Protocol for:

Study No. XSGP-304

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

NCT03738865

Document Date: 17 December 2018

G-PEN (GLUCAGON INJECTION)
PROTOCOL XSGP-304

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

Version 2.1

17 December 2018

XERIS PHARMACEUTICAL SIGNATURE PAGE

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Investigator's Agreement

I have read the XSGP-304 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	Debby Powers Director, Clinical Programs	dpowers@xerispharma.com 844-445-5704 (direct) 512-739-8665 (cell)
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2. SYNOPSIS

Protocol Number: XSGP-304	
G-PEN (GLUCAGON INJECTION) COMPARED TO GLUCAGEN® HYPOKIT® (GLUCAGON) FOR INDUCED HYPOGLYCEMIA RESCUE IN ADULTS WITH T1D: A PHASE 3 MULTI-CENTER, RANDOMIZED, CONTROLLED, SINGLE BLIND, 2-WAY CROSSOVER STUDY TO EVALUATE EFFICACY AND SAFETY	
IND:	115091
EudraCT Number:	2018-002661-19
Project phase:	Phase 3
Compounds:	Xeris G-Pen (glucagon injection) Novo GlucaGen® Hypokit® (glucagon for injection)
Objectives:	The primary objective of this study is to demonstrate that G-Pen 1 mg (test) is not inferior to GlucaGen Hypokit (glucagon, Novo Nordisk) 1 mg (reference), in Type 1 diabetic (T1D) subjects in a state of insulin-induced hypoglycemia. The secondary objective of this study is to evaluate the safety and tolerability of G-Pen 1 mg versus GlucaGen Hypokit 1 mg in the study population.
Endpoints:	The study objectives will be assessed by the comparison of the two study drugs for the following primary and secondary endpoints: **Primary:** For the primary endpoint, groups will be compared for rates of achieving a positive plasma glucose response, defined as either a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) or an increase in plasma glucose concentration > 20 mg/dL (>1.11 mmol/L) within 30 minutes of study drug injection. **Secondary:** For the secondary endpoints, groups will be compared based on each of the following: 1. Rate of achieving a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) within 30 minutes from injection of study drug. 2. Rate of achieving an increase in plasma glucose concentration ≥ 20 mg/dL (≥1.11 mmol/L) within 30 minutes from injection of study drug. 3. Rates of positive symptomatic response, defined as relief of neuroglycopenic symptoms within 30 minutes from a decision to dose. 4. Rates of positive treatment response, defined as exhibiting either a positive plasma glucose response *or* a positive symptomatic response. 5. Time to a positive plasma glucose response from injection of study drug.

	6. Time to administer study drug from a decision to dose. 7. Pharmacodynamic (PD) characteristics of mean plasma glucose concentration (0 to 90 minutes post-dose), maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration versus time curve from time 0 to 90 minutes ($AUC_{(0-90)}$), and area under the concentration versus time curve from time 0 to 180 minutes ($AUC_{(0-180)}$). 8. Time to (a) initial relief and (b) complete resolution of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose. 9. Time to resolution of the overall feeling of hypoglycemia from a decision to dose. 10. Safety endpoints, including: adverse event (AE)/serious adverse event (SAE) rates, and changes in vital signs, laboratory variables, and physical exam/electrocardiogram (ECG) findings. 11. Tolerability endpoints, including: Draize scale scores for injection site erythema and edema as assessed by the investigator, and injection site discomfort and duration as assessed by subject questionnaire responses.
Study design:	This is a multi-center, randomized, active-controlled, single-blind, two-way crossover efficacy and safety inpatient study in adult subjects with T1D. The study will involve two daytime visits at a clinical research center (CRC) or comparable setting, scheduled 7 to 28 days apart. Subjects will be randomly assigned to receive G-Pen glucagon 1 mg during one period and GlucaGen Hypokit 1 mg during the other period.
Study location:	Approximately 8 clinical research centers in North America and Europe.
Study duration:	The estimated duration of study participation for each individual subject is approximately 4 weeks. The estimated duration of the entire study is 8 months.
Sample size:	It is anticipated that approximately 200 subjects will be screened for this study to achieve 122 randomized subjects and a goal of 111 subjects who are evaluable for treatment both periods.
Subjects:	The study will include male and female subjects with T1D between the ages of 18 and 75 years, inclusive, at Screening.
Inclusion Criteria:	1. Males and females diagnosed with T1D for at least 24 months. Women of childbearing potential require a negative urine pregnancy test and must use medically accepted contraception throughout the study and for 7 days after the last dose of study drug. Nursing mothers will be allowed to participate in the study. However, breast feeding during the inpatient study visits (Visits 2 and 3) and for 48 hours after each dose of study drug is not allowed. 2. Current usage of daily insulin treatment that includes having an assigned "correction factor" for managing hyperglycemia.

	3. Age 18 to 75 years, inclusive. 4. Random serum C-peptide concentration < 0.6 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 and dated informed consent form (ICF) completed before any trial-related activities occur.
Exclusion Criteria:	1. Pregnancy 2. Glycated hemoglobin (HbA1c) > 10% at Screening. 3. Body mass index (BMI) > 40 kg/m^2. 4. Renal insufficiency (serum creatinine greater than 3.0 mg/dL) or Stage 2 or greater kidney failure. 5. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) equal to or greater than 3 times the upper limit of normal. 6. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL. 7. Hematocrit $\leq$ 30%. 8. Blood pressure (BP) readings at Screening where systolic blood pressure (SBP) < 90 or > 150 mm Hg, and diastolic blood pressure (DBP) < 50 or > 100 mm Hg. 9. Clinically significant ECG abnormalities. 10. Use of total insulin dose per day > 2 U/kg. 11. Inadequate venous access. 12. Congestive heart failure, New York Heart Association (NYHA) class II, III or IV. 13. History of myocardial infarction, unstable angina, or revascularization within the past 6 months. 14. History of a cerebrovascular accident or with major neurological deficits. 15. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. Any history of breast cancer or malignant melanoma will be exclusionary. 16. Major surgical operation within 30 days prior to Screening. 17. History of or current seizure disorder (other than with suspect or documented hypoglycemia). 18. Current bleeding disorder, treatment with warfarin, or platelet count below 50×10^9 per liter. 19. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (multiple endocrine neoplasia type 2 [MEN 2], neurofibromatosis, or Von Hippel-Lindau disease). 20. History of insulinoma. 21. 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 (dimethyl sulfoxide [DMSO] and trehalose) in the investigational formulation.

	22. History of glycogen storage disease. 23. Subject tests positive for human immunodeficiency virus [HIV], hepatitis C virus [HCV], or hepatitis B virus [HBV] infection (hepatitis B surface antigen positive [HBsAg+]) at Screening. 24. Active substance or alcohol abuse (more than 21 drinks per week for male subjects or 14 drinks per week for female subject). 25. Administration of glucagon within 7 days of Screening. 26. 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. 27. Any other reason the Investigator deems exclusionary.
Study Methods:	Subjects will complete the screening procedures to determine eligibility up to 30 days before enrollment into the treatment period and administration of study drug. Subjects not meeting eligibility criteria may be rescreened 30-days after an initial screen failure. A single re-screen is permitted, and this re-screen is only permissible if the reason for the prior screen failure was for laboratory measurements. Blood for clinical laboratory tests can be redrawn after a 30-day wait; however, other screening procedures do NOT need to be repeated. If the new clinical laboratory test results meet eligibility, the subject may be dosed. Otherwise, the subject is not eligible for dosing or further re-screening. The evening prior to each inpatient study visit, subjects with confirmed plasma glucose not greater than 350 mg/dL (19.44 mmol/L) will be admitted for an overnight stay between 6 and 8 pm. Subjects will be provided a standardized dinner and will continue their usual insulin regimen per PI discretion. At the Investigator's discretion, subjects may receive a standardized snack before midnight the day before treatment. Subjects will be instructed to fast after midnight. If site staffing allows for appropriate oversight, an intravenous (IV) catheter will be placed, and maintenance fluids will be administered. Otherwise, the subject's own infusion pump will be used overnight. The subject's plasma glucose will be monitored overnight, and glucose (IV or oral tablets) and/or insulin (IV or subcutaneous [SC]) will be administered as necessary to maintain plasma glucose within a recommended target range of 80 to 150 mg/dL (4.44 to 8.34 mmol/L). Overnight glucose measurements outside of this recommended range will not be considered protocol deviations. At a minimum, glucose will be assessed by BGM or YSI (not CGM) at midnight, 3 am, and 6 am, with ±30 minutes for these measurements, which will be entered into the EDC. Subjects will continue to fast the morning of the procedure and an IV catheter for blood sampling will be inserted, ideally in the antecubital fossa of the arm. The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow and achieve "arterialized" samples. Subjects will be kept supine and covered under a blanket to maintain warmth. The subject will be eligible to begin the baseline euglycemic steady state period when their plasma glucose is confirmed to be within the range of 70 to 270 mg/dL (3.89 to 15.0 mmol/L). IV insulin will be administered to maintain the plasma glucose within the range of 75 to 115 mg/dL (4.17 to 6.38 mmol/L) for 30 minutes. If the plasma glucose has been maintained within the range of 75 to 115 mg/dL (4.17 to 6.38 mmol/L) for at least 30 minutes, and the insulin infusion rate varies no more than ±20%, the induction procedure may commence.

Eligible subjects will enter a state of insulin-induced hypoglycemia in a gradual and controlled fashion, through a monitored, standardized induction protocol.

During the baseline phase, plasma glucose measurements will be taken every 15 minutes. During the induction phase, plasma glucose measurements will be taken every 10 minutes while glucose is > 80.0 mg/dL (> 4.44 mmol/L) and at 5-minute intervals once plasma glucose is ≤ 80.0 mg/dL (≤ 4.44 mmol/L).

Once the initial plasma glucose measurement < 54.0 mg/dL (< 2.78 mmol/L) is achieved, the IV insulin infusion will be returned to the rate established at the end of the baseline euglycemia steady state period. After 5 minutes, the IV insulin infusion will be stopped, and a confirmatory plasma glucose reading will be taken to determine whether a hypoglycemic steady state has been reached, which is defined as a plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L) and < 54 mg/dL (< 2.78 mmol/L) with an 8-minute linearly extrapolated value for plasma glucose ≥ 42 mg/dL (≥ 2.33 mmol/L).

If the subject is not in a hypoglycemic steady state, plasma glucose should be rechecked at up to two subsequent 5-minute intervals. If the second or third confirmatory glucose is ≥ 42 mg/dL (≥ 2.33 mmol/L) and < 54 mg/dL (< 2.78 mmol/L) with an 8-minute linearly extrapolated value for plasma glucose ≥ 42 mg/dL (≥ 2.33 mmol/L), the subject will be deemed to be within a hypoglycemic steady state.

After the third confirmatory reading, if plasma glucose is < 42 mg/dL (<2.33 mmol/L), the procedure will be terminated, study glucagon will NOT be administered, and the visit will be rescheduled after a minimum 3-day wait.

If plasma glucose is > 54 mg/dL (>2.78 mmol/L) at any of the 3 confirmatory readings, IV insulin will be restarted at the rate used prior to the initial plasma glucose < 54 mg/dL being obtained.

When a state of stabilized insulin-induced hypoglycemia is verified, subjects will be administered the randomly assigned dose of either G-Pen glucagon 1 mg SC or GlucaGen Hypokit 1 mg SC to the abdomen, around the umbilicus at a 90º angle to the skin.

Study drug will not be prepared ahead of time. Rather, preparation of glucagon for administration will begin once the confirmatory plasma glucose reading is obtained, i.e., upon a "decision to dose."

After administration of study drug, plasma glucose will be monitored at 5-minutes intervals for 90 minutes, and afterwards every 30 minutes through 180 minutes posttreatment.

The induction procedure may elicit symptoms of hypoglycemia. Therefore, subjects will complete a questionnaire regarding hypoglycemia symptoms at the start of the hypoglycemia induction period and periodically through180 minutes posttreatment.

After 180 minutes posttreatment, subjects will resume insulin pump therapy, if applicable, and will be given a meal. Subject may be discharged after 180 minutes posttreatment if their plasma glucose is > 100 mg/dL (5.56 mmol/L) and if medically stable. At the Investigator's discretion, subjects' prescribed insulin regimen can be restarted, or the meal can be given sooner, but not earlier than 90 minutes post-glucagon treatment, to prevent hyperglycemia or rebound hypoglycemia.

After a wash-out period of 7 to 28 days, subjects will return to the CRC and the study procedures will be repeated with each subject crossed over to the other treatment. After study-related procedures are performed on each of the treatment days, subjects will be discharged. A Follow-Up Visit will be

	conducted 2 to 7 days after administration of the final dose of study drug as a safety check. Tolerability will be assessed by comparing AE reports between the G-Pen and GlucaGen Hypokit treatment groups. In addition, at the end of each treatment period the subjects will complete questionnaires to assess injection site discomfort, and the Investigator will use a modified Draize scale to evaluate the injection sites after each administration.
Data management and statistical analysis:	Data will be entered into an electronic Case Report Form (eCRF) by the study site personnel. Data will be monitored at on-site visits by Xeris personnel or by a contract research organization (CRO) delegated by Xeris. A stand-alone Statistical Analysis Plan (SAP) will be written to detail all protocol specified analyses. The SAP will take precedence over the protocol. The primary endpoint will be analyzed using an exact test procedure based on the conditional distribution for a maximum clinically acceptable non-inferior margin of ≤5%.
Sample Size Determination:	For the primary analysis, a failure is recorded if the subject's plasma glucose fails to reach a concentration >70 mg/dL (>3.88 mmol/L) *and* fails to increase by at least 20.0 mg/dL (1.11 mmol/L) within 30 minutes of the decision to administer the dose of glucagon. The determination of a constant clinically non-inferior margin for the cure rate difference is generally difficult in practice for a number of reasons. To alleviate this concern, it has been recommended to use an Odds Ratio of success rates for estimation because the corresponding clinically non-inferior margin on the difference scale is getting small when the underlying success rate becomes large and close to 1. In this study, it is expected that the subject's recovery (success rate) will be high and approaching 100%. Since this is a cross-over design and each subject will serve as his/her control, power is improved. The sample size was derived for 80% power of detecting non-inferiority with respect to the Odds Ratio of subject recovery rates at an alpha of 0.025 under a cross-over design. Based on an underlying Odds Ratio of 1.0, and failure rates of 0.2 versus 0.25, 111 subjects are required for the study. With an anticipated 10% drop-out rate, the total sample size for the study is 122 randomized subjects.

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

TABLE OF CONTENTS

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

Abbreviation	Definition
AE	adverse event
ADA	American Diabetes Association
AI	Auto-injector
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{(0-90)}$	area under the concentration versus time curve from time 0 to 90 minutes
$AUC_{(0-180)}$	area under the concentration versus time curve from time 0 to 180 minutes
$AUC_{(0-240)}$	area under the concentration versus time curve from time 0 to 240 minutes
BE	bioequivalence
β-hCG	beta-human chorionic gonadotrophin
BMI	body mass index
BP	blood pressure
CDC	United States Center for Disease Control
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CRF	Case Report Form
CRC	clinical research center
CRO	contract research organization
DBP	diastolic blood pressure
DMSO	dimethyl sulfoxide
ECG	electrocardiogram
EC_{50}	concentration at which a 50% effect is observed
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
GEK	glucagon emergency kits
GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GMP	Good Manufacturing Practice
HbA1c	glycated hemoglobin
HBsAg(+)	hepatitis B surface antigen (positive)
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HIVab	human immunodeficiency virus antibody
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IFU	instructions for use
IM	intramuscular
IND	Investigational New Drug Application
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intra-uterine device
IV	Intravenous(ly)
IWRS	Interactive Web-based Randomization System
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	multiple endocrine neoplasia type 2
min	minute
NDA	New Drug Application
NYHA	New York Heart Association
OTC	over the counter

Abbreviation	Definition
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
QA	Quality Assurance
RBC	red blood cells
rDNA	recombinant deoxyribonucleic acid
RLD	reference listed drug
RTU	ready-to-use
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	Subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedures
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
t_{max}	time to maximum observed concentration
T1D	type 1 diabetes mellitus/type 1 diabetic
T2D	type 2 diabetes mellitus/type 2 diabetic
U.K.	United Kingdom
US	United States
USP	United States pharmacopeia
VAS	visual analog scale
WBC	white blood cells
Xeris	Xeris Pharmaceuticals, Inc.
YSI	Yellow Springs Instruments

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

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

5.2. Secondary Objective

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

5.3. Endpoints

5.3.1. Primary Endpoint

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

5.3.2. Secondary Endpoints

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

1. Rate of achieving a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) within 30 minutes from injection of study drug.
2. Rate of achieving an increase in plasma glucose concentration $\geq$ 20 mg/dL ($\geq$1.11 mmol/L) within 30 minutes from injection of study drug.
3. Rates of positive symptomatic response, defined as relief of neuroglycopenic symptoms within 30 minutes from a decision to dose.
4. Rates of positive treatment response, defined as exhibiting either a positive plasma glucose response *or* a positive symptomatic response.
5. Time to a positive plasma glucose response from injection of study drug.
6. Time to administer study drug from a decision to dose.
7. Pharmacodynamic (PD) characteristics of mean plasma glucose concentration (0 to 90 minutes post-dose), maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration versus time curve from time 0 to 90 minutes ($AUC_{(0-90)}$), and area under the concentration versus time curve from time 0 to 180 minutes ($AUC_{(0-180)}$).
8. Time to (a) initial relief and (b) complete resolution of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose.
9. Time to resolution of the overall feeling of hypoglycemia from a decision to dose.
10. Safety endpoints, including: adverse event (AE)/serious adverse event (SAE) rates, and changes in vital signs, laboratory variables, and physical exam/electrocardiogram (ECG) findings.

11. Tolerability endpoints, including: Draize scale scores for injection site erythema and edema as assessed by the investigator, and injection site discomfort and duration as assessed by subject questionnaire responses.

6. BACKGROUND AND RATIONALE

6.1. Indication

The proposed indication is for the treatment of severe hypoglycemia.

6.1.1. Background

The investigational product is glucagon. Glucagon is a 29 amino-acid polypeptide with a molecular weight of 3485 Daltons. The peptide is secreted by the alpha cells of the islets of Langerhan's in the pancreas, and functions as an anti-hypoglycemic agent and a gastrointestinal motility inhibitor. A single glucagon gene encodes a larger proglucagon biosynthetic precursor in mammals. Tissue-specific processing of proglucagon gives rise to glucagon, and to glicentin, oxyntomodulin, glucagon-like peptide-1 (GLP-1), and glucagon-like peptide-2 (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 a concentration at which a 50% effect is observed (EC_{50}) of ~ 1 nM [Wakelam].

Historically glucagon is being used as rescue therapy for severe hypoglycemia. One of the main complications of diabetes treatment with insulin is the emergence of hypoglycemia, and the absolute or relative excess of therapeutic insulin is the determinant of risk. Hypoglycemia in diabetes is defined by the American Diabetes Association (ADA) as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm" [ADA], and presents as diaphoresis, pallor, nausea, palpitations, tremors, and anxiety. If hypoglycemia becomes severe, symptoms may then include confusion, abnormal behavior, blurred vision, psychomotor abnormalities, loss of consciousness, seizures, and coma [DCCT/EDIC) Study Research Group]. Recent reports have found that from 6% to 10% of deaths of patients with type 1 diabetes mellitus (T1D) are attributable to hypoglycemia [Skrivarhaug, U.K. Hypoglycaemia Study Group]. The 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 T1D, and progressively more frequently over time in type 2 diabetes mellitus (T2D). The U.K. Hypoglycemia Study Group reported an incidence of 110 severe hypoglycemic episodes per 100 patient-years in patients with T1D treated with insulin for < 5 years, and an incidence of 320 episodes per 100 patient-years in those with T1D 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 T2D typically have several hypoglycemic episodes in a given year, one to two of these being severe episodes. There are currently approximately 1.4 million T1D patients and 3.8 million insulin-using T2D patients in the United States (US), as reported by the US Center for Disease Control [CDC]. On average, the total insulin-using patient population experiences about 3 million severe hypoglycemic events per year.

The ADA recommends that all insulin- and sulfonylurea-using diabetics carry glucagon emergency kits (GEKs) and use glucagon as first line therapy in the event of a severe hypoglycemic event [ADA]. However, a recent survey indicates that only approximately 30% of the insulin-using diabetic patients carry GEKs [Close Concerns]. The current standard of care for severe hypoglycemia is an injection of glucagon. Administration of glucagon with current products (i.e. Lilly Glucagon for Injection, and Novo GlucaGen®) is a 9-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose [Glucagon, Novo GlucaGen].

6.1.2. Rationale

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

In response to the unmet medical need for a simple and ready-to-use (RTU) glucagon for episodes of severe hypoglycemia, Xeris Pharmaceuticals, Inc. (Xeris) is developing a glucagon rescue pen referred to as "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, which include the following: a RTU treatment with no reconstitution required; precise and rapid dosing; a hidden needle; enhanced portability and availability due to room-temperature stability, providing 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 (recombinant deoxyribonucleic acid [rDNA] origin) was approved in 1998 and is currently the drug substance identified in two approved New Drug Applications (NDAs) ([NDA 20-928] and [NDA 20-918]). Complete NDA-required pharmacology and toxicology data have been reviewed and accepted by the United States Food and Drug Administration (FDA), as described in Lilly Glucagon (glucagon for injection) and Novo GlucaGen (glucagon for injection) labeling [Glucagon, Novo GlucaGen]. Novo GlucaGen Hypokit 1 mg is sold in the U.K. and European Union (EU) under marketing authorization PL 04668/0027, and pharmacology and toxicology information have been submitted to and accepted by European Medicines Agency (EMA) [Novo Hypokit].

As Xeris G-Pen drug product is produced by solid-phase peptide synthesis (SPPS), which also conserves the glucagon peptide sequence, the rDNA glucagon information is pertinent to the development of G-Pen for the treatment of severe hypoglycemia. A summary of this information can be found in current G-Pen Investigator's Brochure, which is 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 (PK), and toxicology of G-Pen (glucagon injection) is provided in the current G-Pen Investigator's Brochure.

6.3. Description and Composition of Drug Product

Synthetic glucagon is the drug substance in G-Pen. Glucagon current Good Manufacturing Practice (GMP) grade drug product is manufactured, packaged and released by Bachem AG (Bubendorf, Switzerland), conforms with United States pharmacopeia (USP) standards and has a Type II Drug Master File filed with the FDA. G-Pen is a sterile subcutaneous (SC) injectable non-aqueous formulation of glucagon for treatment of severe hypoglycemia. G-Pen delivers 1 mg of glucagon, with trehalose and dimethyl sulfoxide (DMSO) as excipients. The drug product is stored at controlled room temperature (20 to 25°C [68° to 77°F]) prior to use.

G-Pen is supplied in a 1 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 EU and is currently marketed by Eli Lilly & Co. in the US and Canada as Glucagon (Glucagon Injection [rDNA origin]), and by Novo Nordisk in the US, Canada, and EU as GlucaGen® HypoKit®, both reference listed drugs (RLD) at a dose of 1 mg per injection 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 since it was first approved for use in humans in 1960 [FDA CDER #2].

Xeris has completed eight clinical studies using G-Pen, which include the following: A Phase 1 bioequivalence study of G-Pen auto-injector (Configuration A) and G-Pen manual syringe (Configuration B), 4 Phase 2 exploratory studies, a Phase 3 study in pediatric subjects with T1D, and 2 Phase 3 studies in adults with T1D.

Phase 1 Study XSGP-101 was a randomized, open-label, two-way crossover bioequivalence (BE) and safety study in healthy subjects. The study involved two treatment visits scheduled 3 to 7 days apart. Subjects were randomly assigned to a treatment sequence to receive G-Pen glucagon 1 mg SC via Configuration A (auto-injector [AI]) or Configuration B (prefilled syringe [PFS]). Both configurations were administered to the abdomen around the umbilicus. Each treatment visit was preceded by an overnight stay in the clinical study center. PK analyses performed on plasma glucagon area under the concentration versus time curve from time 0 to 240 minutes ($AUC_{(0\text{-}240)}$) and maximum observed concentration (C_{max}) in healthy subjects administered Xeris glucagon 1 mg SC in the abdomen via Configuration A and Configuration B satisfied the bioequivalence (BE) test criterion and established PK bioequivalence. Pharmacodynamic (PD) analyses performed on plasma glucose $AUC_{(0\text{-}240)}$, C_{max}, and time to maximum observed concentration (t_{max}) in healthy subjects administered Xeris glucagon 1 mg SC in the abdomen via Configuration A and Configuration B satisfied the BE test criterion and established PD bioequivalence. Overall, Configuration A and Configuration B administrations

were generally safe and well tolerated; safety findings were generally similar between the two administration groups.

Phase 2 safety/efficacy Study XSGP-201 demonstrated that a 1 mg SC injection of Glucagon RTU was therapeutically equivalent to Lilly Glucagon for Injection 1 mg, when administered to healthy subjects. There were no serious adverse events (SAEs) and adverse events (AEs) were generally mild in nature and similar to the known effects of rescue doses of glucagon. The most commonly reported AE was injection site pain, the incidence of which was significantly higher in the Xeris 0.5 mg and Xeris 1 mg groups compared with the Lilly Glucagon 1 mg group. However, edema and erythema at the injection site occurred infrequently and did not vary significantly with treatment.

Phase 2 Study XSGP-202 was an open-label crossover study in adult T1D subjects that explored the use of Glucagon RTU at doses of 0.5 and 1 mg in the treatment of insulin-induced hypoglycemia. All subjects had a positive response with complete resolution of symptoms by 30 minutes after injection for both treatments. AEs were generally mild and corresponded to known effects of rescue doses of glucagon. A single episode of vasovagal syncope was observed approximately 2 ¼ hours after treatment, which the investigator deemed to meet the definition of an SAE as an important medical event. The attending investigator felt this event was attributable at least in part to the study procedures, which included a post-study meal that was consumed about 90 minutes after treatment. There were no other clinically significant safety findings I this study.

Phase 2 Study XSGO-201evaluated micro-doses of Glucagon RTU administered with an OmniPod® infusion pump and equivalent doses of reconstituted GlucaGen in T1D subjects. Micro-doses of Glucagon RTU (0.3 to 2.0 µg/kg) demonstrated comparable PK and efficacy to GlucaGen as discrete SC infusions with an OmniPod pump. All treatments were well tolerated, no SAEs were observed with either product and AEs were generally of mild severity. Well-defined erythema and edema were the two most common adverse events and they occurred more frequently with Glucagon RTU. Most observations of edema and erythema were mild and transient.

Phase 2 Study XSMP-202 compared the safety and efficacy of oral glucose tablets to mini-doses (0.15 and 0.3 mg) of Xeris Glucagon RTU SC administered to T1D subjects as treatment/prevention of mild to moderate hypoglycemia. A total of 20 subjects between the ages of 18 and 64 years were randomized in this 3-week, 2-period cross-over study with a 3-week follow-up period during which subjects had free choice of using either Glucagon RTU or glucose tablets to treat/prevent hypoglycemia. Glucagon RTU successfully treated mild-to-moderate hypoglycemia and may be a useful alternative to treatment with oral carbohydrate. All treatments were well tolerated, no SAEs were observed and AEs were generally of mild severity and consisted primarily of pain or tingling at the injection site. Observations of edema and erythema were generally mild and transient. Nausea occurred only at the higher dose of 0.3 mg, in one-third of the subjects.

Phase 3 Study XSGP-301 was a non-inferiority, randomized, single-blind, 2-way crossover comparative efficacy and safety trial in adult subjects with T1D. The study demonstrated that G-Pen 1 mg SC was comparable to Lilly Glucagon via an intent-to-treat analysis. The study demonstrated that administration of G-Pen and Lilly Glucagon either increased plasma glucose ≥ 20 mg/dL at 30 minutes post-injection or resulted in a plasma glucose > 70 mg/dL within 30

minutes post-injection. Symptomatic relief of hypoglycemia after glucagon injections was similar for G—Pen compared with Lilly Glucagon, based on the trends observed across average hypoglycemia symptom questionnaire scores. Symptom scores did not differ significantly between treatment groups for average autonomic, neuroglycopenic, or overall symptoms. As expected for both Glucagon RTU and Lilly glucagon, as plasma glucose levels increased, mean hypoglycemia symptom scores decreased with peak symptom relief occurring approximately 30 minutes post injection. G-Pen injections to the abdomen around the umbilicus demonstrated faster absorption when compared to injections to the outer arm and outer leg. Both G-Pen and Lilly Glucagon were generally safe and well tolerated and safety findings were generally similar between the two treatment groups. The most common treatment-emergent adverse event (TEAE) was nausea, which was reported more frequently for subjects after G-Pen treatment compared with Lilly Glucagon.

Phase 3 Study XSGP-303 was a non-inferiority, randomized, single-blind, 2-way crossover comparative efficacy and safety study in adult subjects with T1D. The study demonstrated that G-Pen 1 mg SC was non-inferior to Lilly Glucagon via an intent-to-treat analysis. Overall, this study further supports the conclusion that G-Pen 1 mg SC reverses severe hypoglycemia in a reliable manner that is comparable to Lilly Glucagon 1 mg; and confirmed the results for Symptomatic relief of hypoglycemia after glucagon injection reported in Study XSGP-301. Both G-Pen and Lilly Glucagon treatments were generally safe and well tolerated and safety findings were generally similar between the two treatment groups. There were no SAEs or severe AEs reported in either treatment group. The most common TEAE was nausea, which was reported more frequently in subjects administered G-Pen compared to Lilly Glucagon.

Phase 3 Study XSGP-302 was an efficacy and safety study in pediatric subjects with T1D that evaluated PK and PD. The study included subjects age 2 to < 18 years administered G-Pen 0.5 mg, with subjects age 12 to < 18 years also receiving G-Pen 1 mg after a wash-out period. Statistically significant increases from baseline in mean plasma glucose were observed in each age category ($p<0.001$ for all groups) at 30 minutes after administration of G-Pen. Based on the results of the XSGP-201 study, the transition to the adult dose of G-Pen (0.5 mg to 1 mg) is recommended at 40 to 45 kg, corresponding to the average weight at approximately 12 years of age. Age categories were generally similar with respect to in mean plasma glucose area under the concentration vs time curve from time 0 to 90 minutes ($AUC_{(0-90)}$), C_{max}, and t_{max}. Overall, G-Pen was generally safe and well tolerated in each of the 3 pediatric age groups. There were no AEs leading to discontinuation and no SAEs were reported in this study. Nausea and vomiting were the most commonly reported treatment-emergent adverse events (TEAEs) in this study and were expected for subjects receiving glucagon. While the incidences of injection site discomfort, erythema, and edema were relatively high (at 10 and 30 minutes post G-Pen administration), pain and modified Draize Scale scores were at the low end of the assessment scales.

7. STUDY DESIGN

7.1. Study Overview

This is a multi-center, randomized, active-controlled, single-blind, two-way crossover efficacy and safety in-patient study in subjects with T1D. The study involves two clinical research center (CRC) visits scheduled 7 to 28 days apart. Subjects will be randomly assigned to a treatment sequence for which they will receive G-Pen glucagon 1 mg during one period and GlucaGen Hypokit 1 mg during the other. Each daytime visit will be preceded by an overnight stay in the CRC. Subjects will complete the screening procedures up to 30 days before randomization to determine their eligibility before enrollment into the treatment phase. Subjects not meeting eligibility criteria may be rescreened after a 30-day wait.

During the evening prior to each in-patient study visit, subjects will be admitted for an overnight stay between 6 and 8 pm. At the Investigator's discretion, plasma glucose may be assessed periodically during the overnight stay via CGM, Yellow Springs Instruments (YSI) model 2300 or 2900 or an FDA/CE/Health Canada cleared blood glucose meter (hereafter, simply "glucose meter"). Subjects will be asked to refrain from consuming alcohol during the day prior to the overnight stay. Upon arrival in the evening, plasma glucose will be measured by a blood glucose meter and confirmed to be ≤ 350 mg/dL (≤ 19.44 mmol/L), or the visit will be rescheduled.

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

Subjects will be instructed to fast starting at midnight, at which point an intravenous (IV) catheter will be placed, and maintenance fluids will be administered. Overnight, blood glucose will be confirmed by YSI. BGM or CGM as necessary; these data will be maintained in the source documents only. At a minimum, blood glucose will be assessed by BGM/YSI (not CGM) at midnight, 3 am, and 6 am, with ±30 minutes for these measurements, which will be entered into the EDC.

After midnight, the Investigator should optimize plasma glucose within a target range of 80 to 150 mg/dL (4.44 to 8.33 mmol/L) through the administration of IV/SC insulin and/or IV/oral glucose. If operational considerations at a site preclude IV administration of insulin overnight, no catheter will be placed, and oral glucose tablets and the subject's own insulin infusion pump will be used to optimize blood glucose within a target range of 80 to 150 mg/dL (4.44 to 8.33 mmol/L). This range is considered a target only, and values outside of this range will not be considered protocol deviations.

In the morning of the inpatient study visit, each subject's plasma glucose will be measured and verified to be within the range of 70 to 270 mg/dL (3.89 to 15.0 mmol/L) to confirm their eligibility for continuation to the insulin induction procedure. If this criterion is not met, the visit will be rescheduled after a minimum 3 day wait.

Subjects will continue to fast during the morning of the procedure and another IV catheter for blood sampling will be inserted in their contralateral arm. Ideally, the sampling IV catheter should be placed in a vein within the antecubital fossa. The hand used for blood sampling will be kept warm by use of a heated-hand box to increase blood flow to achieve "arterialized"

samples. The subject will be kept supine and the abdomen and torso will be covered under a blanket to maintain warmth.

The baseline euglycemic steady state period will begin when the plasma glucose is confirmed to be within the range of 70 to 270 mg/dL (3.89 to 15.0 mmol/L). IV insulin will be administered to maintain the plasma glucose concentration within the range of 75 to 115 mg/dL (4.17 to 6.83 mmol/L) for 30 minutes. If the plasma glucose has been maintained within the range of 75 to 115 mg/dL (4.17 to 6.83 mmol/L) for at least 30 minutes and the insulin infusion rate varies no more than ±20%, the induction procedure may commence.

During the induction procedure, the subject will enter a state of hypoglycemia through the administration of regular insulin diluted in normal saline (see Section 7.2), within a controlled and monitored setting. Use of the insulin dose adjustment algorithm will be facilitated by real time data capture, allowing Sponsor personnel to monitor the induction procedures virtually in real time.

The combination of one or more IV bolus doses of insulin along with continuous IV infusion of insulin will be used to gradually decrease a subject's plasma glucose to a target < 54.0 mg/dL (< 3 mmol/L). As per Section 11.2, all plasma glucose levels will be based on the average of two readings taken via YSI glucose analyzer at each time point. Plasma glucose measurements will be taken every 10±5 minutes while glucose is > 65.0 mg/dL (> 3.61 mmol/L) and every 5±2 minutes once plasma glucose is ≤ 65.0 mg/dL (≤ 3.61 mmol/L).

Once the initial plasma glucose measurement < 54.0 mg/dL (< 3 mmol/L) is achieved, the IV insulin infusion will be returned to the rate established at the end of the baseline euglycemia steady state period. After 5 minutes, the IV insulin infusion will be stopped, and up to three confirmatory plasma glucose readings will be taken at subsequent 5-minute intervals to determine whether a hypoglycemic steady state has been reached, which is defined as a confirmatory plasma glucose value ≥ 42 mg/dL (≥ 2.33 mmol/L) and < 54 mg/dL (< 3 mmol/L) with an 8-minute linearly extrapolated value for plasma glucose ≥ 42 mg/dL (≥ 2.33 mmol/L).

If a hypoglycemic steady state is not documented after any of three confirmatory readings, and plasma glucose is < 42 mg/dL (<2.33 mmol/L) after the third confirmatory reading, the procedure will be terminated, study glucagon will NOT be administered, and the visit will be rescheduled after a minimum 3-day wait. At the Investigator's discretion, the subject should be treated with IV glucose or oral carbohydrates, it should be verified that the subject achieved a euglycemic state and is medically stable prior to discharge.

If plasma glucose is > 54 mg/dL (>3 mmol/L) at any of the 3 confirmatory readings, IV insulin will be restarted at the 120% of the rate used prior to the initial plasma glucose < 54 mg/dL being obtained.

If a hypoglycemic state is verified by either the first, second, or third confirmatory reading, the subject will be eligible to receive either G-Pen or GlucaGen Hypokit in one of the randomized treatment sequences shown in Table 3. The time of the Investigator's "decision to dose" will be documented.

Table 3 Randomized Treatment Sequence

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

Plasma glucose levels will be monitored for 180 minutes post-dosing. It is believed that plasma glucose < 54 mg/dL (< 3 mmol/L) will be low enough to generate neuroglycopenic and autonomic symptoms in most subjects, yet high enough (i.e., > 42 mg/dL [> 2.33 mmol/L)]) to avoid the impairment of consciousness. Consequently, subjects will complete a questionnaire about symptoms of hypoglycemia [Nermoen] during the hypoglycemia induction phase, and for 180 minutes after treatment with glucagon.

After a wash-out period of 7 to 28 days, subjects will return to the CRC 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 (see Table 5), subjects will be discharged after consuming a meal as per each site's usual practice. A follow-up visit as a safety check will be conducted 2 to 7 days after administration of the final dose of study drug.

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

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. A predecessor study (XSGP-301), therefore, utilized a comparatively lower rate of insulin infusion at 1 to 2 times the normal basal rate, combined with push of an IV bolus dose of insulin derived from the subject's own self-reported glucose correction factor. About 30% of the procedures performed in Study XSGP-301 resulted in plasma glucose < 40 mg/dL (< 2.22 mmol/L). To get more precision in achieving a steady state of plasma glucose below 50 mg/dL (2.78 mmol/L), individual procedure data from the Study XSGP-301 were fitted to a model of insulin action allowing identification of opportunities for algorithm enhancements. The algorithm was modified accordingly and tested in the model of the procedures representing a broad spectrum of subjects, including the two extremes of insulin sensitivity that were associated with low plasma glucose in Study XSGP-303. The algorithm was further refined for use in the current study based on experiences in the XSGP-303 trial.

Hypoglycemia Induction Procedure

The evening before treatments subjects will be admitted to the CRC and follow the procedures described in Table 5.

Baseline Euglycemic Steady State

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

Induction Start

For the induction, the starting plasma glucose level will be determined as the average of the last three YSI measurements taken during the baseline steady state period (i.e., start of baseline, next after 15 minutes, end of baseline after 30-minute baseline confirmation period). The following procedures will then be performed:

1. Subjects will continue the IV insulin infusion at the final rate of the baseline euglycemic steady state.
2. Subjects then will be given an initial IV bolus push dose of regular insulin diluted in saline:
    a. The dose will be calculated as 75% of the dose estimated to reduce plasma glucose from the subject's starting plasma glucose level to 54 mg/dL (3 mmol/L) based on the subject's self-reported glucose correction factor. This dose will be referred to as "1 bolus (i.e., full bolus dose)" subsequently. The Investigator may use discretion to decrease the amount of the calculated bolus dose based upon the subject's insulin sensitivity factor. However, the Investigator is not allowed to increase the amount of the bolus dose.
    b. Plasma glucose will be measured every 5 to 10 minutes, depending on the current plasma glucose value (see Table 4).
    c. The first insulin adjustment will be made no earlier than 20 minutes after the initial bolus but will otherwise follow the directions for insulin adjustments shown in Table 4.

The Investigator may override the insulin dosing algorithm at their discretion. Note: investigator does not have discretion to give bolus doses once plasma glucose is 65 mg/dL (3.3 mmol/L) or less (see numbers 3.b.i and 4.b.i below).

When plasma glucose is > 80 mg/dL (> 4.44 mmol/L), insulin adjustments should not be made more frequently than every 10 minutes. When plasma glucose is ≤ 80 mg/dL (≤ 4.44 mmol/L), the minimum time between adjustments to decrease, terminate or re-start insulin is either 10 or 5 minutes, as indicated in Table 4.

1. While plasma glucose is > 80 mg/dL (> 4.4 mM/L):
    a. Measure plasma glucose every 10 minutes.
    b. When 10 minutes have passed from the last insulin dose adjustment:
        i. Bolus: If the rate of plasma glucose decrease is < 0.15 mg/dL·min (< 0.01 mM/min), then an additional 1 bolus (full bolus dose) should be administered.

ii. Infusion Rate: If the rate of plasma glucose decrease is < 0.5 mg/dL·min (< 0.03 mM/min), then the insulin infusion rate should be increased by 20%.

2. While plasma glucose is 66 to 80 mg/dL (3.66-4.4 mM/L):
    a. Measure plasma glucose every 5 minutes.
    b. When 10 minutes have passed from the last insulin dose adjustment:
        i. Bolus: If the rate of plasma glucose decrease is < 0.15 mg/dL·min (< 0.01 mM/min), then an additional 1/2 bolus (half-bolus dose) should be administered.
        ii. Infusion Rate:
            1) If the rate of plasma glucose decrease is < 0.33 mg/dL·min (< 0.02 mM/min), then the insulin infusion rate should be increased by 20%.
            2) If the rate of plasma glucose decrease is > 0.5 mg/dL·min (> 0.03 mM/min), then the insulin infusion rate should be decreased by 20%.
3. While plasma glucose is 61 to 65 mg/dL (3.39 to 3.61 mM):
    a. Measure plasma glucose at least every 5 minutes.
    b. When 10 minutes have passed from the last insulin dose adjustment:
        i. Bolus: not allowed.
        ii. Infusion Rate:
            1) If the rate of plasma glucose decrease is < 0.25 mg/dL·min (< 0.01 mM/min), then the insulin infusion rate should be increased by 20%.
            2) If the rate of plasma glucose decrease is > 0.33 mg/dL·min (> 0.02 mM/min), then the insulin infusion rate should be decreased by 20%.
4. While plasma glucose is 54 to 60 mg/dL (3 to 3.33 mM):
    a. Measure plasma glucose at least every 5 minutes.
    b. When 10 minutes have passed from last insulin adjustment:
        i. Bolus: not allowed.
        ii. Infusion Rate:
            1) If the rate of plasma glucose decrease is < 0.15 mg/dL·min (< 0.008 mM/min), then the insulin infusion rate should be:
                a. Increased by 20%, or

b. Set at 120% of the previous rate if the infusion was previously set at the baseline rate or decreased by 50%. Note: This escalation in rate can be performed every 5 minutes until the rate of decrease is > 0.15 mg/dL·hr (> 0.008 mM/hr)

3) If the rate of plasma glucose decrease is greater than 0.25 up to 0.33 mg/dL·min (>0.014 - 0.02 mM/min), then the insulin infusion rate should be decreased 20%.

4) If the rate of plasma glucose decrease is greater than 0.33 up to 0.50 mg/dL·min (>0.002 - 0.03 mM/min), then the insulin infusion rate should be decreased 50%.

5) If the rate of plasma glucose decrease is > 0.5 mg/dL·min (> 0.03 mM/min), then the insulin infusion rate should be stopped. After 5 minutes, the insulin infusion should be restarted at the rate used at the end of the baseline period.

5. If the plasma glucose is < 54 mg/dL (< 3 mM), then the IV insulin infusion should be returned to the baseline insulin infusion rate used at the end of the baseline period for 5 minutes, and then stopped.

Induction Termination

At any time, the induction procedure may be terminated at the Investigator's discretion. If the procedure is terminated, appropriate measures (oral or IV glucose) will be administered at the Investigator's discretion. If a subject exhibits signs of coma or convulsions, a IV bolus dose of dextrose will be given per standard of practice. Signs and symptoms should be monitored, and if the subject's condition fails to improve in a timely manner, additional dextrose or other medical interventions may be given at the Investigator's discretion.

Note: Study glucagon should NOT be administered as hypoglycemia rescue in this context.

Euglycemia will be confirmed and the subject should be medically stabilized per Investigator discretion before being released. The treatment visits should be rescheduled after a minimum 3-day wait.

If an SAE occurs during hypoglycemia induction, the procedure will end, and IV insulin will be safely withdrawn. Causality should be fully assessed by both the Investigator and the Sponsor.

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

Table 4 Insulin Dose Adjustments

Plasma Glucose		Measurement Interval (minutes)	Target Rate of Plasma Glucose Decrease	Insulin Bolus Criteria	Insulin Basal Rate Adjustment Criteria
(mg/dL)	(mmol/L)				
> 80	> 4.44	10	> 0.5 mg/(dL·min) (> 0.03 mM/min)	If plasma glucose ↓ < 0.15 mg/(dL·min) (< 0.01 mM/min); give 1 bolus	If plasma glucose ↓ < 0.5 mg/dL·min (< 0.03 mM/min), ↑ 20% (10 min)
66-80	3.66-4.44	5	0.33-0.5 mg/(dL·min) (0.02-0.03 mM/min)	If plasma glucose ↓ < 0.15 mg/(dL·min) (<0.01 mM/min); give ½ bolus	If plasma glucose ↓ < 0.33 mg/dL·min (< 0.02 mM/min), ↑ 20% (10 min)
					If plasma glucose ↓ > 0.5 mg/dL·min (> 0.03 mM/min), ↓ 20% (10 min)
61-65	3.39-3.61	5	0.25-0.33 mg/(dL·min) (0.014-0.02 mM/min)	Not allowed	If plasma glucose ↓ < 0.25 mg/dL·min (< 0.01 mM/min), ↑ 20% (10 min)
					If plasma glucose ↓ > 0.33 mg/dL·min (> 0.02 mM/min), ↓ 20% (10 min)
54-60	3-3.33	5	0.15-0.25 mg/(dL·min) (0.008-0.014 mM/min)	Not allowed	If plasma glucose ↓ < 0.15 mg/dL·min (<0.008 mM/min), ↑ 20% (10 min); or If insulin infusion rate was previously set to baseline or the insulin infusion rate was ↓ by 50%, then set new insulin infusion rate at 120% of the prior rate (5 min) Note: This escalation in rate can be performed every 5 minutes until the rate of decrease is > 0.15 mg/dL·hr (> 0.008 mM/hr)
					If plasma glucose ↓ >0.25 up to 0.33 mg/dL·min (>0.014-0.02 mM/min), ↓ insulin infusion rate 20% (10 min) If plasma glucose ↓ >0.33-0.50 mg/dL·min (>0.02 up to 0.03 mM/min), ↓ insulin infusion rate 50% (5 min) If plasma glucose ↓ > 0.5 mg/dL·min (>0.03 mM/min), Stop infusion; then set insulin infusion rate to baseline level (5 min)
< 54	< 3	5	0	Not allowed	Set to baseline level for 5 minutes, then Stop

↓=decrease, ↑=increase, min=minutes. [Note: if the plasma glucose decline is within the target range, keep the insulin infusion constant]

7.3. Interruption and Termination of Dosing

As described in Section 7.1 , administration of study glucagon is only permitted if a subject meets the criteria for a hypoglycemic steady state. Administration of study glucagon to a subject not in a hypoglycemic steady state will be deemed a major protocol violation.

At 30 minutes post-glucagon administration, if a subject fails to achieve an increase of plasma glucose of at least 20 mg/dL (1.11 mmol/L), appropriate measures (oral or IV glucose) will be taken at the Investigator's discretion.

Post-administration of study glucagon, if a subject exhibits signs of coma or convulsions, a IV bolus dose of dextrose will be given per standard of practice. Signs and symptoms should be monitored, and if the subject's condition fails to improve in a timely manner, additional dextrose or other medical interventions may be given at the Investigator's discretion.

Note: A second dose of study glucagon should NOT be administered as hypoglycemia rescue in this context.

Euglycemia will be confirmed and the subject should be medically stabilized per Investigator discretion before being released. If applicable, completion of a subsequent treatment visit will be at the discretion of the Investigator in consultation with the Medical Monitor.

8. ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

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

8.1. Inclusion Criteria

1. Males and females diagnosed with T1D for at least 24 months. Women of childbearing potential require a negative urine pregnancy test and must use medically accepted contraception throughout the study and for 7 days after the last dose of study drug. Nursing mothers will be allowed to participate in the study. However, breast feeding during the inpatient study visits (Visits 2 and 3) and for 48 hours after each dose of study drug is not allowed.
2. Current usage of daily insulin treatment that includes having an assigned "correction factor" for managing hyperglycemia.
3. Age 18 to 75 years, inclusive.
4. Random serum C-peptide concentration < 0.6 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 and dated informed consent form (ICF) completed before any trial-related activities occur.

8.2. Exclusion Criteria

1. Pregnancy
2. Glycated hemoglobin (HbA1c) > 10% at Screening.
3. Body mass index (BMI) > 40 kg/m^2.
4. Renal insufficiency (serum creatinine greater than 3.0 mg/dL) or Stage 2 or greater kidney failure.
5. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) equal to or greater than 3 times the upper limit of normal.
6. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL.
7. Hematocrit $\leq$ 30%.
8. Blood pressure (BP) readings at Screening where systolic blood pressure (SBP) < 90 or > 150 mm Hg, and diastolic blood pressure (DBP) < 50 or > 100 mm Hg.
9. Clinically significant electrocardiogram (ECG) abnormalities.
10. Use of total insulin dose per day > 2 U/kg.
11. Inadequate venous access.
12. Congestive heart failure, New York Heart Association (NYHA) class II, III or IV.

13. History of myocardial infarction, unstable angina, or revascularization within the past 6 months.
14. History of a cerebrovascular accident or with major neurological deficits.
15. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. Any history of breast cancer or malignant melanoma will be exclusionary.
16. Major surgical operation within 30 days prior to Screening.
17. History of or current seizure disorder (other than with suspect or documented hypoglycemia).
18. Current bleeding disorder, treatment with warfarin, or platelet count below 50×10^9 per liter.
19. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (multiple endocrine neoplasia type 2 [MEN 2], neurofibromatosis, or Von Hippel-Lindau disease).
20. History of insulinoma.
21. 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 and trehalose) in the investigational formulation.
22. History of glycogen storage disease.
23. Subject tests positive for human immunodeficiency virus [HIV], hepatitis C virus [HCV], or hepatitis B virus [HBV] infection (hepatitis B surface antigen positive [HBsAg+]) at Screening.
24. Active substance or alcohol abuse (more than 21 drinks per week for male subjects or 14 drinks per week for female subject).
25. Administration of glucagon within 7 days of Screening.
26. 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.
27. Any other reason the Investigator deems exclusionary.

8.3. Randomization

Subjects who meet all eligibility criteria, who reach the baseline euglycemia steady state, and who the Investigator deems appropriate to begin the induction procedure (see Section 10.2) at the first treatment visit will be randomized for the study. The randomization schedule will be produced by the Study statistician a priori for loading and implementing in the Interactive Web-based Randomization System (IWRS). Using a permuted random block assignment, stratified by site, subjects will be randomly assigned to receive either Treatment Sequence 1 (G-Pen → GlucaGen Hypokit) or Treatment Sequence 2 (GlucaGen Hypokit → G-Pen).

Once a subject has been randomized, information regarding the glucagon (G-Pen or GlucaGen Hypokit) to be administered to the subject at each of the treatment visits will be viewable by study staff in the Dose Administration form in the electronic data capture (EDC) system.

8.4. Subject Numbers

Subjects will be screened, and if eligible, enrolled and eventually randomized for the study. All screened subjects will be entered in the EDC. As each subject is added to the EDC system, they will be assigned a Screening number, which will consist of a unique 2-digit site code (starting with 01) and a unique 2-digit sequential number (starting with 01 at each site) indicating the sequence at which the subject was screened for eligibility. This Screening number will remain with the subject through enrollment and randomization, and will be considered their Subject identification (ID) if randomized into the study.

Subjects will be eligible for rescreening. 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 for laboratory-based eligibility after a 30 day wait. If this occurs, the subject will maintain the same Screening number, but will have all eligibility reviewed and reconfirmed prior to enrollment.

9. STUDY TREATMENTS

9.1. Allocation to Treatment

Subjects will be randomly assigned to one of the two treatment sequences to receive the blinded study drug (see Table 3). A total of 122 subjects will be randomized, with a goal of having an approximately equal number of subjects randomized to each of the two treatment sequences. If there are subjects who are enrolled, but fail to be randomized, compensatory enrollment may be utilized to achieve at least 122 subjects who are randomized for the study. Once a subject is randomized, the subject will be analyzed for the study. Each subject will receive a single SC injection to the abdomen around the umbilicus on each of the two treatment days, with a period of 7 to 28 days between treatment 1 and treatment 2.

9.2. Blinding

For this study, the subject but not the Investigator will be blinded (single-blind design). The G-Pen 1 mg device makes a series of two audible clicks when the dose is administered. To help ensure blinding, the subject will wear headphones that play music to mask sound during dosing procedures. The subject's ability to see the injection equipment and procedure will be obstructed by use of a blindfold placed prior to dosing. The subject will be instructed not to talk with the study staff about their impression of which product he/she received at a visit until the end of the second treatment sequence. At which time, the subject will be asked to guess what their first treatment was, and what their second treatment was from the choices of "Xeris Glucagon, G-Pen, administered by auto-injector" or "Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe". The subject's responses will be recorded in the electronic Case Report Form (eCRF) for the Subject Study Drug Assignment Questionnaire (see Appendix 5).

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

9.3. Drug Supplies

9.3.1. Drug Product Formulation and Packaging

Xeris G-Pen 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 to 25°C [68° to 77°F]) prior to use.

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

9.3.2. GlucaGen Hypokit for Injection

GlucaGen Hypokit (Novo Nordisk) will be purchased commercially and provided by Xeris. The glucagon will be stored at the CRC pharmacy according to labeled storage conditions.

9.3.3. Preparation, Dispensing and Administration

G-Pen will be supplied as 0.2 mL of non-aqueous solution in a plastic Crystal Zenith 1 mL long syringe loaded into a Molly disposable AI. Subcutaneous administration will be performed by a qualified CRC staff member who has read the written Instructions for Use provided by Xeris.

In the case of GlucaGen Hypokit, a new vial of lyophilized glucagon will be fully reconstituted immediately prior to abdominal administration using 1 mL of sterile diluent provided in the commercial kit as per the GlucaGen Hypokit Summary of Product Characteristics (SmPC) and Prescribing Instructions [Novo Hypokit].

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

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

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

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

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

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

9.3.4. Drug Storage and Drug Accountability

Unless notified otherwise by the Sponsor, all supplied G-Pen auto-injectors and GlucaGen Hypokit kits are to be stored at controlled room temperature (20°C to 25°C [68° to 77°F]). Excursions between 15° and 30° C (59° and 86 °F) that are experienced in pharmacies, hospitals,

and warehouses, and during shipping are allowed. Drug solution should be clear and of a water-like consistency at time of use.

The Investigator or an approved member of the study staff will ensure that the study drugs 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 an appropriate course of action taken, regarding the future use of the study drugs, upon consultation with Xeris.

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

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

9.4. Concomitant Medications

All subjects must be questioned about concomitant medications at each visit. Medications taken within 4 weeks before Day 1 will be documented in the eCRF. Any changes to a subject's concomitant medication regimen after the first treatment on Day 1 will also be documented in the eCRF.

Except for those medications (e.g., warfarin) listed under the exclusion criteria (see Section 8.2) and other current 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 subject's medications during study participation unless deemed medically necessary.

10. STUDY PROCEDURES

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

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

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

Subjects will be instructed to complete a Screening Visit at least 3 days (to allow for receipt of blood test results), and no more than 30 days prior to the anticipated date of the first Treatment Visit (Day 1). The following evaluations will be completed during the Screening Visit to confirm subjects meet eligibility criteria for this study:

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

Once laboratory results are obtained and a final determination of eligibility is made, subjects will be contacted to schedule the first treatment visit. While immediate re-testing of laboratory results is not allowed, subjects failing to meet laboratory-based eligibility criteria may be rescreened after a 30-day wait. A single re-screening is permitted, and this re-screening is only permissible if the reason for the prior screen failure was for laboratory measurements. Blood for

clinical laboratory tests can be redrawn after a 30-day wait; however, other screening procedures do NOT need to be repeated. If the new clinical laboratory test results meet eligibility, the subject may be dosed. Otherwise, the subject is not eligible for dosing or further re-screening.

10.2. Treatment and Follow-Up Phase

Subjects will be instructed to eat normal meals during the day but to refrain from alcohol, and to follow their usual insulin regimen prior to their evening clinic arrival. Subjects will be instructed to arrive at the clinic between 6 and 8 pm on Day -1, having not had dinner.

10.2.1. Visit 2 – Treatment 1 (Day -1 and Day 1)

The following procedures will be carried out at Visit 2.

10.2.1.1. Day -1

Clinic Arrival

1. Plasma glucose (via glucose meter) will be assessed. If the result is > 350.0 mg/dL (19.44 mmol/L), no further procedures should be performed, and the visit should be rescheduled after a minimum 24-hour wait.
2. The subject will be questioned regarding any changes in concomitant medications will be documented in the eCRF, 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.

   If it has been more than 30 days since Visit 1 (i.e., the visit is occurring outside of the allowed time window), venous blood will be collected for a repeat of baseline hematology and serum chemistry assessments. However, the visit may continue based on qualification at the Screening visit.
   Note: At check-in for Visit 3, venous blood will be collected for a repeat of hematology and serum chemistry assessments as baseline for the first dose of study glucagon.
4. Full vital signs will be assessed after a 5-minute seated rest. It will be confirmed that the subject continues to meet eligibility requirements for SBP and DBP. Other assessments of vital signs will be made during the visit as specified in the footnotes to Table 5.

Evening Meal in Clinic

1. A standardized healthy meal will be provided to the subject (see Section 7.1) with a goal of completion by 9 pm.
2. The subject should follow their normal prescribed regimen for insulin per PI discretion, including meal-time correction, until midnight.

10.2.1.2. Day 1

Overnight Monitoring (starting at approximately midnight)

1. Subjects will be instructed to fast, taking nothing but water and oral glucose tablets if necessary, starting at approximately midnight and will be monitored for compliance by the CRC staff.
2. An IV catheter will be placed in one arm, maintenance fluids will be started, and the subject's insulin pump will be discontinued, if applicable. If use of an overnight IV is not possible due to site staffing considerations, use of the subject's own insulin infusion pump or SC insulin will be used overnight.
3. Plasma glucose will be monitored overnight by CGM, YSI or glucose meter; these data will be kept in the source documents. At a minimum, glucose will be assessed by BGM or YSI (not CGM) at midnight, 3 am, and 6 am; these data will be entered into the EDC. IV glucose or oral glucose tablets will be given and/or insulin will be administered by IV or infusion pump as necessary to optimize achieving plasma glucose within a target range of 80 to 150 mg/dL (4.44 to 8.33 mmol/L). If the glucose is outside the recommended target range, it will not be considered a protocol deviation.
4. Ideally, about 1 hour prior to the start of the Morning Procedures outlined below, subjects will be transitioned from SC to IV administration of insulin; any use of IV glucose will be discontinued.
5. If the subject has plasma glucose < 270 mg/dL (< 15.0 mmol/L) in the morning as measured by YSI, then the subject will be eligible to begin the Morning Procedures.

Morning Procedures (starting at approximately 6 am)

1. In the morning, plasma glucose (via YSI) will be assessed, and if > 270.0 mg/dL (> 15.0 mmol/L), the visit will be rescheduled after a minimum 3-day wait. Otherwise, the subject will be administered IV insulin to induce a baseline euglycemic steady state.
2. If not already placed, an IV catheter will be placed for administration of insulin and maintenance fluids.
3. A second IV catheter will be placed for blood sampling, ideally located in a vein within the antecubital fossa.

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

Baseline Euglycemic Steady State (early morning)

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

Hypoglycemia Induction Procedure (following baseline euglycemic steady state)

Induction Start

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

1. Subjects will continue the IV insulin infusion at the final rate of the euglycemic steady state.
2. Subjects will be given an initial IV bolus push dose of regular insulin diluted in saline:
    a. The dose will be calculated as 75% of the dose estimated to reduce plasma glucose from the subject's starting plasma glucose level to 54 mg/dL (3.0 mmol/L) based on the subject's self-reported glucose correction factor. This dose will be referred to as "1 bolus (full bolus dose)" subsequently.
    b. Plasma glucose will be measured no less frequently than every 10 minutes.

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

Insulin Dose Adjustments

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

Randomization

Once the initial bolus dose of insulin has had time to take effect and the subjects is observed to be in a controlled rate of glucose decline, which will generally occur at approximately 30 to 60 minutes after the beginning of the induction period, the subject will be randomly assigned to receive either G-Pen or GlucaGen Hypokit in one of the treatment sequences shown in Table 3.

Confirmation of Hypoglycemic Steady State

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

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

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

1. If any of the confirmatory measurements meets the criteria for hypoglycemic steady state, the subject will be eligible to receive study glucagon, and further confirmatory plasma glucose measurement are not required.

2. If the final confirmatory plasma glucose value is < 42 mg/dL (< 2.33 mmol/L), the procedure will be terminated, study glucagon will NOT be administered, and the visit will be rescheduled after a minimum 3-day wait. At the Investigator's discretion, the subject should be treated with IV glucose or oral carbohydrates, it should be verified that the subject achieved a euglycemic state and is medially stable prior to discharge.
3. If any of the confirmatory plasma glucose measurements are > 54 mg/dL (> 3 mmol/L), then the IV insulin infusion will be re-started, and insulin adjustments will be made as per the induction procedure described above (see Table 4). Once another initial plasma < 54 mg/dL (< 3 mmol/L) is obtained, the sequence of up to 3 confirmatory plasma glucose readings will repeated.

Note: If a subject fails to achieve a hypoglycemic steady state within 60 minutes of the first plasma glucose measurement < 54 mg/dL (< 3 mmol/L), the procedure will be terminated, and the visit re-scheduled after a minimum 3-day wait.

Decision to Dose

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

Preparation and Administration of Study Drug

1. Once the induction procedure has begun and glucose < 54 mg/dL (< 3 mmol/L) is predicted to occur within approximately 1 hour, the study staff member who will be performing the study drug injection should be notified that the induction procedure is reaching conclusion. At this time the study staff member will bring the appropriate unopened test article (pouched G-Pen or Novo GlucaGen Hypokit kit) to the bedside, as assigned by the EDC system.
2. Once the hypoglycemic steady state is confirmed, the Investigator will confirm that it is appropriate to administer study drug to the subject. The clock time of this "Decision to Dose" will be captured in the source documents.
3. At this point, the subject will receive the blindfold and headphones with music playing to maintain the blind.
4. The treatment administrator will then open the study drug container (kit or pouch) and begin preparation of the glucagon for administration following the applicable IFU. An Investigator should verify that the contents of the vial of lyophilized GlucaGen Hypokit have been fully reconstituted prior to administration.
5. Subcutaneous administration of the study drug will be made to the abdomen around the umbilicus as per Section 9.3.3. Clock time of study drug administration will be recorded in the source documents. After study drug injection, the study product will be disposed in a location away from the subject in a manner that maintains the blind. After disposal, the blindfold and headphones will be removed from the subject.
6. Following study drug administration, plasma glucose will be measured every 5±2 minutes through 90 minutes, and every 30±2 minutes thereafter through 180 minutes post-dosing.

7. At 180 minutes post-dosing, the subject will resume insulin therapy and be given a meal as per the standard practice at each site. The subject can be discharged from the clinic if their plasma glucose is >100 mg/dL (> 5.55 mmol/L) and the subject is deemed medically stable.
8. After study drug administration and before 180 minutes post-dosing, if rising glucose levels are observed and if deemed medically necessary, insulin therapy or other medical intervention may be initiated by the Investigator.
    a. Such intervention is not recommended to occur before 90 minutes post-dosing of study drug.
    b. Plasma glucose data and assessments of neuroglycopenic symptoms will be censored after the time of intervention, per the statistical analysis plan.
    c. These interventions (such as insulin, carbohydrates, or a meal) prior to 180 minutes post study drug administration should be captured in the source documents, and further glucose measurements may be performed at the discretion of the Investigator.

Hypoglycemia Symptom Assessments

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

1. Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure (baseline),
2. Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure,
3. Just before study drug is administered,
4. Every 5±2 minutes after glucagon is administered until 90 minutes post-dosing, and every 30 minutes (coinciding with plasma glucose measurements) between 90 and 180 minutes post study drug administration.

Local Tolerability and Adverse Events

Local tolerability and AEs will be assessed as follows:

1. Subjects will complete a Visual Analog scale (VAS) questionnaire regarding injection site discomfort (Appendix 2) at 30±5, 90±5, and 180±5 minutes after injection of study drug.
2. Subjects will complete an Injection Site Discomfort Description and Duration Questionnaire at 30±5 minutes post-dosing. If discomfort is ongoing at 30 minutes post-dosing, the questionnaire will be updated before the subject leaves the clinic to document the final duration.
3. The Investigator will use the modified Draize scales (Appendix 3) to assess erythema and edema formation at the injection site at 30±5, 90±5, and 180±5 minutes after injection of study drug. If any scores remain > 1 at the 180-minute evaluation, the subject may leave the clinic but will be instructed to contact a study staff member if the condition fails to resolve. The CRC will make every attempt to ensure that the same investigator will assess the injection sites on the subject, during both treatment visits.

Note: Even if the plasma glucose measurements have been stopped after 90 minutes, the Draize scale assessments should continue to 180 minutes post study drug injection.

4. AEs reported by the subject or observed by an Investigator during the visit will be recorded in the eCRF.

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

The subject will return to the CRC 7 to 28 days after the first Treatment Visit. The procedures that will be repeated at Visit 3 are described in Section 10.2.1. Note that venous blood will be collected for a repeat of baseline hematology and serum chemistry assessments at Visit 3. At Visit 3, the subject will cross over to receive the other study drug, which will be administered at the time of Decision to Dose, so that each subject will have received one dose of G-Pen and one dose of GlucaGen Hypokit during the study. At the end of Visit 3, the subject will be asked to guess what their first treatment was, and what their second treatment was from the choices of "Xeris Glucagon, G-Pen, administered by auto-injector" or "Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe". The subject's responses will be recorded in the eCRF for the Subject Study Drug Assignment Questionnaire (see Appendix 5).

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

The subject will attend a Follow-Up Visit within 2 to 7 days after completing the final dosing visit or premature discontinuation. This visit will include the following assessments:

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

In case of any premature discontinuation 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, family members, or emergency

contacts via email and telephone. If such efforts fail, a certified letter should be sent to the subject's last known address requesting they contact study CRC.

In all circumstances, every effort should be made to document subject outcome, per the follow-up. Information regarding the reason for not completing the study will be recorded in the eCRF. The Investigator should inquire about the reason for withdrawal, request that the subject return for a Final Visit, and further 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 drug 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 described 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	Visit 2 Treatment 1	Visit 3 Treatment 2	Visit 4 Follow-up
	Day -30 to -3	Check-in: Day -1 Dose 1: Day 1	Target[1] Check-in: Day 7 Dose 2: Day 8 (Dose 1 + 7-28 days)	Target[1] Day 10-15 (Dose 2 + 2-7 days)
Informed consent	x	—	—	—
Medical history and demographics	x	—	—	—
Inclusion/exclusion review	x	—	—	—
Concomitant medications	x	x	x	x
Height, weight, and physical exam[2]	x	—	—	x
12-lead ECG	x	—	—	x
Vital signs [3]	x	x[3]	x[3]	x
Urine pregnancy test	x	x	x	x
Urine drug screen	x	—	—	—
Hematology & clinical chemistry	x	(x)	x	x
HbA1c and C-peptide	x	—	—	—
HIV, HCV and HBV	x	—	—	—
Gold scale for hypoglycemia unawareness	x			
Evening admission, dinner meal	—	x	x	—
Overnight fast and glucose monitoring from midnight	—	x	x	—
Hypoglycemia induction and confirmation of steady state	—	x	x	—
Randomization	—	x	—	—
Administration of study medication	—	x	x	—
Hypoglycemia Symptom questionnaire	—	x	x	—
Injection site discomfort scales	—	x	x	—

Assessment	Visit 1 Screening Day -30 to -3	Visit 2 Treatment 1 Check-in: Day -1 Dose 1: Day 1	Visit 3 Treatment 2 Target[1] Check-in: Day 7 Dose 2: Day 8 (Dose 1 + 7-28 days)	Visit 4 Follow-up Target[1] Day 10-15 (Dose 2 + 2-7 days)
Draize scales for erythema/edema	—	x	x	—
Venous plasma glucose (PD)[4]	—	X[5]	X[5]	—
Review AE(s)	—	x	x	x
Subject Study Drug Assignment Questionnaire	—	—	x	—

AE=adverse events, BP=blood pressure, ECG= electrocardiogram, HbA1c=glycated hemoglobin, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, PD=pharmacodynamic, (X)=repeat if the visit is occurring outside of the allowed time window (i.e., more than 28 or 30 days have passed since the prior visit), YSI= Yellow Springs Instruments.

[1] Visit 3 should begin (i.e., admission to the CRC between 6 and 8 pm the day before treatment) 7 to 28 days after Visit 2; Visit 4 should occur 2 to 7 days after Visit 3.

[2] Excluding breast, pelvic and genitourinary exams. Note: height assessment is not required at Visit 4.

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

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

[5] If plasma glucose is > 350.0 mg/dL (>19.44 mmol/L) upon clinic arrival or if the plasma glucose the morning after the overnight stay is > 270.0 mg/dL (> 15.0 mmol/L) the visit should be rescheduled.

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 manner.

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 Assessments (Table 5). In addition, visits to the site must occur within the pre-defined windows outlined in this protocol; otherwise, they will be considered protocol deviations.

11.1. Blood Volume

There will be approximately 50 PD blood samples of approximately 2 mL drawn at each Treatment Visit for a total of about 100 mL of blood per visit. The two treatment visits will be 7 to 28 days apart. There will be 10.5 mL blood samples drawn at Screening, Visit 3 and at the Follow-up Visit for analysis of a clinical chemistry panel and hematology, with an additional 10.5 mL blood sample drawn at Screening for eligibility determination (HbA1c, C-peptide, and Serology). A total of approximately 250 mL of blood will be drawn over the duration of the study (Table 6).

Table 6 Frequency and Volume of Blood Collections

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening Visit 1	Treatment Visits 2 & 3	Follow-Up Visit 4	
Clinical Chemistry	7.5	1	1-2[a]	1	22.5-30
Hematology	3	1	1-2[a]	1	9-12
HbA1c	3	1	-	-	3
C-peptide	2.5	1	-	-	2.5
Serology	5	1	-	-	5
PD[1]	2	-	~50/visit	-	200
Total	-	-	-	-	242-252.5

HbA1c=glycated hemoglobin, PD=pharmacodynamic, (a)perform at V3, perform at V2 only if the visit is occurring outside of the allowed time window (i.e., more than 30 days have passed since the prior visit),
[1] Plasma glucose measurements (1 to 2 mL each) 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

Hematology	Chemistry	Urine	Laboratory
WBC count	Glucose	β-hCG[1]	HbA1c
RBC count	Creatinine	Drug screen[2]	C-peptide
Hemoglobin	Na^+		HIVab
Hematocrit	K^+		HCVab
Platelet count	Ca^{++}		HbsAg
	Albumin		
	Alkaline Phosphatase		
	AST		
	ALT		

ALT=alanine aminotransferase, AST=aspartate aminotransferase, β-hCG=beta-human chorionic gonadotrophin, HbA1c=glycated hemoglobin, HbsAg=hepatitis B surface antigen, HCVab=hepatitis C virus antibody, HIVab=human immunodeficiency virus antibody, RBC=red blood cell, WBC=white blood cell.
[1] 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.
[2] Drug screening performed at Screening will include: cocaine, THC, opiates, amphetamines, methamphetamine, and phencyclidine. Analytes other than those listed above may be included in the test kits provided to the sites. Investigator will exercise discretion in allowing or excluding a subject from study participation based on a positive test for one of these analytes 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).. Except as noted below, continuation in the study requires all tests to be negative.

A central laboratory will be utilized for analysis of all blood analyses except for 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, and normal ranges for the central laboratory.

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

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

During treatment visits, plasma glucose concentrations will be measured using a bedside YSI rapid glucose analyzer model 2300 or 2900. At each time point specified in Section 10, the results of both the black and white leads to one decimal place will be recorded in the source

documents, with the average of the two values rounded up to the nearest one decimal place accepted as the plasma glucose level for the time point as per the following examples.

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

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

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

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

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

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

Table 8 Conversion Table for Plasma Glucose Values

mg/dL	mmol/L
42.0	2.33
43.0	2.39
49.9	2.77
50.0	2.78
54.0	3.00
60.0	3.33
61.0	3.39
65.0	3.61
66.0	3.66
70.0	3.89
75.0	4.17
80.0	4.44
85.0	4.72
100	5.55
115.0	6.38
150.0	8.33
270.0	15.0
350.0	19.44

11.3. Electrocardiogram (12-lead ECG)

Single, supine 12-lead ECGs will be obtained at the pre-defined time-points outlined in the Schedule of Assessments (Table 5) as follows:

- 12-lead ECGs should be performed after the subject has rested quietly for at least 5 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 Assessments (Table 5). Additional or changes to collection times, or collection of BP and heart rate using automated devices is permitted, as necessary, to ensure appropriate subject 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 mm Hg. The subject should be rested for at least 5 minutes before the BP is obtained. Measurements of both the BP and heart rate must be taken at least 2 minutes apart and recorded in the eCRF.

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 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 sequence 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 a 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.

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

As part of ongoing safety reviews conducted by the Sponsor, any non-SAE 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 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 that at any dose:

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

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

12.5. Severity Assessment

On the AE eCRF, the Investigator will use the adjectives “mild,” “moderate,” or “severe” to describe the maximum intensity of the AE. These intensity grades are defined as follows in Table 9.

Table 9 AE Severity Assessment

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

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

subject/event outcome or action criteria. Accordingly, a severe event is not necessarily a serious event.

12.6. Causality Assessment

The Investigator will answer "yes" or "no" to the following question when assessing causality between an adverse event to the study drug, where an answer of "yes" designates the event as related to study drug and a "no" designates the event as not related to study drug: "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 eCRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable (Section 12.9).

12.7. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response and recorded on the appropriate eCRF. 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 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 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 or its designee(s) immediately, whether or not it is considered treatment-related. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Telephone and e-mail reports must be confirmed promptly either by facsimile or by overnight courier or mail.

Under 21 Code of Federal Regulations (CFR) 312.32(c), Xeris or its designee(s) is required to notify the FDA and all participating Investigators in an Investigational New Drug Application (IND) safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical

trials or any other source as soon as possible, but no later than 15 calendar days after the safety information is received and a determination is made that the information qualifies for reporting.

12.10. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the eCRF. AEs should be reported using concise medical terminology on the eCRFs 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 or its designee.

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

12.12. Pregnancy

The active pharmaceutical product in Xeris G-Pen is glucagon, which is in Pregnancy Category B. Female subjects of child bearing potential 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 enrolled in the treatment phase. At both Treatment Visits and at the Follow-Up Visit (i.e., Visits 2, 3 and 4), pregnancy testing will be repeated. Any subject who is found to be pregnant at one of the Treatment Visits will be withdrawn from the study immediately and no further study treatments will be given. Pregnancy at the follow-up visit will be noted, but the visit will be completed. Any pregnancy in a subject who received at least one dose of study drug will be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy). Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

12.13. Subject Monitoring

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

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

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

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

13. DATA ANALYSIS AND STATISTICAL METHODS

13.1. General Approach

Detailed methodology for descriptive and inferential statistical analyses of the data collected in the XSGP-304 study will be documented in the statistical analysis plan (SAP). The SAP will be prepared by the Sponsor's contract research organization (CRO) and agreed upon by the Sponsor. The SAP will be finalized and approved by signature and dates prior to locking the database. Additional graphical representations of the results may be produced after review of the data (post hoc). The SAP will take precedence over the protocol. The primary objective of the study is to test whether G-Pen is no worse than the GlucaGen Hypokit for injection in terms of hypoglycemia relief. Any major modifications of the definition of the Primary Endpoint or analysis will be reflected in a protocol amendment.

13.2. Sample Size Calculation

For the primary endpoint analysis, a failure is recorded if the subject's plasma glucose fails to reach a concentration >70 mg/dL (>3.88 mmol/L) *and* fails to increase by at least 20.0 mg/dL (1.11 mmol/L) within 30 minutes of the decision to administer the dose of glucagon. The determination of a constant clinically non-inferior margin for the cure rate difference is generally difficult in practice for a number of reasons. To alleviate this concern, it has been recommended to use an Odds Ratio of cure rates because the corresponding clinically non-inferior margin on the difference scale is getting small when the underlying cure rate becomes large and close to 1 [Lui and Chang(a)]. In this study, it is expected that the recovery (cure rate) will be high and approaching 100%. Since this is a cross-over design and each subject will serve as his/her control, power is improved.

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

13.3. Primary Endpoint

The primary endpoint comparison will be performed using both the Intention to Treat (ITT) and the per-protocol (PP) populations. The evaluable set for the PP population will be defined as all randomized subjects who, during both study periods, successfully complete the insulin induction procedure, fulfill the criteria for having achieved a hypoglycemic steady state, and successfully receive a dose of both study drugs (G-Pen followed by GlucaGen Hypokit, or GlucaGen Hypokit followed by G-Pen). For analysis of the primary endpoint, a failure for the study treatment (G Pen or GlucaGen Hypokit) will be recorded if the increase in plasma glucose remains < 20 mg/dL (< 1.11 mmol/L) throughout the 0- to 30-minute period from injection of study drug, while a success is defined as an increase in plasma glucose ≥ 20 mg/dL (≥ 1.11 mmol/L) in subjects from a state of insulin-induced hypoglycemia within the 0- to 30-minute period from injection of study drug.

Non-inferiority will be established based on the calculated 95% confidence interval for the difference in failure rates between G-Pen and GlucaGen Hypokit. Non-inferiority will be declared if the upper limit of the 95% confidence interval for the difference in failure rates is ≤ 5%; where the absolute failure rate of G-Pen treatment is ≤ 5%.

13.4. Secondary Endpoints

The following secondary endpoints will be assessed:

1. Rate of achieving a positive plasma glucose response, defined as either a plasma glucose concentration > 70 mg/dL (> 3.88 mmol/L) or an increase in plasma glucose concentration > 20 mg/dL (>1.11 mmol/L) within 30 minutes from injection of study drug.
2. Rates of positive symptomatic response, defined as relief of neuroglycopenic symptoms 30 minutes from a decision to dose.
3. Rates of positive treatment response, defined as exhibiting either a positive plasma glucose response *or* a positive symptomatic response.
4. Time to a positive plasma glucose response from injection of study drug.
5. Time to administer study drug from time to a decision to dose.
6. PD characteristics of mean plasma glucose concentration (0 to 90 minutes post-dose), C_{max}, t_{max}, $AUC_{(0-90)}$, and area under the concentration versus time curve from time 0 to 180 minutes ($AUC_{(0-180)}$).
7. Time to (a) initial relief and (b) complete resolution of autonomic and neuroglycopenic symptoms of hypoglycemia from a decision to dose.
8. Time to resolution of the overall feeling of hypoglycemia from a decision to dose.
9. Safety endpoints, including: AE/ SAE rates, and changes in vital signs, laboratory variables, and physical exam/ECG findings.
10. Tolerability endpoints measured at 30, 90, and 180 minutes post-dosing, including: Draize scale scores for injection site erythema and edema as assessed by the investigator, and injection site discomfort and duration as assessed by subject questionnaire responses.

13.4.1. Pharmacodynamic Analyses

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

Pharmacodynamic characteristics, including: plasma glucose area under the concentration versus time curve (AUC), C_{max}, and t_{max}, time to achieve a ≥ 20.0 mg/dL (≥ 1.11 mmol/L) increase from glucose nadir, and time to reach ≥ 70.0 mg/dL (≥ 3.89mmol/L), will be compared between the treatment groups from time of glucagon administration. Comparison between the treatment groups will be performed using a mixed model with treatment, period and sequence as terms.

13.4.2. Hypoglycemia Symptoms

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

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

The time to the minimal score post baseline will be described and compared between the treatment groups using a mixed model with treatment, period and sequence as terms. Similarly, the time to first reporting of "no" for the overall hypoglycemia question ("Do you currently feel hypoglycemic?") will be described and compared between the groups.

13.4.3. Glucagon Preparation Time

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

13.5. Safety Analysis

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

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

- AEs and SAEs
- 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 visual analog scale (VAS) and ordinal pain scales (Appendix 2).
    - Erythema and or edema formation at site of injection assessed using the Draize scale (Appendix 3).

13.5.1. Adverse Events

All verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT), and study drug. AE collection will begin from the time of informed consent. Listings of all AEs (including non-

TEAEs), SAEs, and TEAEs leading to study drug discontinuation will be provided by treatment group, site, subject, verbatim term, MedDRA SOC and PT, start and end dates, seriousness flag, severity, relationship to study drug, action taken with study treatment, frequency, and outcome.

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

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

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

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

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

13.5.2. Laboratory Safety Assessments

Laboratory values (biochemistry and hematology) will be flagged if outside the normal range and a listing of clinically significant abnormal values will be presented. Laboratory assessments will be summarized at Screening and at the Follow-up Visit. Significant deviations/changes from the Screening Visit to the Final Visit will be documented as AEs if the Investigator judges them to be clinically significant.

13.5.3. 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 study will be recorded as AEs if the Investigator judges them to be clinically significant.

13.5.4. Vital signs and body weight

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

13.5.5. ECG

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

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

13.5.6. 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.

13.6. Subgroup Analysis

Analysis of subgroups is not planned or powered for this study. Any subpopulations analyzed will be described in the SAP.

13.7. Demographics and Baseline Characteristics

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by the Sponsor, as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guidance, and the applicable regulatory requirements.

This study will be monitored by the Sponsor in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance (QA) department, IRB/EC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, Investigators agree to this requirement.

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

15. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS

15.1. Case Report Forms/Electronic Data Record

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

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

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

Completion of eCRFs will be accomplished using a 21 CFR Part 11 compliant web-based EDC system. Sites will use existing computers to enter all other study-related data into the EDC system.

The Investigator has the responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs 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 eCRFs must be signed by the Investigator or by an authorized study staff member to attest that the data contained in the eCRFs is true. Any corrections to entries made in the eCRFs 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 eCRFs must match the data in those charts. In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at Xeris and clearly identify those data that will be recorded in the eCRF, and for which the eCRF will stand as the source document. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses to eCRF queries.

15.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Xeris, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, 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 ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from Xeris before disposing of any records, even if retention requirements have been met.

15.3. Monitoring

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

The Xeris 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/IEC review, with the stipulation that subject confidentiality will be maintained in accordance with regional, local, and federal regulations (including Health Insurance Portability and Accountability Act of 1996 [HIPAA] requirements). The monitor will also be responsible for confirming adherence to the study protocol, inspecting eCRFs and source documents, and ensuring the integrity of the data. Electronic 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 postal mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve all questions raised, and difficulties detected by the monitor.

15.4. Audits and Inspections

The Investigator understands that regulatory authorities, the IRB/IEC, and/or Xeris or their designees have the right to access all eCRFs, 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 study will be conducted in compliance with the current version of Declaration of Helsinki, ICH E6, local and regional ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable CFR (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 G-Pen Investigator's Brochure, prior to the initiation of the study.

16.2. Institutional Review Board and Ethics Committee

The IRB/IEC 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/IEC for review and approved before the enrollment of any subject into the study. Study drug may not be shipped to the Investigator until Xeris has received a copy of the letter or certificate of approval from the IRB/IEC for the protocol and any protocol amendments.

All types of subject recruitment or advertising information must be submitted to Xeris or its designee and to the IRB/IEC 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/IEC should be notified immediately, and the amendment forwarded to the IRB/IEC 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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Xeris.

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 to de-identify the study subject. In the case of data transfer, Xeris 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/IEC and Xeris 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 member 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 ICF. Receipt of written informed consent will be documented in each subject's or potential subject's eCRF. 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 or its designee and to the IRB/IEC for review and approval prior to implementation. Advertisements approved by the IRB/IEC 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 should be notified immediately. In addition, the Investigator will inform Xeris 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. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

17.1. 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 and the Investigator. All protocol modifications must be reviewed and approved by the IRB/IEC before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to subjects do not require preapproval by the IRB/IEC. However, the IRB/IEC 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. All departures from the protocol must be fully documented in the source documents and the eCRFs of the subjects involved. Protocol deviations will be tracked in an electronic system implemented by the Sponsor or designated representative.

17.2. Study Termination

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB/IEC, safety problems resulting in subject deaths, or at the discretion of Xeris 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 will promptly notify the Investigators and document the reason for study termination. Specific procedures for termination will be arranged by the Sponsor in coordination with the Investigators. After notification, the Investigators must contact all participating subjects within 7 days. All study materials must be collected and all eCRFs completed to the greatest extent possible, and all study materials must be returned to Xeris or its designee within an additional 28 days.

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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 90 minutes post-dosing. (Data will be collected 18 times).
- Every 30±5 minutes (coinciding with plasma glucose measurements) between 90 and 180 minutes post study drug dosing (90 minutes, 120 minutes, and 180 minutes).
  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 30±5 and 90±5 minutes after injection of study drug, and again at 180±5 minutes after injection of study drug. The 180-minute evaluation after injection of study drug is still required even if glucose monitoring ends at an earlier timepoint. The subject will complete 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.

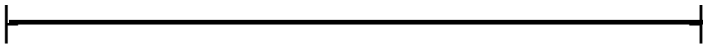
Note: If a subject is unable to physically complete the questionnaire, the subject will indicate the point on the VAS corresponding to their level of discomfort, and study staff will enter a vertical line at that point. Documentation will be provided on each completed questionnaire as to who completed 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 completed by the subject at 3**0±5** minutes after injection of study drug. Any subject reporting discomfort other than "none," should complete Question 1b at the same time. All subjects should also answer Question 1c at the end of the visit (180 ±5 mins post-injection). The goal is for the subject to report the qualitative nature and duration of discomfort, if any, associated with injection of study drug, ignoring any transient pain associated with needle insertion.

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

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

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

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

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

_____Itching

_____Tingling, twitching or numbness

_____Irritation (e.g., burning, stinging)

Other or additional comments:_____

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

_____Less than 1 minute

_____1-2 minutes

_____3-5 minutes

_____6-9 minutes

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

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

_____ Minutes

APPENDIX 3. DRAIZE SCALE

- *Study Personnel Instructions:* The modified Draize Scale as shown in the table below will be used for physical examination/rating of abnormalities at the injection site.
- The injection site should be examined for formation of both erythema and edema and results recorded in the Case Report Form. Evaluations of the injection site should be performed at 30±5 and 90±5 minutes after injection of study drug, and again at the end of the treatment visit at 180±5 minutes after injection of study drug. The 180-minute evaluation is still required even if glucose monitoring ends at an earlier timepoint.

Erythema Formation		**Edema Formation**	
Description	**Score**	**Description**	**Score**
No erythema	0	**No edema**	0
Very slight erythema Barely perceptible	1	**Very slight edema** Barely perceptible	1
Well defined erythema	2	**Well defined edema**	2
Moderate erythema	3	**Moderate edema** Raised approx. 1 mm	3
Severe erythema Beet redness to slight eschar formation	4	**Severe edema** Raised more than 1 mm and beyond exposure area	4

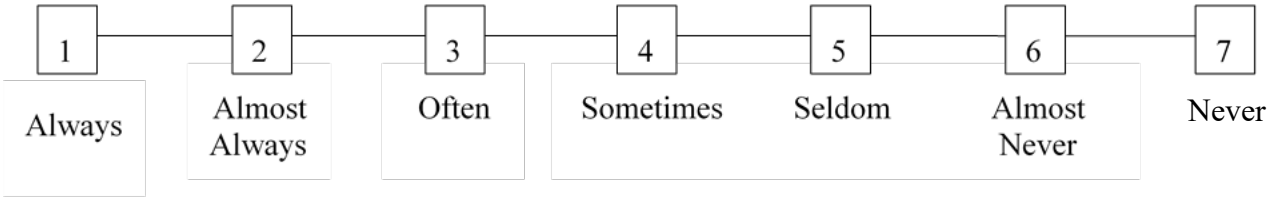
APPENDIX 4. GOLD SCALE

Hypoglycemia Awareness

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

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

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



Your score: _____

APPENDIX 5. SUBJECT STUDY DRUG ASSIGNMENT QUESTIONNAIRE

Study Personnel Instructions: The subject will be instructed not to talk with the study staff about their impression of which product he/she received until the end of the second treatment visit. Before leaving the clinic at the end of Visit 3, the subject should complete the questions below to indicate which study treatment they believe they received at each visit. Please ensure that the subject checks only one box for each question and does not select each treatment more than once. If the subject indicates they do not know, please ask them to make a guess.

Subject Instructions: Please respond to the following questions by picking only one of the two choices per question.

*1a. Which study drug do you believe you received during your first treatment visit, which occurred before today's visit. (Check **one**):*

☐ **Xeris Glucagon, G-Pen, administered by auto-injector**

☐ **Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe**

*1b. Which study drug do you believe you received during your second treatment visit, which happened today. (Check **one**):*

☐ **Xeris Glucagon, G-Pen, administered by auto-injector**

☐ **Comparator Glucagon, GlucaGen Hypokit, administered by needle and syringe**