G-PEN™ (GLUCAGON INJECTION)
PROTOCOL XSGP-302

A PHASE 3 STUDY TO EVALUATE THE GLUCOSE RESPONSE OF G-PEN™ (GLUCAGON INJECTION) IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES

Version 1.3

December 6, 2016

INVESTIGATOR'S AGREEMENT

I have received and read the current Investigator's Brochure for G-Pen™ (glucagon injection). I have read the XSGP-302 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	Address and Telephone Number
Clinical Study Leader	Dr. Nilay Shah Medical Officer Emmes Corporation	401 North Washington Street Suite 700 Rockville, MD 20850 nshah@emmes.com Phone: 301-251-1161
Medical Monitor & 24-Hour emergency contact	Dr. Poul Strange Medical Director Xeris Pharmaceuticals, Inc.	Pstrange@imdcro.com Phone: 606-897-0505 x213 Fax: 609-897-0555

2. SYNOPSIS

Protocol Number XSGP-302	
A PHASE 3 STUDY TO EVALUATE THE GLUCOSE RESPONSE OF G-PEN™ (GLUCAGON INJECTION) IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES	
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)
Objectives:	The primary objective of this study is to assess the increase in plasma glucose from baseline to 30 minutes in subjects in a low normal glycemic state after injection of an age-appropriate dose of G-Pen™ (glucagon injection), in each of three age groups (2.0-<6.0 years, 6.0-<12.0 years and 12.0-<18.0 years) of pediatric patients with type 1 diabetes mellitus (T1D). Secondary objectives of this study include: 1. In the 12-<18 year-old age group, to additionally assess the plasma glucose change from baseline to 30 minutes after administration of G-Pen™ (glucagon injection) at a dose of 0.5 mg. 2. Determine G-Pen™ (glucagon injection) pharmacokinetics for each age group, and 3. Determine the safety and tolerability of G-Pen™ (glucagon injection) for each age group.
Study design:	This is a sequential efficacy and safety study in pediatric patients with T1D. Subjects using insulin injections will be administered IV insulin and subjects using an insulin pump will have the basal rate increased to induce a low normal glycemic state and will then receive an age-appropriate dose of G-Pen™ (glucagon injection) in a clinical research center (CRC) or comparable setting. Subjects ages 2-<12 will complete a single treatment visit and will receive a 0.5 mg dose of G-Pen™. Subjects ages 12-<18 will receive a 1 mg dose of G-Pen™ at an initial treatment visit, and will be given the 0.5 mg dose at a second visit occurring 7-28 days later.
Study location:	Approximately 8 US-based pediatric clinics.
Study duration:	Estimated duration of study participation for individual subjects is approximately 2-6 weeks. Estimated duration of the study is 5 months.

Sample size:	Approximately 48 subjects are anticipated to be screened for this study, and approximately 24 (up to 8 per cohort) will receive study drug to achieve the goal of 18 evaluable subjects equally distributed (n=6 per cohort) across the three age groups: 2.0-<6.0, 6.0-<12.0 and 12.0-<18.0 years.
Subjects:	Male or female patients with T1D ages 2.0-<18.0 years, inclusive.
Inclusion Criteria:	1. Males or females diagnosed with T1D for at least 6 months at Screening. 2. Current usage of daily insulin treatment. 3. Age 2.0 <18.0 years, provided that subject will be <18.0 years for the duration of the study. 4. Willingness of subject and adult guardian to follow all study procedures, including attending all clinic visits. 5. Parent or guardian has provided written informed consent and assent has been obtained from subjects if appropriate for age according to IRB requirements.
Exclusion Criteria:	1. Pregnant and/or Nursing: For subjects 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 participating in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the female uses a diaphragm and spermicide and the male uses a condom), or abstinence. 2. Renal insufficiency (serum creatinine of ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]). 3. Serum ALT or AST equal to or greater than 3 times the upper limit of normal 4. 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. 5. Hematocrit of less than or equal to 30%. 6. Mean of triplicate BP readings at Screening where SBP or DBP >95% of normal for age and height percentile. 7. Use of > 2.0 U/kg total insulin dose per day. 8. Inadequate venous access. 9. Current seizure disorder. 10. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease). 11. History of insulinoma. 12. 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. 13. History of glycogen storage disease. 14. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.

	15. Active use of alcohol or drugs of abuse. 16. Administration of glucagon within 14 days of the first treatment visit. 17. 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. 18. Any reason the principal investigator deems exclusionary.
Brief outline of treatments:	Subjects will complete the screening procedures up to 30 days before dosing to determine eligibility before enrollment in the treatment phase. For treatment visits, subjects will arrive at the clinical center in the morning, having fasted for at least 8 hours prior to dosing. The following procedures will be performed: • The glucose level will be checked: o If >300 mg/dL, ketones will be checked. o If ketones are found to be moderate or greater, the visit will be postponed. • Assessment of any severe hypoglycemic events (requiring the assistance of another person) since the screening visit: o If a severe hypoglycemic event has occurred in the 2 weeks prior to the admission, the visit will be postponed until it has been at least 2 weeks since the last severe hypoglycemic event. • For females of child-bearing potential, a urine pregnancy test will be performed: o If positive, the subject will be discontinued from the study. • Insertion of intravenous catheter for blood sampling: o Those subjects using injection therapy will have a second intravenous catheter inserted in the other arm for insulin infusion. **Procedures for Insulin Infusion** **Insulin Pump Users:** At the start of the test, the basal insulin rate will be increased by approximately 25-50% to provide a gradual decline in blood glucose. A small priming bolus dose of insulin equal to approximately one hour of the subject's usual basal dose may also be given at the discretion of the investigator in addition to the 25-50% increase in the basal insulin. • The basal insulin rate may be increased an additional amount and additional bolus insulin doses may be given at the discretion of the investigator in order to get a gradual decline in glucose concentration. **Insulin Injection Users:** If the starting glucose level is >200 mg/dL, a priming dose of 2-4 units of IV insulin may be given. An intravenous infusion of regular insulin diluted in normal saline at a rate of 1 mU/kg/min will be administered. The infusion rate will be adjusted as necessary to reach the target glucose level of <80 mg/dL.

	For Both Pump and Injection Users: For all subjects, plasma glucose levels will be measured using a bedside rapid glucose analyzer (Analox, YSI or equivalent). During the insulin infusion, glucose levels will be measured no more than 10 minutes apart while the plasma glucose level is ≥100 mg/dL and no more than 5 minutes apart when the plasma glucose level is <100 mg/dL. Once a plasma glucose level of <80 mg/dL is reached, the basal rate will be returned to normal for subjects using an insulin pump and the insulin infusion will be stopped for subjects using insulin injections. If the starting plasma glucose is <80 mg/dL, no additional insulin will be given and the procedures below will be followed. Dosing with glucagon will be at 5 minutes following a measurement of plasma glucose < 80 mg/dL. Subjects will receive a subcutaneous injection of G-Pen™ glucagon at an age appropriate dose (0.5 mg for 2-<12 years, 0.5 or 1.0 mg for 12-<18 years). Plasma glucose will be measured at bedside at -5 and 0 minutes, and every 5 minutes for 90 minutes after dosing. In addition, blood samples will be collected at -5, 0, 10, 20, 30, 45, 60, 90, 120, and 180 minutes and stored at -80 ±20 C for determination of plasma glucagon concentration. Body weight may limit the number of blood draws (see below). After this, the subject will be given a meal and will receive insulin according to her or his normal dosing regimen. The subject can then leave the clinic. Tolerability will be assessed by comparing adverse event reports between the groups. Subjects will also complete age-appropriate questionnaires concerning injection site discomfort. In addition, modified Draize scales will be used by an investigator to evaluate the injection site at 10, 30 and 180 minutes following administration, as appropriate. **Volume of Blood Draws** The maximum blood volume to be collected will not exceed 5% of the subject's blood volume. The number of blood draws will be reduced for subjects who do not weigh enough to allow for the full schedule to be completed. Early collections (-5 to 30 minutes) will be preferred over later blood draws, and Pharmacodynamics samples will be prioritized over Pharmacokinetic samples.
Data management and statistical analysis:	Data will be entered from the source (e.g Case Report Forms) into Advantage eClinical an Electronic Database Capture (EDC) system by site personnel. Data will be monitored remotely and at on-site visits by the Clinical Research Associate (CRA). Both primary and secondary endpoints will be summarized descriptively within each of the 3 age groups. Mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Count and percentage variables will be presented for discrete variables. The primary endpoint will also be compared to 0 change using a simple t-test. Pharmacokinetic data will be analyzed descriptively by dose/age cohort.
Sample Size Determination:	Based on results of a prior study, G-Pen™ (glucagon injection) is expected to increase glucose by minimally 25 mg/dL from baseline within 30 minutes of administration in every subject. Assuming a standard deviation of 18 mg/dL, a

	sample size of 6 subjects per cohort has been chosen to provide 90% power to detect an increase of plasma glucose from baseline to 30 minutes after treatment.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum Plasma Concentration
CGM	Continuous Glucose Monitor
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 assess the increase in plasma glucose of subjects from baseline to 30 minutes in subjects in a low normal glycemic state after injection of an age-appropriate dose of G-Pen™ (glucagon injection), in each of three age groups (2.0-<6.0 years, 6.0-<12.0 years and 12.0-<18.0 years) of pediatric patients with type 1 diabetes mellitus (T1D).

5.2. Secondary Objectives

The secondary objectives of this study are:

- In the 12-<18 year-old age group, to additionally assess the plasma glucose change from baseline to 30 minutes after administration of G-Pen™ (glucagon injection) at a dose of 0.5 mg.
- Determine G-Pen™ (glucagon injection) pharmacokinetics for each age group.
- Determine the safety and tolerability of G-Pen™ (glucagon injection) for each age group.

5.3. Endpoints

5.3.1. Primary Endpoint

The primary endpoint for this study is an evaluation of change in plasma glucose following treatment with G-Pen™, with an emphasis on the increase from baseline to 30 minutes post-dosing.

5.3.2. Secondary Endpoint

The secondary endpoints for this study are as follows:

- Pharmacokinetic parameters, including: descriptive analysis of $AUC_{0\text{-}120m}$, C_{max} and Tmax of the different age cohorts.
- Pharmacodynamic characteristics, including: plasma glucose $AUC_{0\text{-}120m}$, Cmax, Tmax and time to achieve an increase in plasma glucose of at least 25 mg/dL.
- Safety-related parameters including:
    - Vital signs
    - Incidence of adverse events (AEs) and serious adverse events (SAEs)
    - Subjective injection site discomfort using the Faces Pain Scale [FPS-R]
    - Subjects with sufficient comprehension will further describe the nature and duration of any injection site discomfort using a second questionnaire (Appendix 1).
    - Erythema and/or edema formation at site of injection assessed by an investigator using the modified Draize scale (see Appendix 2)

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 occurrence 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, 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, UK Hypoglycaemia Study Group]. The American Diabetes Association (ADA) 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 [UK 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.

In children, the T1D Exchange clinic registry has shown that severe hypoglycemia is relatively common. The registry indicates that the most severe form of hypoglycemia resulting in seizure or loss of consciousness was more common in participants 2-<6 years old than in the older children (9.6% in 2-<6 years, 5.2% in 6-<13 years, and 6.3% in 13 -<18 years). After adjusting for age, severe hypoglycemia was more common in participants who were non-Hispanic black ($p<0.001$), were from families with lower annual household income ($p<0.001$), were without private health insurance ($p<0.001$), had longer duration of diabetes ($p<0.001$), had higher HbA1c ($p=0.001$), and used multiple daily injections (MDI) for insulin delivery (compared with pump users, $p<0.001$). In a multivariate analysis, associations were similar, except there was not a significant association of severe hypoglycemia with either the average HbA1c in the prior 12 months or method of insulin delivery [Cengiz].

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. Because glucagon is unstable in solution, 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]. For adults and for children weighing more than 44 lbs (Lilly Glucagon) or 55 lbs (Novo GlucaGen HypoKit), the recommended dose of glucagon is 1 mg by subcutaneous (SC), IM or IV injection. For children weighing less than 44 lbs (Lilly Glucagon) or 55 lbs (Novo GlucaGen HypoKit), the recommended dose of glucagon is 0.5 mg.

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™. The G-Pen™ will utilize 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. The G-Pen™ (glucagon injection) delivers 0.5 or 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 a 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 packaged in a sealed pouch. The 0.5 and 1 mg versions of G-Pen™ are distinguished by two strikingly different labeling colors utilized on the carton, pouch, and injector device.

6.4. Clinical Experience with Glucagon

Glucagon has a long history of medical use in the US, and is currently marketed by Eli Lilly & Co. as Glucagon (Glucagon Injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both Reference Listed Drug (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 sequential efficacy and safety study in pediatric patients with T1D. Subjects will be administered insulin to induce a low normal glycemic state and will then receive an age-appropriate dose of G-Pen™ (glucagon injection) in a clinical research center (CRC) or comparable setting.

Subjects ages 2-<12 will complete a single treatment visit and will receive a 0.5 mg dose of G-Pen™. Subjects ages 12-<18 will receive a 1 mg dose of G-Pen™ at an initial treatment visit, and will be given the 0.5 mg dose at a second visit occurring 1-4 weeks later (Table 3). Patients will complete the screening procedures up to 30 days before dosing to determine eligibility before enrollment to the treatment phase.

Table 3: Treatment sequence

Subject Age	Dose 1	Dose 2
2.0-<12.0	G-Pen™ 0.5 mg	Not applicable
12.0-<18.0	G-Pen™ 1 mg	G-Pen™ 0.5 mg

The procedure to evaluate the efficacy of G-Pen™ (glucagon injection) consists essentially of inducing a low normal glycemic state by administration of insulin. For subjects using an insulin pump, the basal rate will be increased to induce a gradual decrease in blood glucose. For subjects using long-acting insulin, an IV infusion of regular insulin diluted in normal saline will be started to effect a decrease in blood glucose. The exact procedures to be followed are outlined below in Section 7.2.

For subjects using injection insulin therapy, a combination of one or more bolus doses of insulin along an infusion of insulin will be used to decrease a subject's plasma glucose to a target <80 mg/dL. The insulin infusion will be stopped once the plasma glucose is <80 mg/dL. For subjects using an insulin pump, the basal rate will be increased until the target of <80 mg/dL is reached. A priming bolus equal to approximately 1 hour of basal insulin may also be given at investigator discretion.

After a confirmatory plasma glucose of <80 mg/dL is obtained at least 5 minutes after stopping the insulin infusion, the subject will be treated subcutaneously in the upper arm, leg or abdomen with the age-appropriate dose of G-Pen™ (glucagon injection) administered sc (see Section 9.3.2). Blood glucose levels will be monitored for 90 minutes post-dosing.

After a wash-out period of 7 to 28 days, subjects ages 12.0-<18.0 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 treatment days, subjects will be discharged after receiving a standardized meal and their usual dose of insulin. A follow-up phone call as a safety check will be conducted 3 ± 14 days following administration of the final dose.

Tolerability will be assessed by examining adverse event reports. In addition, subjects will complete age-appropriate questionnaires concerning injection site discomfort and an investigator

will use modified Draize scales to evaluate the injection site at 10±5, 30±5 and 180±5 minutes following administration.

7.2. Procedures for Insulin Infusion

Insulin injection users will receive intravenous insulin to reduce the glucose level while insulin pump users will have the basal insulin rate increased to achieve a blood glucose reduction. The value in handling pump users this way is that the delivery of subcutaneous insulin and the restoration of the usual basal rate when the glucose target level is achieved are more similar to real-world conditions than giving IV insulin. In addition, use of the insulin pump only requires one IV line, an important consideration in a pediatric study.

Insulin Pump Users: At the start of the test, the basal insulin rate will be increased by approximately 25-50% to provide a gradual decline in blood glucose. A small priming bolus dose of insulin equal to approximately one hour of the subject's usual basal dose may also be given at the discretion of the investigator in addition to the 25-50% increase in the basal insulin. The basal insulin rate may be increased an additional amount and additional bolus insulin doses may be given at the discretion of the investigator in order to get a gradual decline in glucose concentration.

Insulin Injection Users: If the starting glucose level is >200 mg/dL, a priming dose of 2-4 units of IV insulin may be given. An intravenous infusion of regular insulin diluted in normal saline at a rate of 1 mU/kg/min will be administered. The infusion rate will be adjusted as necessary to reach the target glucose level of <80 mg/dL.

For Both Pump and Injection Users: For all subjects, plasma glucose levels will be measured using a bedside rapid glucose analyzer (Analox, YSI or equivalent). During the insulin infusion, glucose levels will be measured no more than 10 minutes apart while the plasma glucose level is ≥100 mg/dL and no more than 5 minutes apart when the plasma glucose level is <100 mg/dL. To reduce the volume of blood draws, a continuous glucose monitor (CGM) may be used to assess glucose levels during the induction phase only. However before treatment is given, BG <80 mg/dL will be confirmed by bedside glucose analyzer.

Once a plasma glucose level of <80 mg/dL is confirmed, the basal rate will be returned to normal for subjects using an insulin pump and the insulin infusion will be stopped for subjects using insulin injections.

If the starting plasma glucose is <80 mg/dL, no additional insulin will be given. If a plasma glucose level of <80 mg/dL is not achieved within 3 hours of starting the insulin infusion, treatment with study drug should not be given, and the visit should be rescheduled after a minimum 7-day wash-out.

7.3. Interruption and Termination of Dosing

Dosing will be paused for any SAE which 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.

Visits in which glucagon is not given will not be included in the primary analyses. A visit will be considered completed for purposes of the sample size when glucagon is given and there is at least one blood glucose measurement 30 or more minutes after the glucagon injection.

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 T1D for at least 6 months at Screening.
2. Current usage of daily insulin treatment.
3. Age 2.0 <18.0 years, provided that subject will be <18.0 years for the duration of the study.
4. Willingness of subject and adult guardian to follow all study procedures, including attending all clinic visits.
5. Parent or guardian has provided written informed consent and assent has been obtained from subjects if appropriate for age according to IRB requirements.

8.2. Exclusion Criteria

1. Pregnancy or Nursing: For subjects 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 7 days after the last dose of study medication in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the female uses a diaphragm and spermicide and the male uses a condom), or abstinence.
2. Renal insufficiency (serum creatinine of ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]).
3. Serum ALT or AST equal to or greater than 3 times the upper limit of normal
4. 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.
5. Hematocrit of less than or equal to 30%.
6. Mean of triplicate BP readings at Screening where SBP or DBP >95% of normal for age and height percentile.
7. Use of > 2.0 U/kg total insulin dose per day.
8. Inadequate venous access.
9. Current seizure disorder.
10. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
11. History of insulinoma.
12. 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.

13. History of glycogen storage disease.
14. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
15. Active use of alcohol or drugs of abuse.
16. Administration of glucagon within 14 days of the first treatment visit.
17. 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.
18. Any reason the principal investigator deems exclusionary.

8.3. Enrollment

A subject will be considered enrolled after the informed consent form is signed by the parent/guardian, assent is provided if needed per IRB requirements, and eligibility is confirmed.

9. STUDY TREATMENTS

9.1. Allocation to Treatment

Subjects will be allocated to treatment based on age at the Screening Visit to receive the appropriate dose(s) of study medication (see Table 3). Prior to treatment, age should be confirmed to ensure the age-appropriate dose of study drug is administered. Subjects who are expected to reach their 18th birthday before completion of study treatment should not be enrolled.

Approximately 24 patients will be enrolled to treatment with a goal of completing 18 subjects, or roughly 6 evaluable subjects per age cohort.

9.2. Blinding

For this study, subject and investigator will be unblinded.

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 0.5 or 1 mg synthetic glucagon peptide dissolved in a primary DMSO solvent, with trehalose added as a stabilizing excipients. The appropriate amount of 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 a SHL Molly™ single-use, disposable auto-injector, and packaged in a sealed pouch. The 0.5 mg and 1 mg dose devices are distinguished by two strikingly different labeling colors utilized on the carton, pouch, and injector device. 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 and labeled under cGMP by SHL Group (DeerField Beach, FL), both Xeris Pharmaceuticals' contract manufacturers.

9.3.2. Preparation, Dispensing and Administration

G-Pen™ (glucagon injection) will be supplied as 0.1 mL or 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 3).

The injection site should be rotated between subjects such that the first subject at a particular site will receive injection(s) in the arm, the next subject will receive injection(s) in the leg, and the next subject, in the abdomen. This cycle will be repeated for every 3 subjects.

For subjects ages 12-<18 who will receive two treatments, 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.

Note: Numbing cream should not be used at injection sites, though it may be used at the discretion of the investigator for other study procedures (e.g., placement of IV catheters or blood draws).

9.3.3. 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, and will return the products to Xeris or destroy them according to local regulation and applicable Xeris Pharmaceuticals SOPs, following directions from Xeris Pharmaceuticals.

9.4. Concomitant Medications

All subjects and their adult guardians must be questioned about concomitant medications at each visit. Medications taken within 4 weeks before Day 0 will be documented in Advantage eClinical. Subjects will be encouraged to avoid making changes to their concomitant medication regimen during their participation in the study. Any changes to a subject's concomitant medication regimen after the first Treatment on Day 0 will also be documented in Advantage eClinical.

With the exception of other agents that are currently considered investigational, 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 subject'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 4.

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

Subjects will be screened to confirm they meet the inclusion/exclusion criteria for the study. Prior to completing any screening activities, the investigator or study team member will obtain informed consent from each subject and their adult guardian 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 (to allow for receipt of blood test results), and no more than 30 days prior to the anticipated date of the first treatment visit (Day 0). The following evaluations will be completed during the screening visit to confirm subjects meet eligibility criteria for this study:

1. Assessment of inclusion/exclusion criteria by a qualified member of the study staff, including a review of the subject's medical history and medications.
2. Measurement of height and weight.
3. Physical examination, excluding breast, pelvic and genitourinary exams.
4. Assessment of vital signs, including triplicate measurements of BP, after a 5-minute seated rest.
5. Urine pregnancy test for females of childbearing potential.
6. Collection of venous blood for the following tests as outlined in the Schedule of Activities: hemoglobin A1C, complete blood count (without differential), metabolic set (including creatinine, liver set, and electrolytes) (Table 6).

Once laboratory results are obtained and a final determination of eligibility is made, subjects will be contacted to schedule the first treatment visit. 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 Phase

The subject will arrive to the clinic in the morning, having fasted for at least 8 hours prior to dosing, at which time the following procedures will be completed:

10.2.1. Treatment Visit 1 (Day 0)

The following procedures will be carried out at this visit.

1. The subject will be asked about any severe hypoglycemic events (requiring the assistance of another person) since the screening visit.

   a. If a severe hypoglycemic event has occurred in the 2 weeks prior to the admission, the visit will be postponed until it has been at least 2 weeks since the last severe hypoglycemic event.

2. If it has been more than 30 days since the Screening Visit, venous blood will be collected for a repeat of baseline hematology and serum chemistry assessments. However, the treatment visit may continue based upon qualification at the Screening Visit.
3. The subject will be questioned and any changes in concomitant medications will be documented in the CRF.
4. For females of child-bearing potential, a urine pregnancy test will be performed
   a. If positive, the subject will be discontinued from the study.
   b. Full vital signs, including triplicate BP, will be assessed after a 5-minute seated rest. Heart rate and single BP will be repeated immediately prior to dosing and at 30, 60, 120 and 180 minutes post, with ± 10 minutes per collection time point.
5. Insertion of intravenous catheter for blood sampling.
   a. Starting plasma glucose level will be assessed:
      i. If >300 mg/dL, ketones will be checked
      ii. If ketones are found to be moderate or greater, the visit will be postponed.
6. Optional placement of a CGM for assessment of glucose levels during the induction phase.
   a. If used, the CGM will be calibrated against glucose measurements obtained from the point-of-care, rapid glucose analyzer.
7. Insulin infusion will be started as described in Section 7.2.
   a. Those subjects using injection therapy will have a second intravenous catheter inserted in the other arm for insulin infusion.
   b. Plasma glucose levels will be measured no more than 10 minutes apart while the plasma glucose level is ≥100 mg/dL and no more than 5 minutes apart when the plasma glucose level is <100 mg/dL.
8. Once an initial plasma glucose measurement < 80 mg/dL is achieved,
   a. The basal rate will be returned to normal for subjects using an insulin pump and the insulin infusion will be stopped for subjects using insulin injections.
   b. A first baseline PK blood sample should be collected at the point that plasma glucose first reaches a concentration < 80 mg/dL.
9. After 5 minutes, a confirmatory plasma glucose measurement will be performed.
   a. If plasma glucose remains < 80 mg/dL, collect a second baseline PK blood sample, and begin administration of the study drug (see Section 9.3.2).
   b. If plasma glucose has risen to ≥ 80 mg/dL, return to step 7b and repeat the process.
10. Following study dosing, plasma glucose will be measured every 5±2 minutes until 90 minutes post-dosing.

11. Additional blood samples will be collected at 10, 20, 30, 45, 60, 90, 120, and 180 minutes post-dosing, with ± 5 minutes per collection, and processed and stored at -80 ± 20 C for determination of plasma glucagon levels.
12. After completing all collections and procedures at 180 minutes post-dosing, the subject will be given a meal as per the standard practice at each site, and their usual dose of insulin. The subject can then leave the clinic after plasma glucose is confirmed to be between 70 and 180 mg/dL.
13. Local tolerability will be assessed as follows:
    a. Subjects will complete age-appropriate questionnaires regarding injection site discomfort (Appendix 1) at 10±5 and 30±5 minutes post-dosing, and again at 180±5 minutes post-dosing if the FPS score reported at 30 minutes is > 0.
    b. An investigator will use the modified Draize scales (Appendix 2) to assess erythema and edema formation at the injection site at 10±5 and 30±5 minutes following administration. Any injection site with a score > 0 for either erythema or edema at 30 minutes post-dosing will be re-evaluated for both at 180±5 minutes post-dosing.
14. Adverse events reported by the subject or observed by an investigator will be recorded in Advantage eClincial and managed as medically appropriate.

If a subject exhibits signs of distress at any time post-dosing or if plasma glucose drops below < 70 mg/dL, glucose tablets may be given at the discretion of the investigator. Signs and symptoms should be monitored and if the subject's condition fails to improve within 15 minutes, additional glucose tablets or other intervention (e.g., IV dextrose) may be given at the discretion of the investigator. Every attempt should be made to complete all remaining safety and efficacy evaluations, to the extent this can be done while safeguarding the subject.

10.2.2. Treatment Visit 2 (7-28 days after the first treatment)

Subjects ages 12-<18 will return for a second visit at least 7 days and no more than 28 days following the first treatment visit. The procedures to be followed at this visit are as listed in Section 10.2.1, but the 0.5 mg dose of G-Pen™ (glucagon injection) will be given. If scheduled more than 28 days after the first treatment, body weight will be assessed at the second treatment visit.

10.2.3. Follow-Up Phone Call (3-14 days after the final treatment)

The parent or guardian will be contacted by telephone within 3-14 days of completing each dosing visit or premature discontinuation. This phone call will include the following assessments:

1. Review of changes in concomitant medications.
2. Adverse event questioning by asking the subjects to respond to a non-leading question such as "how do you feel?"

If the subject cannot be reached by 14-days post-treatment, a registered letter will be sent to the parent/guardian to facilitate scheduling of the follow-up phone call.

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. In any circumstance, 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 exposed to at least one dose of study drug, a follow-up phone call should be completed as per Section 10.2.3.

If a subject is to be withdrawn from the study during a treatment visit, every attempt should be made to complete all remaining safety and efficacy evaluations, to the extent this can be done while safeguarding the subject.

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 4: Schedule of Assessments

Assessment	Screening CRC Visit Day -30 to -3	Treatment 1 CRC Visit Day 0	Treatment 2* CRC Visit 7-28 days after first treatment	Follow-up Phone call 3-14 days after each treatment
Informed consent	x	—	—	—
Inclusion/exclusion review	x	—	—	—
Height and weight	x	—	(x)	—
Physical exam [a]	x	—	—	—
Demographic data	x	—	—	—
Medical History	x	—	—	—
Concomitant medications	x	x[b]	x[b]	x[b]
Urine pregnancy test, if applicable	x	x	x	—
Hematology/Clinical chemistry	x	—	—	—
HbA1c	x	—	—	—
Vital signs	x	x	x	—
Overnight fast from midnight	—	x	x	—
Administration of study medication	—	x	x	—
Subject questionnaires for injection site discomfort	—	x	x	—
Draize scales for erythema/edema	—	x	x	—
Glucagon levels (PK)[c]	—	x	x	—
Venous blood glucose (PD)[d]	—	x	x	—
Adverse events (AE)	x	x	x	x[b]

*Subjects ages 12-<18 only.
(x) Applies to weight only; repeat if >28 days have passed since the Treatment 1 visit.

[a] Excluding breast and pelvic/genital exams.
[b] Changes from prior visit.
[c] Venous blood at -5, 0, 10, 20, 30, 45, 60, 90, 120, and 180 minutes post dose, with ±2 minutes per collection for the samples from -5 and 0 minutes, and ±5 minutes for later samples.
[d] Via rapid glucose analyzer at -5, 0, and every 5 minutes post dose to 90 minutes, with ±2 minutes per collection.

11. ASSESSMENTS

Every effort should be made to ensure that the protocol 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 samples collected, all efforts must be made to obtain these samples at the same clock time as well as 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 10 PK samples of 2 cc each drawn for a total of about 80 cc per treatment visit. This may be reduced by use of a CGM during the induction phase. Subjects ages 2-<12 will complete a single treatment visit, while subjects 12-<18 will complete two such visits 7 to 28 days apart. There will be a 13.5 cc sample at Screening for a clinical chemistry panel, hematology and HbA1c determination. A total of about 94 cc of blood will be drawn over the total study for subjects 2-<12 years of age and about 174 cc for subjects ages 12-<18 (Table 5).

Table 5: Frequency and Volume of Blood Collections

Sample Type	Sample Volume (mL)	Blood Volume (mL) by Sample Type/Visit			Total Volume (mL)
		Screening	Treatment Visit #1	Treatment Visit #2	
Clinical Chemistry	7.5	7.5	-	-	7.5
Hematology	3	3	-	-	3
HbA1c	3	3	-	-	3
Pharmacodynamics[a]	2	-	40-60*	40-60*	60/120
Pharmacokinetics	2	-	20	20	20/40
Total	2-7.5	13.5	60-80	60-80	93.5/173.5

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

Volume of Blood Draws

The maximum blood volume to be collected will not exceed 5% of the subject's blood volume. The number of blood draws will be reduced for subjects who do not weigh enough to allow for the full schedule to be completed. Early collections (-5 to 30 minutes) will be preferred over later blood draws, and PD samples will be prioritized over PK samples.

11.2. Clinical Laboratory Tests

The tests outlined in Table 6 will be performed at the specified time points described in the Schedule of Activities.

Table 6: Clinical and Safety related Laboratory Tests Performed at Site

Hematology	Chemistry	Urine	Laboratory
WBC count RBC count Hemoglobin Hematocrit Platelet count	Glucose Creatinine Na^+ K^+ Ca^{++} Albumin Alkaline Phosphatase AST/SGOT ALT/SGPT	β-hCG[a]	HbA1c Glucagon levels

[a] Female subjects of childbearing potential require a negative urine 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.

Each site's local laboratory will be utilized for analysis of all variables with the exception of urine pregnancy tests, glucagon and rapid plasma glucose measurements made during treatment visits. Local laboratory procedures will be followed. Each laboratory will provide their Clinical Laboratory Improvement Act (CLIA) certification and normal ranges to the Sponsor or its designee.

Each site will locally source point-of-care urine pregnancy tests.

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 outlined in a manual that will be provided by the lab to all investigators prior to initiation of the study.

During post-treatment evaluations, plasma glucose levels will be measured using a bedside rapid glucose analyzer (Analox, YSI or equivalent). The glucose analyzer will be calibrated before each subject visit and sites will maintain a log of calibration results. To reduce the total volume of blood needed for smaller subjects, a continuous blood glucose monitor may be substituted during the induction phase only (see Section 7.2).

11.3. Vital Signs

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

BP and heart rate will be measured in the supine 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, or
- 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 the exception that 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 entry of applicable information into Advantage eClinical. For AEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event resolves or stabilizes at a level acceptable to the investigator to consider it closed, and the Medical Monitor should 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 a 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 begins from the time the subject provides informed consent, through the Follow-up Visit. All adverse events will be followed until resolution or the subject is medically stable or the subject exits the study.

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 existing 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 an AE 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

If required 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 7 below.

Table 7: 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'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. 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.

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, relevant information must be entered into Advantage eClinical within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, updates to Advantage eClinical must be made within 24 hours, 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 or the per-protocol follow-up period, must be reported to the CRA immediately, whether or not it is considered treatment-related. Initial SAE reports must be followed by detailed descriptions. These should include copies of redacted hospital case records and other documents when requested, all of which must be uploaded directly into Advantage eClinical. 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, including suspected unexpected serious adverse reactions, will be carried out by the Sponsor in accordance with applicable regulations.

To the extent required by local regulations, the investigator must notify the IRB of the occurrence of SAEs, in writing, as soon as is practicable. 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 by the Sponsor for submission to the FDA and any other applicable authorities.

12.12. Pregnancy

The active pharmaceutical product in Xeris Pharmaceuticals' G-Pen™ (glucagon injection) is Glucagon, which is in Pregnancy Category B. Any subject found to be pregnant at any time during the study will be withdrawn from the study immediately. If a pregnancy is reported or initiated within 7 days following administration of the study medication, the pregnancy will be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy) and reported using the pregnancy case report form. Any pregnancy outcome that meets the criteria for an SAE will be reported both as a SAE and on the pregnancy Case Report Form.

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 of the day. The principal investigator or designated sub-investigator will also be on call for the remainder of the study. 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 their 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. Sample Size Determination

In Phase 2 study XSGP-201, healthy normal adults were dosed with G-Pen™ after an overnight fast with baseline plasma glucose values that were similar to the target (< 80 mg/dL) planned for this study. The mean increase in glucose at 30 minutes post-dosing was approximately 35 mg/dL (SD = 18). Based on these findings, a sample size of 6 subjects per cohort has been chosen to provide 90% power to detect an increase of plasma glucose from baseline to 30 minutes after treatment, assuming a type 1 error rate of 5%.

13.2. Pharmacokinetic and Pharmacodynamic Analyses

The pharmacokinetic endpoints will be derived from the individual serum glucagon profiles. The pharmacodynamic endpoints will be derived from the individual glucose profiles. All endpoints will be analyzed descriptively within each of the 3 age groups. Mean, standard deviation, median, minimum and maximum will be presented for continues variables. Count and percentage will be presented for discrete variable.

13.2.1. Primary endpoint

The primary endpoint is the change in plasma glucose at 30 minutes post-dosing from baseline, which is defined as the average of the two plasma glucose measurements (i.e., -5 and 0 minutes) completed immediately prior to dosing. Last observation carried forward (LOCF) will be applied for subjects who drop out before 30 minutes post-dosing or who otherwise have missing primary endpoint data (e.g. missed blood draws). In additional to the descriptive summary, a simple t-test will be used to compare the glucose change from baseline to zero change within each of the 3 age groups.

13.2.2. Pharmacokinetic Secondary Endpoints:

The data for each age cohort and the overall population will be analyzed descriptively, including $AUC_{0\text{-}120m}$, C_{max} and T_{max}.

13.2.3. Pharmacodynamic Secondary Endpoints:

Time for plasma glucose to increase by ≥25 mg/dL from baseline, $AUC_{0\text{-}120m}$, Cmax and Tmax will be analyzed descriptively for each age cohort and by dose for subjects ages 12-<18.

13.3. Safety Analysis

The following variables will be evaluated for safety purposes:

- Adverse events and serious adverse events.
- Vital signs
- Local tolerability, including:
    - Subjective injection site discomfort as reported by subjects using age-appropriate discomfort scales (Appendix 1).

- Erythema and or edema formation at site of injection assessed using the Draize scale (Appendix 2).

13.3.1. Adverse events:

All AEs will be coded by the Sponsor or its designee 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. 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.

13.3.3. Vital signs:

Vital signs will be summarized by descriptive statistics.

13.3.4. 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.).

13.4. Subgroup Analysis

No subgroup analyses are planned for this study.

13.5. Interim Analysis

No interim analysis is planned for this study.

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, 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, 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 "case report form" (CRF) should be understood to refer to either a paper form or an electronic data record, or both. A complete set of CRFs 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 are true.

In some cases, data may be entered directly into electronic CRFs as part of a web-based electronic data collection (EDC) system. When data are entered directly, eCRFs will be considered as source documents. Other electronic data will be uploaded into the EDC system directly from downloads of devices or from datasets provided by laboratories that are processing blood samples. These electronic data will be considered as source documents.

Other data will be collected first on paper worksheets or CRFs and then transcribed into the EDC system. In such cases, the paper forms will be considered source documents for the electronic entries. In some cases, source documents are hospital records or the subject's chart. In these cases, data collected in the CRFs must match the data in those charts. A document should be available that clearly identifies which data are being entered directly into the electronic CRF, and which data have a paper source.

Any corrections to entries made in the CRFs must be dated, initialed and explained (if necessary) and should not obscure the original entry. An equivalent electronic process will utilized for changes to eCRFs or other changes to data entered into the EDC system.

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 clinical research associate (CRA) or auditor) will contact the investigator and conduct regular visits to the clinical site. The CRA 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 CRA 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 CRA/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The CRA 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 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 or its designee.

16.3. Subject Information and Consent

Potential eligibility will be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained from the parent/guardian and assent will be obtained from the subject if required per local IRB requirements. For potential study subjects who are considered potentially eligible

for the study based on a routine-care exam, the study protocol will be discussed with the potential study subject and parent/guardian by a study investigator and clinic coordinator. The parent/guardian will be given the Informed Consent Form to read. The parent/guardian will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study. Subjects of appropriate age (per IRB requirements) will either be given the Child Assent Form to read or it will be read to the child. If the parent/guardian agrees to have the child participate, the Informed Consent Form and Child Assent Form (if applicable) will be signed. A copy of the consent form and the assent form (if applicable) will be provided to the parent/guardian and another copy will be added to the subject's chart or retained by the center research staff. The signed informed consent and assent (if applicable) documents must be available for verification by the study monitors at all times.

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 or its designee 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.

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 is defined as the date the investigator reviews the last subject's final safety data and determined that no further evaluation is required for the subject to complete the trial.

18. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

18.1. Protocol Modifications and Deviations

The principal investigator and the sponsor's representative 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.

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APPENDIX 1. INJECTION SITE DISCOMFORT ASSESSMENT

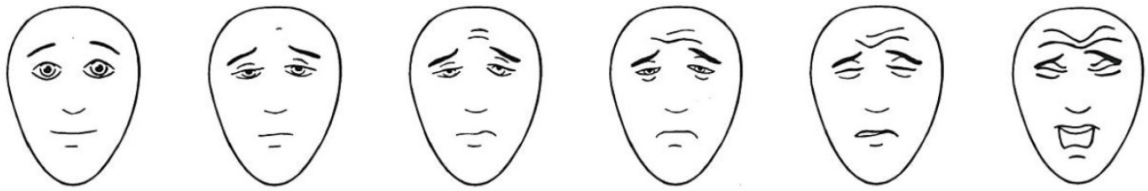
Faces Pain Scale – Revised (FPS-R)

Investigative Site Instructions: The subject should complete the FPS-R regarding 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 if the FPS score at **30±5** minutes is > 0. The subject completes the FPS by choosing the face that corresponds to their current level of pain. 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.

Show the faces to the subject and provide the following instructions, using the words "hurt" or "pain," whichever seems right for a particular subject:

"These faces show how much something can hurt. This face [point to the face on far left] **shows no pain. The faces show more and more pain** [point to each from left to right] **up to this one** [point to face on far right] **– It shows very much pain. Point to the face that shows how much you hurt right now."**

Score the chosen face 0, 2, 4, 6, 8 or 10, counting left to right, so 0 = no pain and 10 = very much pain.



Injection Site Discomfort Description and Duration Questionnaire

Study Personnel Instructions: Question 1a should be completed by the subject at **10±5** minutes following the injection of study drug. Any subject reporting discomfort other than "none," should complete question 1b. Any subject reporting duration of discomfort of "at least 10 minutes" should complete follow-up question 1c at the end of the study visit. 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.

Subject Instructions: Please answer question 1a and, if they apply 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 2. 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 approximately 180±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 3. INSTRUCTIONS FOR USE