood sample should be collected at the point that plasma glucose first reaches a concentration < 50.0 mg/dL.

g. After 5 minutes, a confirmatory plasma glucose measurement will be performed.

i. If plasma glucose remains < 50.0 mg/dL, randomized study drug will be administered (see Section 9.3.3) after collection of a second baseline PK blood sample.

ii. If plasma glucose has risen to ≥ 50.0 mg/dL, the IV insulin infusion will be restarted and the sequence repeated until there are two consecutive plasma glucose readings < 50.0 mg/dL on record. Note: Only 2 total baseline PK samples should be collected, even if the IV insulin is restarted. The initial PK sample is collected at the first point that a plasma glucose < 50.0 mg/dL is obtained. The second is collected after the confirmatory reading < 50.0 mg/dL is obtained, even if this is more than 5 minutes separated from the initial PK collection.

Note: If consecutive readings of plasma glucose < 50.0 mg/dL are not achieved within 3 hours of the start of the hypoglycemia induction phase, the visit should be terminated. In this case:

i. Study drug should NOT be given.

ii. The visit should be terminated and rescheduled after a 7-day minimum wash-out period.

iii. If appropriate, insulin pump therapy should be restarted and a meal provided. The subject can leave the clinic after plasma glucose is confirmed to be between 70 and 180 mg/dL.

h. Following study drug administration, plasma glucose will be measured every 5±2 minutes until 90 minutes post-dosing. Note: At their discretion, investigators may continue to monitor glucose levels for safety during the remainder of the visit.

i. At any time post-dosing if a subject exhibits signs of coma or convulsions, or if plasma glucose remains < 60.0 mg/dL at 30 minutes post-dosing, a 25 mL IV bolus dose of 50% dextrose will be given. Signs and symptoms should be monitored and if the subject's condition fails to improve within 15 minutes, additional dextrose or other intervention may be given at the discretion of the investigator.

j. Additional blood samples will be collected at 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes post-dosing with ± 5 minutes per collection, and processed and stored at -70C for determination of plasma glucagon and potentially insulin levels (see Table 5).

k. At 240 minutes post-dosing, the subject will resume pump therapy, if applicable, and will be given a meal. The subject can then leave the clinic after plasma glucose is confirmed to be between 70 and 180 mg/dL. Note: If necessitated by rising glucose levels, insulin pump therapy can be re-started as early as 120 minutes post-dosing. Additionally, IV insulin can be administered to non-pump using subjects to prevent hyperglycemia, starting at 120 minutes post-dosing with glucagon.

8. Subjects will complete a questionnaire regarding severity of hypoglycemia symptoms (Appendix 1) at various time points, including:
    a. Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure.
    b. Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure.
    c. Just before study drug is administered, and
    d. Every 5±2 minutes after glucagon is administered until all symptoms have abated (i.e., all symptoms have score = 1) or 45 minutes post-dosing, whichever occurs first.
9. Local tolerability will be assessed as follows:
    a. Subjects will complete a Visual Analog (VAS) questionnaire regarding injection site discomfort (Appendix 2) at 10±5 and 30±5 minutes post-dosing, and again at 240±5 minutes post-dosing if VAS score reported at 30 minutes is > 0 mm.
    b. Subjects will complete an Injection Site Discomfort Description and Duration Questionnaire at 10±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.
    c. An 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 240±5 minutes post-dosing. If any scores remain > 1 at the 240-minute evaluation, the subject may leave the clinic but will be instructed to contact study staff if the condition fails to resolve.
10. Adverse events reported by the subject or observed by an investigator 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 followed at this visit are as listed in Section 10.2.1, with the exception of items #4 as no blood work is required at Visit 3. At this visit, the other study medication will be given, so that between the two dosing visits, each subject will have received G-Pen™ (glucagon injection) once and Lilly Glucagon once.

10.2.3. Visit 4 - Follow-Up (Day 10-42)

The subject will attend a follow-up visit within 3-14 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
3. Body weight.
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. 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 Screening Day -60 to -3	Visit 2 Treatment 1 Day 0	Visit 3* Treatment 2 Day 7-28	Visit 4* Follow-up Day 10-42
Informed consent	x	—	—	—
Medical History & Demographics	x	—	—	—
Inclusion/exclusion review	x	—	—	—
Concomitant medications	x	x	x	x
Height, weight & physical exam[a]	x	—	—	x
12 lead ECG	x	—	—	x
Vital signs	x	x[b]	x[b]	x
Urine pregnancy test	x	x	x	x
Urine drug screen	x	—	—	—
Hematology	x	(x)	—	x
Clinical chemistry	x	(x)	—	x
HbA1c and C-peptide	x	—	—	—
HIV, HCV and HBV	x	—	—	—
Randomization	—	x	—	—
Overnight fast from midnight	—	x	x	—
Administration of study medication	—	x	x	—
Hypo. symptom questionnaire	—	x	x	—
Injection site discomfort scales	—	x	x	—
Draize scales for erythema/edema	—	x	x	—
Glucagon levels (PK)[d]	—	x	x	—
Venous blood glucose (PD)[e]	—	x[c]	x[c]	—
Review adverse events (AE)	—	x	x	x

[a] Excluding breast, pelvic and genitourinary exams. Note: height assessment is not required at Visit 4.
[b] Temperature, respiration, HR and triplicate BP (after >5 min seated rest) will be performed prior to hypoglycemia induction. HR and single BP will be repeated immediately prior to, and at 30, 60, 120 and 240 minutes post-dosing, with ±5 minutes for all procedures.
[c] If blood glucose is > 270 mg/dL upon clinic arrival, the visit should be rescheduled.
[d] Venous blood at -5, 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes post dose, with ±2 minutes for the collections at -5 and 0 minutes, and ±5 minutes for all other samples
[e] Via rapid glucose analyzer before and during hypoglycemia induction, and at -5, 0, and every 5 minutes post dose through 90 minutes, with ±2 minutes for all collections
(X) = repeat if more than 30 days have passed since Visit 1.
*Visit 3 should occur 7-28 days following Visit 2, and Visit 4 should occur 3-14 days following Visit 3.

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 30 PD samples of about 2cc each and 11 PK samples of 8.5 cc each drawn at each treatment visit for a total of about 214 cc of blood per visit. These two studies will be 7 to 28 days apart. There will be a 10.5 cc sample at Screening and the Follow-up Visit for a clinical chemistry panel and hematology, with an additional 15.5 cc sample at Screening for eligibility determination. A total of about 344 cc of blood will be drawn over the total study, an amount that will not exceed 4.6cc / kg body weight for a 75 kg subject (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	-	1	15
Hematology	3	1	-	1	6
HbA1c/C-peptide	3	1	-	-	3
C-peptide	5	1	-	-	5
Serology	7.5	1	-	-	7.5
Pharmacodynamics[a]	2	-	c. 30/visit	-	120
Pharmacokinetics	8.5	-	c. 11/visit	-	187
Total	2-8.5	5	c. 41/visit	2	343.5

[a] Single plasma glucose measurements at bedside via rapid glucose analyzer.

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 Performed at Site

Hematology	Chemistry	Urine	Laboratory
WBC count	Glucose	β-hCG[a]	HbA1c
RBC count	Creatinine	Drug screen[b]	C-peptide
Hemoglobin	Na^+		Glucagon levels[c]
Hematocrit	K^+		Insulin levels[d]
Platelet count	Ca^{++}		HIVab
	Albumin		HCVab
	Alkaline Phosphatase		HBsAg
	AST/SGOT		
	ALT/SGPT		

[a] 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.
[b] Drug screening performed at Screening will include: cocaine, THC, opiates, amphetamines, methamphetamine, and phencyclidine. 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.
[c] To be performed on a subset of subjects only (see Section 13.2.1).
[d] To be performed for individual subjects only in the event of treatment failure.

A central laboratory will be utilized for analysis of all variables with the exception of urine tests, PK samples (glucagon and insulin) and 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, including PK samples, as well as point-of-care urine pregnancy tests.

Rapid urine drug screen kits will be provided to sites by Xeris. If a subject tests positive for 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.

A central analytical lab will analyze the PK samples collected in this study. The procedures for preparing, storing and shipping PK samples to the analytical lab will be provided in a laboratory manual that will be provided to all sites prior to the start of the study To the extent possible based on available storage space at the sites, PK samples will be batched so as to reduce the

overall number of shipments. The main and back-up PK samples (i.e., Aliquots 1 and 2) for a particular subject should NEVER be included in the same shipment.

During treatment visits, plasma glucose levels will be measured using a bedside YSI rapid glucose analyzer. 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.

11.3. Electrocardiogram (12-lead ECG)

Single, supine 12-lead ECGs will be obtained at the pre-defined time-points outlined in 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 dominant arm will be used throughout the study. 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 closed. For an unresolved AEs to be considered stable, the 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 inpatient hospitalization or extends hospitalization
- Results in persistent or significant disability
- Is another important medical event

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in hospitalization or death. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent a SAE outcome, the important medical event should be reported as 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 8 below.

Table 8: 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 of an adverse event to 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.

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.

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 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 the Sponsor or its designee.

12.12. Pregnancy

The active pharmaceutical product in Xeris Pharmaceuticals' G-Pen™ (glucagon injection) 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 4 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. Efficacy

The primary objective is to verify that the G-Pen is non-inferior to control in terms of hypoglycemia relief. The primary comparison will be performed using the intent-to treat (ITT) cohort defined as all subjects randomized to one of the two sequence groups: G-Pen followed by control, or control followed by G-Pen. A failure for either treatment will be recorded if plasma glucose remains ≤ 70.0 mg/dL throughout the 0-30 minute period from the drug administration. Consistent with ICH Guideline E9, excluded from the ITT analysis will be subjects who fail to meet all eligibility criteria and/or are randomized to treatment, but receive neither study drug.

The following scoring system will be applied to all subjects in the ITT cohort. If a G-Pen failure is observed then the treatment failure score = 1; similarly the control failure score = 1 if a control failure is observed. If the G-Pen treatment outcome is missing then the treatment failure score = 0.2. A missing control outcome yields a control failure score = 0.1. An observed successful plasma glucose rising above 70.0 mg/dL within 30 minutes yields a failure score = 0, for either treatment. Therefore, all subjects in the ITT cohort will have G-Pen and control failure scores [Koch].

13.1.1. Primary Endpoint:

The G-pen acceptance criterion will be based on the sample mean of the treatment minus control failure scores from each subject in the ITT population. If Dht is 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:

$$Dht + 2.6\ SE \leq 0.1.$$

This criterion, particularly the value 2.6, 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%.

13.1.2. Sample Size Calculation:

Using the above criterion, a sample size of 75 subjects yields probabilities of G-Pen acceptance of over 90% if the population failure rates of G-Pen and control are equal, and the rate of missing observations is within 15%. These results were obtained using Monte Carlo simulations with G-Pen and control total failure rates up to 5%, and with G-Pen success Control failure, or G-Pen failure Control success within 1%.

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, with the missing outcome being

stochastically independent of the Success, 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, 75 independent draws were made from the multinomial distribution determined by the probabilities from the 9 cells, and the sample mean, 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).

Approximately 80 subjects will be randomized at approximately 8 clinical sites with a goal of no single center accounting for > 20% of the total randomization.

13.2. Pharmacokinetic and Pharmacodynamic Analyses

The pharmacokinetic endpoints will be derived from the individual plasma glucagon and insulin profiles. The pharmacodynamic endpoints will be derived from the individual glucose profiles.

13.2.1. Pharmacokinetic Secondary Endpoints:

The data for each of the ethnicities/races and the overall population will be analyzed descriptively with AUC, C_{max} and t_{max}. Consistent with the objectives of the study (see Section 5.2) PK data will be analyzed from the first 12 subjects to complete treatment with G-Pen in each of the following major ethnicities and races in the US: non-Hispanic Whites, Hispanics, and African-Americans.

13.2.2. Pharmacodynamic Secondary Endpoints:

Time for plasma glucose to reach >70.0 mg/dL, AUC, Cmax and Tmax will be compared between the treatment groups using a mixed model with treatment, period and sequence as terms.

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

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

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

13.3.1. Adverse events:

All AEs will be coded by the Medical Monitor using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and study drug. A summary table indicating the number and the percentage of exposed subjects having at least one AE will be made.

13.3.2. Laboratory safety assessments:

Laboratory values (biochemistry and hematology) will be flagged if outside the normal range. A listing of abnormal values will be presented in an end of text (EOT) listing. The individual values will be listed indicating values outside normal range. Laboratory assessments will be summarized at Screening and at end of trial.

13.3.3. 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.

13.3.4. Vital signs and body weight:

Vital signs will be summarized by descriptive statistics.

13.3.5. ECG:

Any deviation from normal ranges of the measured laboratory parameters will be documented and followed as appropriate. The Investigator's evaluations will be summarized in an EOT listing.

Clinically 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.

13.3.6. 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.

13.4. Subgroup Analysis

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

13.5. Interim Analysis

If the total number of subjects with criterion failures (counted in a blinded fashion) exceeds 4, a monitoring statistician not otherwise involved with study conduct may provide an unblinded determination the distribution by treatment group for futility, and communicate a finding of futility to Xeris' upper management for further decisions, while the study team remains blinded. Success will not be tested and no penalty for this futility only check is planned.

More specific details regarding the analyses outlined in 13.1-13.5 will be provided in the Statistical Analysis Plan (SAP) for this protocol.

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

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record, or both. A CRF is required and should be completed for each individual subject. The completed original CRFs 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.

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

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), 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 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 any and all questions raised and difficulties detected by the monitor.

15.4. Audits and Inspections

The investigator understands that regulatory authorities, the IRB, 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/IEC 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 (IRB)

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 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 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 should be notified immediately and the amendment forwarded to the IRB 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. All correspondence with the IRB should be retained in the Investigator File. Copies of IRB 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 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 for review and approval prior to implementation. Advertisements approved by the IRB 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

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 before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to subjects do not require preapproval by the IRB. However, the IRB 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.

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, safety problems, 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 investigator documenting the reason for study termination, and specific procedures for termination will be arranged by the sponsor in coordination with the investigator. After notification, the investigator 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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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 45 minutes post-dosing, whichever occurs first.

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 240±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.

No Discomfort Worst Possible Discomfort

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 a duration of discomfort of "at least 10 minutes" should complete follow-up question 1c at the end of the study visit. 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 ± 5 and 30 ± 5 minutes post-treatment, and again at the end of the treatment visit (i.e., at 240 ± 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. INSTRUCTIONS FOR USE