CSI-GLUCAGON™ (CONTINUOUS SUBCUTANEOUS GLUCAGON INJECTION)

PROTOCOL XSGO-AF01

FIXED RATE CONTINUOUS SUBCUTANEOUS GLUCAGON INFUSION (CSGI) VS PLACEBO IN TYPE 1 DIABETES MELLITUS PATIENTS WITH RECURRENT SEVERE HYPOGLYCEMIA: EFFECTS ON COUNTER REGULATORY RESPONSES TO INSULIN INDUCED HYPOGLYCEMIA

Version 4.0

21-Dec-2018

Xeris Pharmaceutical Signature Page:

XSGO-AF01

Version 4.0

21-Dec-2018

Medical Director:	26 Dec 2018
Khaled Junaidi, MD, Medical Director	
Clinical Operations:	22 Dec 2018
Martin Cummins, Vice President, Clinical Development	
Regulatory:	
Amy Ghering, PhD, Director of Regulatory	26 DEC 2018
Biostatistics:	
Nicole Close, PhD	24Dec2018

INVESTIGATOR'S AGREEMENT

I have read the XSGO-AF01 protocol version 4.0 dated 21-Dec-2018 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

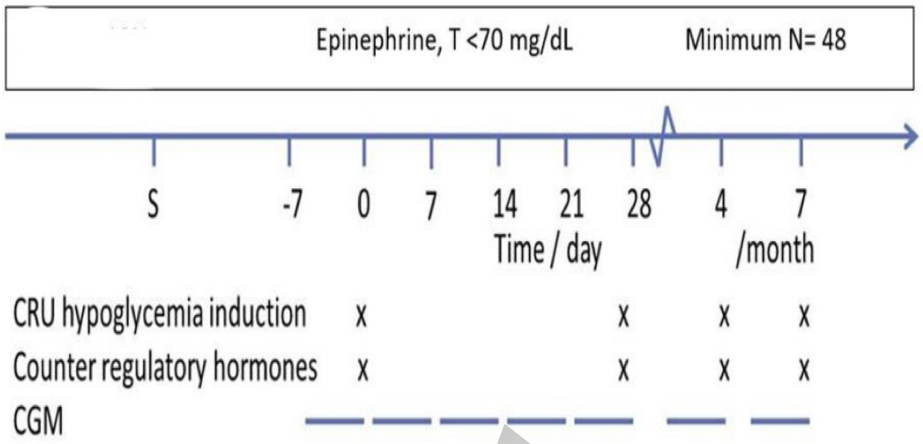
Table 1: Emergency Contact Information

Role in Study	Name & Title	Email Address & Telephone Number
Sponsor's Study Leader & primary contact	Joy Geallis Clinical Project Manager	JGeallis@xerispharma.com 815-546-9130
Medical Monitor & 24-hour emergency contact	Khaled Junaidi, MD Medical Director	kjunaidi@xerispharma.com 312-517-1461

2. SYNOPSIS

Protocol Number: XSGO-AF01	
Fixed Rate Continuous Subcutaneous Glucagon Infusion (CSGI) vs Placebo in Type 1 Diabetes Mellitus Patients with Recurrent Severe Hypoglycemia: Effects on Counter-Regulatory Responses to Insulin-Induced Hypoglycemia	
Principal Investigator:	Each participating clinical site will nominate a physician who, based on training and experience, will serve as principal investigator for that site. The Sponsor will qualify the Investigator.
IND:	120653
Project phase:	Phase 2a
Compound(s):	G-Pump™ (glucagon infusion)
Objectives:	Primary Objective: The change from baseline in plasma epinephrine will be compared between subjects who have received either 4 weeks of continuous subcutaneous glucagon infusion (CSGI) or placebo. After 30 minutes of a maintained insulin-induced hypoglycemia clamp (plasma glucose (PG) < 50 mg/dL), these hormone levels will be measured in adult type 1 diabetes (T1D) subjects with hypoglycemia associated autonomic failure (HAAF). The secondary objectives are to: 1. Compare change from baseline in cumulative glucose infusion required to maintain glucose at 50 mg/dL for the first 30 minutes after the 50 mg/dL is achieved. 2. Compare changes from baseline in the other counter-regulatory hormones: norepinephrine, glucagon, cortisol and growth hormone. 3. Compare changes from baseline to week 4 in subject responses to a validated symptom questionnaire administered during induced hypoglycemia. 4. Compare changes from baseline to week 4 in continuous glucose meter (CGM)-derived hypoglycemia parameters of: a. Proportional time spent with interstitial glucose < 70, 60, and 50 mg/dL. b. Rate of hypoglycemic event episodes at thresholds of < 70, 60, and 50 mg/dL.

	5. Compare change from baseline to week 4 in CGM-derived parameters of: a. Average glucose and proportional time: i. Time within range with PG 70 - 180 mg/dL, ii. Time above range with PG ≥ 180 mg/dL. iii. Time below range < 70 mg/dL b. Plasma glucose standard deviation. 6. Describe subject reported hypoglycemic events: a. Symptomatic events confirmed with self-monitored glucose < 70 mg/dL. b. Symptomatic events with no accompanying glucose meter reading or a reading ≥ 70 mg/dL. c. Asymptomatic events of self-monitored glucose < 70 mg/dL. d. Severe hypoglycemia as defined by affected consciousness of hypoglycemic origin confirmed by a glucose meter reading <36 mg/dL, requiring external assistance, or prompt recovery upon hypoglycemia treatment. 7. Describe change from baseline to week 4 of unawareness measured by the Gold scale. 8. Describe basal, bolus and total daily insulin dose changes by treatment group. 9. Describe the time course of the endpoints (primary and secondary 1-7) from week 4 through the rest of the study. 10. Describe non-serious and serious adverse events by treatment group 11. Describe change from baseline through week 4 of serum concentrations of glucagon while still on the CSGI, and glucagon antibodies.
Study design:	This is a prospective, randomized, double-blind, parallel trial with the primary endpoint analysis after 4 weeks treatment with CSGI or placebo. As both the low and high dose group use the same formulation the dose will be determined by infusion. To preserve the blind, the placebo is administered by matching infusion methods to CSGI .

	Study Schematic  After a run-in on CGM, subjects will have key hormones of their hypoglycemia counter regulatory response quantified using a stepwise hypoglycemia induction. They will then receive investigational product for 4 weeks before discontinuation and reassessment of the same hypoglycemia counter regulatory response. Treatment stops at 4 weeks, but subjects will continue blinded for 6 additional months to investigate duration of response with assessments at 3 and 6 months.
Study location:	Approximately 6-8 clinical research centers in the United States.
Study duration:	The estimated duration of study participation for individual subjects is approximately 7.5 months. The estimated duration of the entire study is 1 year from first patient in to last patient out.
Sample size:	The primary hypothesis is to evaluate change from baseline to 4 weeks of plasma epinephrine concentration after 30 minutes of induced hypoglycemia with plasma glucose <50mg/dL between treatment groups. Sample size is based on a hierarchical hypothesis test in which the comparison of treatment groups will be implemented in the following order: CSGI (combined groups -high and low dose) versus placebo CSGI high dose versus placebo CSGI low dose versus placebo CSGI high dose versus CSGI low dose

	Using this method, an alpha of 5% will be preserved for each hypothesis test where the next ordered test will only be conducted if statistical significance is achieved for that hypothesis. Final calculations are based on 80% power and an alpha of 5%, to demonstrate a plasma epinephrine increase compared to placebo of 1.5 nmol/l given and SD of 1.34 nmol/l at an induced PG of 50 mg/dl. Sixteen subjects per group (CSGI high dose, CSGI low dose, and placebo) are required based on the minimum sample size estimate for a comparison against placebo (N=42). To account for attrition, a total of 48 subjects will be randomized for the study.
Subjects:	Male or female type 1 diabetes mellitus patients with recurrent severe hypoglycemic episodes indicative of hypoglycemia associated autonomic failure (HAAF) ages 21-64 years, inclusive.
Inclusion Criteria:	1. Males or females diagnosed with type 1 diabetes mellitus for at least 24 months. 2. Random serum C-peptide concentration < 0.6 ng/ml at Screening. 3. Age 21-64 years, inclusive, at screening. 4. Documented Hypoglycemia unawareness as evidenced by a Gold Scale score ≥4, at screening 5. Medical history of an episode of severe hypoglycemia as reported by patient < 50 mg/dL, in the 1 year prior to screening. 6. Current use of multiple daily dosing insulin treatment (< 1 U/(kg*day) total daily dose) either administered with subcutaneous injections or continuous subcutaneous insulin infusion (CSII). 7. Performs monitoring of glucose minimally 3 times a day. Patients using continuous glucose monitoring for monitoring should continue to do so during the course of the study. 8. Willingness to provide informed consent and follow all study procedures, including using the Medtronic smartphone application "iPRO2mylog" for diabetes data logging and attending all scheduled visits.
Exclusion Criteria:	1. HbA1c ≥ 10% at Screening. 2. Chronic kidney disease stage 4 or 5. 3. Hepatic disease, including serum ALT or AST greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3 g/dL. 4. Hematocrit of less than or equal to 30% at Screening. 5. Clinically significant ECG abnormalities at Screening.

6. Congestive heart failure, NYHA class III or IV.
7. History of myocardial infarction, unstable angina or revascularization within the past 6 months.
8. History of a cerebrovascular accident with residual neurologic deficit.
9. Current seizure disorder, unrelated to hypoglycemia.
10. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
11. History of insulinoma.
12. 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.
13. Major surgical operation within 90 days prior to Screening.
14. Current bleeding disorder, treatment with anticoagulants, or platelet count below 50,000/mL at Screening.
15. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO, trehalose) in the investigational formulation.
16. History of glycogen storage disease.
17. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
18. Active substance or alcohol abuse (more than 21 drinks/wk. for males or 14 drinks/wk. for females). Subjects reporting active marijuana use and/or testing positive for THC via rapid urine test will be allowed to participate in the study at the discretion of the investigator. Subjects positive for other drugs of abuse via rapid urine test who report use of a prescription or OTC medication that would explain such a finding will be allowed to participate at the discretion of the investigator.
19. Administration of glucagon within 7 days of Screening.
20. Pregnant and/or Lactating. For subjects of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study and for at least 1 month after participating in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the female uses a diaphragm and spermicide and the male uses a condom), or abstinence.
21. Inadequate venous access.
22. Participation in other studies involving administration of an investigational drug or interventional device within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and

	during the four weeks of study product administration in the current study. 23. Any reason the principal investigator deems exclusionary.
Brief outline of treatments:	*Baseline Qualification:* Subjects will continue their insulin regimen as usual throughout the study, adjusted by the investigator to achieve ADA recommended targets. After enrollment, the subjects will require approximately one week of CGM data prior to their baseline hypoglycemia induction procedure. Subjects will enter a run-in phase of 1 week wearing a blinded CGM device. Subjects will arrive in the Clinical Research Unit (CRU) the morning of the planned hypoglycemia induction procedure. The CGM data will be retrieved. The following CGM criteria must be met: a minimum of 6 days must be recorded using the CGM before the subject will be inserted with a new CGM device. If the CGM criteria are not met, the subject is inserted with another CGM for renewed baseline period. Should the second baseline period not yield eligible CGM data, the subject will stop further participation in the screening procedures. The subject will fast after midnight. They will remain fasting until the end of the hypoglycemia procedure the following day. CGM data will be checked for a minimum of six days of data and a confirmation that the subject did not have a hypoglycemic event, < 70 mg/dL during the previous 8 hours. *Hypoglycemia induction procedure:* Insulin induced hypoglycemia (PG < 50 mg/dL as measured by YSI) is achieved through a hyperinsulinemic clamp procedure. The plasma glucose should be verified to be between the 80-120 mg/dL. The IV insulin infusion rate is then increased to 20 mU/(body surface area(BSA)*min) as a set rate and the subject's plasma glucose is stabilized at 100±10 mg/dL for minimally 60 minutes, through adjustments in continuous IV glucose. After this 60 minute stable period, the plasma glucose will be reduced to 70 mg/dL by decreasing the continuous IV glucose infusion rate. When the plasma glucose has been stable at 70+/-5 mg/dL for 20 minutes, a hypoglycemia symptom questionnaire administered, which will be repeated after 10 minutes. The hypoglycemia induction will then begin, decreasing the continuous IV glucose infusion rate to bring the plasma glucose down to < 50 mg/dL. Plasma glucose is measured every 5 minutes and the continuous IV glucose infusion rate is adjusted to achieve the target glucose concentration of < 50 mg/dL. When the target plasma glucose of < 50 mg/dL has been achieved, blood samples for the assessment of counter regulatory hormones are drawn, and the hypoglycemia questionnaire is administered. Plasma glucose concentration will be measured and maintained at 50+/-5 mg/dL for 30 minutes after which another set of blood samples for assessment of counter regulatory hormones are drawn and the hypoglycemia questionnaire re-administered. The insulin infusion is then stopped, and plasma glucose is

	raised to >70 mg/dL through the continuous IV glucose. The continuous IV glucose infusion is stopped once the subject's PG > 70 mg/dL and the subject will be given a standardized meal. The subject is monitored until deemed medically stable for discharge, per investigator discretion. *Visit Overview:* After the completion of the first study visit (the baseline hypoglycemia induction procedure), the investigator will train the subjects to load, prime, and use of the modified OmniPod. In this training, the subject will learn to prepare and use an OmniPod at a suitable infusion site. This includes direct observation of the subject when they attach and initiate the device, by the investigational staff. The subject is then randomized to a study treatment and begins therapy in the CRU. The assigned study treatment will be 4 weeks in duration. They are initially provided with a 1-week supply of blinded study drug and OmniPods. The subjects will return weekly for a safety check, CGM device data retrieval, new sensor insertion, and receipt of study supplies. The subject is expected to complete at least 90% of the study therapy during the 4-week treatment period. After 4 weeks of study therapy, the subject will return to the clinic. The study product will be stopped and the CGM data retrieved before a repeat of the hypoglycemia induction procedure as described above. 12 weeks after study treatment, the subjects will return to the CRU for insertion of a CGM device. One week later (13 weeks after completing study treatment), the CGM will be retrieved and the subject will undergo the hypoglycemia induction procedure as described above. At 25 weeks after study treatment, the subjects will return to the CRU for insertion of a CGM device. One week later (26 weeks after completing study treatment), the CGM will be retrieved and the subject will undergo the hypoglycemia induction procedure as described above. After completion of the hypoglycemia induction procedure at 26 weeks, the subject's participation in the study is completed.
Data management and statistical analysis:	Data will be entered into an electronic Case Report Form by site personnel. Data will be monitored at on-site visits by Xeris personnel or by a CRO acting as Xeris' agent. Data will be reviewed on an ongoing basis for missing values, out of range values and missingness. The primary analysis for the study is the comparison of the change from baseline of plasma epinephrine concentration during induced hypoglycemia with PG <50 mg/dL between CSGI and placebo, and to evaluate if there is a difference between CSGI high dose and low dose versus placebo after 4 weeks of blinded treatment.

	The analysis of the primary endpoint will be performed using a two-group t-test for each hypothesis test in the hierarchy, while preserving alpha at 0.05. CSGI (high and low dose combined) will first be tested against placebo, and if the difference is statistically significant <0.05, CSGI high dose versus placebo will be tested. If statistically significant <0.5, then CSGI low dose versus placebo will be tested, and if statistically significant, CSGI high dose versus CSGI low dose will be tested. Analyses of the secondary endpoints including CGM and hormone variables will be conducted with descriptive and inferential statistics. Responses to the Gold scale and hypoglycemia symptom questionnaire will be analyzed using Chi-square tests. The mean endpoints (3-6) from week 4 through the end of study will be presented graphically to assess the time course. Adverse events, laboratory safety variables (Screening to Day 28), physical examination, vital signs, ECG (Screening to Day 28), and local tolerability data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
BSA	Body Surface Area
CGM	Continuous Glucose Monitor
CHO	Carbohydrate
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
CRC	Clinical Research Center
CRO	Contract Research Organization
CSGI	Continuous Subcutaneous Glucagon Infusion
SCII	Continuous Subcutaneous Insulin Infusion
DMSO	Dimethyl sulfoxide
ECG	Electrocardiogram
GCP	Good Clinical Practice
GLP	Good Lab Practice
GIR	Glucose Infusion Rate
HAAF	Hypoglycemia Associated Autonomic Failure
HbA1c	Glycated hemoglobin

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
im	Intramuscular
IRB	Institutional Review Board
IIR	Insulin Infusion Rate
IUD	Intra-uterine Device
IV	Intravenous
kg	Kilogram
L	Liters
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PG	Plasma Glucose
PK	Pharmacokinetic

RBC	Red Blood Cells
rDNA	Recombinant
RLD	Reference Listed Drug
SAE	Serious Adverse Event
sc	Subcutaneous
THC	Tetrahydrocannabinol
Tmax	Time to Maximum Plasma Concentration
T1D	Type 1 Diabetes Mellitus
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organization
YSI	Yellow Springs Instrument

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective is to compare the plasma epinephrine concentration after 30 minutes of induced hypoglycemia (PG <50mg/dL) in adult T1D subjects with HAAF, who have received 4 weeks of treatment with either CSGI or placebo.

5.2. Secondary Objectives

The secondary objectives are to:

1. Compare change in cumulative glucose infusion to maintain glucose at 50 mg/dL for the first 30 minutes after the 50 mg/dL is achieved.
2. Compare changes in the other counter-regulatory hormones: norepinephrine, glucagon, cortisol and growth hormone.
3. Compare changes from baseline to week 4 in subject responses to a validated hypoglycemia symptom questionnaire administered during induced hypoglycemia.
4. Compare changes from baseline to week 4 in CGM-derived hypoglycemia parameters of:
    a. Proportional time spent with interstitial glucose < 70, 60 and 50 mg/dL.
    b. Rate of hypoglycemic event episodes at < 70, 60, and 50 mg/dL.
5. Compare change from baseline to week 4 in CGM-derived parameters of:
    a. Average glucose, proportional time with 70 ≤ PG < 180 mg/dL, and proportional time with PG ≥ 180 mg/dL.
    b. Plasma glucose standard deviation.
6. Describe subject reported hypoglycemic events:
    a. Symptomatic events confirmed with self-monitored glucose < 70 mg/dL.
    b. Symptomatic events with no accompanying glucose meter reading or a reading ≥ 70 mg/dL.
    c. Asymptomatic events of self-monitored glucose < 70 mg/dL.
    d. Severe hypoglycemia as defined by affected consciousness of hypoglycemic origin confirmed by a glucose meter reading <36 mg/dL, requiring external assistance, or prompt recovery upon hypoglycemia treatment.
7. Describe change from baseline to week 4 of unawareness measured by the Gold scale.
8. Describe basal, bolus and total daily insulin dose changes by treatment group.
9. Describe the time course of the endpoints (primary and secondary 1-7) from week 4 through the rest of the study.
10. Describe non-serious and serious adverse events by treatment group

11. Describe change from baseline through week 4 of serum concentrations of glucagon while still on the CSGI, and serum and plasma glucagon antibodies.

5.3. Endpoints

5.3.1. Primary Endpoint

The primary endpoint is change from baseline of plasma epinephrine concentration, from time zero and after 30 minutes of induced hypoglycemia with PG <50mg/dL. This assessment is performed for each hypoglycemia induction procedure.

5.3.2. Secondary Endpoints

The secondary endpoints for this study include:

- intravenous glucose infusion rate (GIR).
- Other counter regulatory hormones norepinephrine, glucagon, cortisol and growth hormone plasma concentrations.
- Symptoms of hypoglycemia (if present) as documented using the hypoglycemia symptom questionnaire (Appendix 1).
- Various CGM derived variables (Secondary Objectives 4 & 5).
- Hypoglycemia awareness assessment by the Gold scale.
- Safety-related parameters including:
  - Reported hypoglycemic events..
  - Insulin dose.
  - Vital signs.
  - Physical exam.
  - ECG.
  - Plasma glucagon and serum glucagon antibodies.
  - Standard safety laboratory parameters.
  - Incidence of adverse events (AEs) and serious adverse events (SAEs).
  - Subjective injection site discomfort as reported by subjects using a 100-mm VAS and other questionnaires (Appendix 3).
  - Erythema and/or edema formation at site of injection assessed by an investigator using the modified Draize scale (see Appendix 4).

6. BACKGROUND AND RATIONALE

6.1. Indication

The proposed indication is for the prevention of severe hypoglycemia in diabetes mellitus patients with recurrent severe hypoglycemia.

6.1.1. Background

Approximately 20% of the type 1 diabetes mellitus (T1DM) population suffers from recurrent severe hypoglycemia, which is of considerable consequence to the affected persons in rare cases leading to death and to the health care systems as the treatment often involves acute care and even hospitalization.

For many of these people a key component of the underlying pathology is hypoglycemia associated autonomic failure (HAAF). Hypoglycemic events decrease autonomic responsiveness further increasing the risk of subsequent hypoglycemic events thus constituting a vicious cycle. It has been shown scrupulous hypoglycemia avoidance at least partially restores autonomic function and diminishes the risk of hypoglycemia and that this effect lasts for years in some patients.

T1DM patients, with time, lose not only Langerhans' islet B-cell, but also A-cell function leading to glucagon deficiency. As the primary counter regulatory hormone to insulin this increases the risk of hypoglycemia substantially. The risk of HAAF increases as endogenous glucagon is diminished or lost. Administrating exogenous glucagon to partially replace the missing endogenous glucagon may therefore, similar to the scrupulous hypoglycemia avoidance, restore autonomic function and diminish the increased hypoglycemia risk.

In support of that hypothesis, continuous subcutaneous administration of low dose glucagon has been shown to decrease the number of nocturnal hypoglycemic events in T1DM (Edelman, ADA annual scientific sessions, 2006).

Glucagon is indicated for the treatment of severe hypoglycemia in a 1 mg dose. Xeris has used its biocompatible, non-aqueous peptide/protein reformulation technology to create a concentrated, low volume, stable glucagon formulation. This glucagon formulation has successfully been delivered using the Omnipod®.

6.1.2. Rationale

6.1.2.1. Hypoglycemia Associated Autonomic Failure (or Impairment) Identification

The Gold score is based on the response to a single question and has the advantages of being simple to execute and being supported by numerous investigations since the 1990's.

6.1.2.2. Duration

The present study tests the hypothesis that 4 weeks of continuous subcutaneous infusion of low dose glucagon will increase counter regulatory hormone response to insulin induced hypoglycemia. This is consistent with the finding that scrupulous avoidance of hypoglycemia has been demonstrated to partially restore autonomic responses to hypoglycemia in this population.

To obtain preliminary data describing the duration of such response, subjects are retested 3 and 6 months after the cessation of the investigational product.

6.1.2.3. Glucagon Infusion Rate Selection

A previous study (Edelman, ADA annual scientific sessions, 2006) evaluating continuous glucagon administration for the prevention of hypoglycemia tested doses at 2, 4 and 8 ng/(kg*min) and found apparently no effect at 2 ng/(kg*min), weak indications of effect at 4 ng/(kg*min) and, given a modest sample size, reasonably clear effect at 8 ng/(kg*min) with some but limited room for further effect.

These findings would suggest doses in the vicinity of 4 and 16 ng/(kg*min) corresponding to 19.2 and 76.8 µg/hr for an 80-kg person would be well chosen in this proof-of-concept study. As further development would most likely lead to a device with a fixed infusion rate, the glucagon doses chosen for the study are 20 and 80 µg/hr, or given the formulation concentration of 5 mg/ml, infusion rates of 4 and 16 µl/hr. For the pump setting that measures in insulin U100 units that corresponds to 0.4 and 1.6 U/hr.

This highest dose to be tested in the study will allow a greater than 10x safety margin based on findings from a 28-day toxicology study in rats conducted with Xeris glucagon (see current Investigator's Brochure).

6.1.2.4. Insulin Dose Adjustments

Constant infusion of low rate of glucagon may be expected to elevate glucose not only during circumstances that may have led to hypoglycemia, but also when not needed. To avoid glycemic escape, subjects' glucose data will be reviewed weekly and insulin doses adjusted accordingly by the clinical personnel.

6.1.2.5. Hypoglycemia induction

The hypoglycemia induction using a high continuous IV insulin infusion rate countered by a continuous IV glucose infusion is standard for HAAF protocols as published in a substantial body of literature. The planned insulin infusion rate of 20 mU/(BSA*min) is somewhat smaller than what is used in other studies but is still a sufficiently high rate to bring most subjects into hypoglycemia.

6.2. Non-Clinical Pharmacology and Toxicology Experience with Glucagon

Native glucagon for injection (bovine, porcine origin) was approved for use in humans in 1960 [FDA CDER #1]. The 29 amino acid sequence of pancreatic glucagon is identical in humans, cows, pigs, dogs, and rats, and is also conserved in biosynthetic versions of glucagon [Eistrup]. Glucagon for injection (rDNA origin) was approved in 1998 and is currently the subject of two approved NDAs ([NDA 20-928] and [NDA 20-918]). Complete NDA-required pharmacology and toxicology data have been reviewed and accepted by the FDA, as described in Lilly Glucagon [rDNA origin] for injection and Novo GlucaGen® (glucagon [rDNA origin] for injection) labeling [Glucagon, Glucagen]. As Xeris' drug product is produced by solid-phase peptide synthesis (SPPS), which also conserves the glucagon peptide sequence, the rDNA

glucagon information is pertinent to the development of Xeris' glucagon formulation. A summary of this information can be found in Xeris' current Investigator's Brochure, which will be provided to each investigator participating in this study.

6.2.1. Nonclinical Pharmacology and Toxicology of Xeris Investigational Non-Aqueous, Synthetic Glucagon

Information on the nonclinical pharmacology, pharmacokinetics and toxicology of Xeris' glucagon formulation is referenced to Xeris' current Investigator's Brochure.

6.3. Description and Composition of Drug Product

Synthetic glucagon is the drug substance in Xeris' glucagon formulation. Glucagon cGMP grade is manufactured, packaged and released by Bachem AG (Bubendorf, Switzerland), conforms with USP standards and has a Type II DMF filed with the FDA. Xeris' glucagon formulation is a sterile subcutaneous injectable non-aqueous formulation for treatment of severe hypoglycemia. Xeris' glucagon formulation contains 5 mg/ml of glucagon, with trehalose and DMSO as excipients. Xeris' glucagon formulation is supplied in 1.0 mL vials. The drug product is stored at controlled room temperature (20-25°C) prior to use.

6.4. Clinical Experience with Glucagon

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

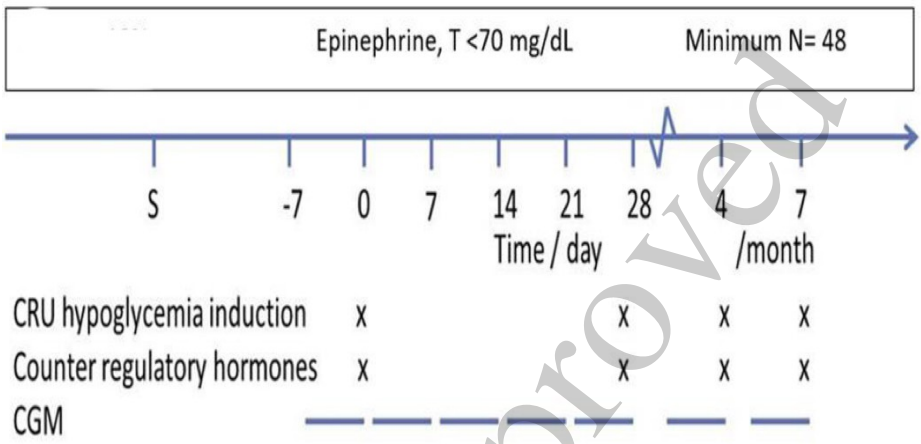
Since 2013 when the first IND for Xeris formulation went into effect, multiple clinical studies have been successfully completed including two studies utilizing the Omnipod for delivery. Details are provided in Xeris' current Investigator's Brochure.

7. STUDY DESIGN

7.1. Study Overview

This is a prospective, randomized, double-blind, parallel trial with the primary analysis after 4 weeks treatment with CSGI or placebo. As both the low and high dose group use the same formulation, the dose will be determined by infusion. To preserve the blind, the placebo therefore is administered by matching infusion methods to CSGI (high and low infusion rates, split to create the appearance of a 4-group trial on the schematic).

Study Schematic:



After a 1-week run-in on CGM, subjects will have key hormones of their hypoglycemia counter regulatory response quantified using a stepwise hypoglycemia induction. They will then receive investigational product for 4 weeks before discontinuation and reassessment of the same hypoglycemia counter regulatory response.

Treatment stops at 4 weeks, but subjects will continue blinded for 6 additional months to investigate duration of response with assessments at 3 and 6 months. The primary endpoint will be tested at 4 weeks post randomization, but the double blind will remain intact until the end of the study.

Baseline Qualification:

Subjects will continue their insulin regimen as usual throughout the study, adjusted by the investigator to achieve ADA recommended targets.

After enrollment, the subjects will require approximately one week of CGM data prior to their baseline hypoglycemia induction procedure. Subjects will enter a run-in phase of 1 week wearing a blinded CGM device.

Subjects will arrive in the Clinical Research Unit (CRU) the morning of the planned hypoglycemia induction procedure. The CGM data will be retrieved. The following CGM criteria must be met: a minimum of 6 days must be recorded using the CGM before the subject will be fitted with a new CGM device. If the CGM criteria are not met, the subject is inserted with another CGM for renewed baseline period. Should the second baseline period not yield eligible CGM data, the subject will stop further participation in the screening procedures.

The subject will fast after midnight. The subject's arms are cannulated venously, one side for both insulin and glucose infusion and the other side for venous sampling. The subject will stop their own insulin treatment and receive IV insulin and IV glucose to maintain their plasma glucose between 80 to 120 mg/dL, as measured by either BGM or YSI. They will remain fasting until the end of the hypoglycemia procedure the following day.

Hypoglycemia induction procedure:

In the morning, insulin induced hypoglycemia (PG < 50 mg/dL as measured by YSI) is achieved through a hyperinsulinemic clamp procedure.

The plasma glucose should be verified to be between the 80-120 mg/dL. The IV insulin infusion rate is then increased to 20 mU/(body surface area(BSA)*min) as a set rate and the subject's plasma glucose is stabilized at 100±10 mg/dL for minimally 60 minutes, through adjustments in continuous IV glucose. After this 60-minute stable period, the plasma glucose will be reduced to 70 mg/dL by decreasing the continuous IV glucose infusion rate. When the plasma glucose has been stable at 70+/-5 mg/dL for 20 minutes, a hypoglycemia symptom questionnaire administered, which will be repeated after 10 minutes.

The hypoglycemia induction will then begin, decreasing the continuous IV glucose infusion rate to bring the plasma glucose down to < 50 mg/dL. Plasma glucose is measured every 5 minutes and the continuous IV glucose infusion rate is adjusted to achieve the target glucose concentration of < 50 mg/dL. Hypoglycemia assessment will be administered every five minutes from this point until the end of the induction and PG recovery phase. When the target plasma glucose of < 50 mg/dL has been achieved, blood samples for the assessment of counter regulatory hormones are drawn. Plasma glucose concentration will be measured and maintained at 50+/-5 mg/dL for 30 minutes after which another set of blood samples for the assessment of counter regulatory hormones are drawn and the hypoglycemia questionnaire re-administered. The insulin infusion is then stopped, and plasma glucose is raised to >70 mg/dL through the continuous IV glucose. The continuous IV glucose infusion is stopped once the subject's PG > 70 mg/dL and the subject will be given a standardized meal. The subject is monitored until deemed medically stable for discharge, per investigator discretion.

Visit Overview:

After the completion of the first study visit (the baseline hypoglycemia induction procedure), the investigator will train the subjects to load, prime, and use the modified OmniPod. In this training, the subject will learn to prepare and use an OmniPod at a suitable infusion site. This includes direct observation of the subject when they attach and initiate the device, by the investigational staff.

The subject is then randomized to a study treatment and begins therapy in the CRU. The assigned study treatment will be 4 weeks in duration. They are initially provided with a 1-week supply of blinded study drug and OmniPods. The subjects will return weekly for a safety check, CGM device data retrieval, new sensor insertion, and receipt of study supplies. The subject is expected to complete at least 90% of the study therapy during the 4-week treatment period.

After 4 weeks of study therapy, the subject will return to the clinic. The study product will be stopped and the CGM data retrieved before a repeat of the hypoglycemia induction procedure as described above.

After 12 weeks after study treatment, the subjects will return to the CRU for insertion of a CGM device. One week later (13 weeks after completing study treatment), the CGM will be retrieved and the subject will undergo the hypoglycemia induction procedure as described above.

After 25 weeks after study treatment, the subjects will return to the CRU for insertion of a CGM device. One week later (26 weeks after completing study treatment), the CGM will be retrieved and the subject will undergo the hypoglycemia induction procedure as described above.

After completion of the hypoglycemia induction procedure at 26 weeks, the subject's participation in the study is completed.

7.2. Interruption and Termination of Dosing

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

8. ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

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

8.1. Inclusion Criteria

1. Males or females diagnosed with type 1 diabetes mellitus for at least 24 months.
2. Random serum C-peptide concentration < 0.6 ng/ml at Screening.
3. Age 21-64 years, inclusive, at screening.
4. Documented Hypoglycemia unawareness as evidenced by a Gold Scale score ≥4, at screening
5. Medical history of an episode of severe hypoglycemia as reported by patient < 50 mg/dL, in the 1 year prior to screening.
6. Current use of multiple daily dosing insulin treatment (< 1 U/(kg*day) total daily dose) either administered with subcutaneous injections or continuous subcutaneous insulin infusion (CSII).
7. Performs monitoring of glucose minimally 3 times a day. Patients using continuous glucose monitoring for monitoring should continue to do so during the course of the study.
8. Willingness to provide informed consent and follow all study procedures, including using the Medtronic smartphone application "iPRO2mylog" for diabetes data logging and attending all scheduled visits.

8.2. Exclusion Criteria

1. HbA1c ≥ 10% at Screening.
2. Chronic kidney disease stage 4 or 5.
3. Hepatic disease, including serum ALT or AST greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3 g/dL.
4. Hematocrit of less than or equal to 30% at Screening.
5. BP reading at Screening where SBP <90 or >150 mm Hg, or DBP <50 or >100 mm Hg.
6. Clinically significant ECG abnormalities at Screening.
7. Congestive heart failure, NYHA class III or IV
8. History of myocardial infarction, unstable angina or revascularization within the past 6 months.
9. History of a cerebrovascular accident with residual neurologic deficit.

10. Current seizure disorder, unrelated to hypoglycemia.
11. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
12. History of insulinoma.
13. 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.
14. Major surgical operation within 90 days prior to Screening.
15. Current bleeding disorder, treatment with anticoagulants, or platelet count below 50,000/mL at Screening.
16. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO, trehalose) in the investigational formulation.
17. History of glycogen storage disease.
18. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
19. Active substance or alcohol abuse (more than 21 drinks/wk. for males or 14 drinks/wk. for females). Subjects reporting active marijuana use and/or testing positive for THC via rapid urine test will be allowed to participate in the study at the discretion of the investigator. Subjects positive for other drugs of abuse via rapid urine test who report use of a prescription or OTC medication that would explain such a finding will be allowed to participate at the discretion of the investigator.
20. Administration of glucagon within 7 days of Screening.
21. Pregnant and/or Lactating. For subjects of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study and for at least 1 month after participating in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the female uses a diaphragm and spermicide and the male uses a condom), or abstinence.
22. Inadequate venous access.
23. Participation in other studies involving administration of an investigational drug or interventional device within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and during the four weeks of study product administration in the current study.
24. Any reason the principal investigator deems exclusionary.

Waivers to the inclusion/exclusion criteria will not be granted

8.3. Enrollment

Screening will continue until 48 subjects are qualified and randomized for the study. Subjects will not be considered enrolled in the study until the time of randomization

8.4. Allocation to Treatment

Subjects will be assigned a unique Screening number upon entry in the eCRF, which will consist of a unique 2-digit site code (starting with 01) and a 2-digit subject number (starting with 01 at each site) indicating the sequence at which the subject was screened for eligibility. Subjects will keep this number throughout the study.

The randomization scheme is 1:1:1 for high dose, low dose and placebo. Each group will have 16 subjects, but the placebo group will be matched to high and low infusion rates (8 in each group). The randomization is stratified by site.

When the subject is qualified and the hypoglycemia induction procedure begins day 1, the subject will be randomized by the study coordinator by either a central randomization or by logging into the IWRS and requesting a treatment allocation. The site personnel will receive the blinded treatment allocation number for the study drug product.

8.5. Blinding

For this study, subjects, investigators and study staff will be blinded.

The investigator has access to break the blind if necessary in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult the Sponsor prior to breaking the blind. When the blinding is broken, the reason must be fully documented and entered in the CRF.

8.6. Supplies

8.6.1. Investigational Product

8.6.1.1. Drug Product Formulation and Packaging

CSI-Glucagon™ is a room temperature stable, non-aqueous, injectable liquid formulation of glucagon. The formulation consists of 5 mg/mL synthetic glucagon peptide dissolved in a primary DMSO solvent, with trehalose added as a stabilizing excipient. A volume of 1 mL of formulation is filled into West Pharmaceutical's 2 mL Crystal Zenith® pre-filled cyclic olefin polymer (plastic) vial with Flurotec® coated stopper. The drug product is stored at controlled room temperature (20-25°C) prior to use.

8.6.1.2. Matching Placebo

The placebo consists of the vehicle for CSI-Glucagon, so it contains DMSO and trehalose, but no glucagon. The placebo is indistinguishable from the investigational drug and will be stored under the same conditions.

8.6.2. Drug Delivery Devices

All OmniPod® devices to be used in the study are FDA approved and will not be modified in any way from their original state as provided by the manufacturer.

All devices will be stored at the hospital pharmacies where the clinical investigation takes place or in the investigators' offices prior to use in the clinical trial.

8.6.3. Preparation, Dispensing and Administration

CSI-Glucagon™ and placebo will be supplied as 1 mL of non-aqueous solution in plastic Crystal Zenith (CZ) 2 mL vials. CSI-Glucagon™ will be transferred to the OmniPod® using the syringe and the fill needle supplied by the pump manufacturer. DMSO-compatible B Braun Injekt F® Low Waste Syringe 1 mL will be supplied by Xeris as backup. Each vial of CSI-Glucagon™ will be used to fill a single OmniPod® pump. If CSI Glucagon™ is not transferred into the OmniPod® within one hour of being drawn up into the syringe, the syringe, needle and drug should be discarded, and a fresh vial, needle and syringe should be used to fill the pod.

8.6.4. Drug Storage and Drug Accountability

Unless notified otherwise by the Sponsor, all supplied Xeris' investigational product is to be stored at controlled room temperature between 20°C to 25°C (68° to 77°F), and drug solution should be clear and of a water-like consistency at time of use.

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

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

The investigator must maintain adequate records documenting the receipt, use, loss or other disposition of the investigational drug products and supplies. Used and unused investigational product will be returned to Xeris. Other used supplies will be destroyed according to local regulation and site level SOPs following accountability by Xeris Pharmaceuticals or its designee.

8.7. CGM Devices

Sites will be supplied with sufficient iPRO2 recorder devices to have a dedicated device for each subject. The sites will store this device between the CGM data gathering periods and will clean the devices before return to Xeris at the end of the study.

The sites will be supplied sufficient sensors for the study.

Subjects using their own CGM may continue to use their own device during the study, but these will not be re-supplied through the study.

8.8. Glucose Meters for Self-Monitoring and Calibration of the CGM Devices

Subjects will be supplied Contour Next meters and strips for use during the CGM data collection periods of the study. Subjects must use the supplied meter during these periods of the study, and may use it at other times during the study, but are not required to do so.

8.9. Subject Data Log and Smartphone

The study will capture diabetes management data using the iPRO2mylog application on their own device. The application is available in Apples' and Google's respective online stores. Xeris will make smartphones available for subjects, during the course of the study, if they do not own a compatible smartphone.

8.10. Concomitant Medications

Subjects should be on a stable dose of all concomitant medications for at least 30 days prior to Screening. All subjects must have their concomitant medications reviewed at each visit. Medications taken within 4 weeks before Day 1 will be documented in the CRF. Any changes to a subject's concomitant medication regimen will be documented. Investigators are encouraged to avoid adding to or changing a participant's medications until week 4 of study participation unless deemed medically necessary.

There are not medications that are specifically prohibited during participation in this study, except the medications (e.g., anticoagulants) listed under the exclusion criteria (see Section 8).

9. STUDY PROCEDURES

9.1. Outpatient Insulin Dose Adjustment During Run-in and Treatment Phases Weeks -1-4

Subjects' insulin doses should be reviewed and adjusted to maintain current ADA recommended glycemic targets of pre-prandial PG of 80-130 mg/dL and post-prandial PG<180 mg/dL, per investigator's discretion.

9.2. CGM, Glucose Meter, Electronic Diary and Pump Data

CGM, glucose meter, electronic diary data, and insulin pump data for CSII users should be collected weekly. The subject is expected to return to the clinic for data upload. The Medtronic iPRO2 platform will be familiarized with both the investigator and the subject.

9.3. Euglycemia Maintenance Procedure

The subject will begin fasting at midnight. The subject must have been fasting for a minimum of eight hours before the induction procedure may begin.

Upon the subject's early morning arrival to clinic*, their plasma glucose should be maintained within a target range between 80-120 mg/dL, via IV insulin infusion and/or IV glucose infusion. This target range should be obtained as soon as possible. The plasma glucose should be remeasured every 30 minutes and appropriately treated until it reaches the desired target range has been reached. Afterwards, the plasma glucose may be rechecked every hour.

*Per institutional/departmental policy and the approval of the sponsor a subject may be brought in the evening prior to the induction procedure.

Table 3: Recommended Guidelines for Insulin Infusion Rate Management Following Measured PG

Below Goal Range Less than 90 mg/dL	Within Goal Range 90-120 mg/dL	Above Goal Range Over 120 mg/dL
Less than 70 mg/dL • Turn off infusion • Follow Hypoglycemia orders*** • Recheck BG and re-retreat every 15. Then proceed according to the appropriate column of this table for next measured BG. **70 – 80 mg/dL** • Turn off infusion. • Check BG in 30 minutes. • Once BG is > 80mg/dl resume insulin infusion after moving one column to the **left** **80-90 mg/dL** **If BG decreased by 30 mg/dL or more, or previous BG 80-90 mg/dL** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard move **left** to ¼ Standard Algorithm and adjust rate per BG. • If already at ¼ algorithm, may remain there. **If BG decreased less than 30 mg/dL and/or previous BG was in goal range** • Adjust rate in **current** algorithm per BG.	**If BG decreased by >30 mg/dL between checks** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard, move **left** to ¼ Standard (Low) Algorithm and adjust rate per BG **If BG DECREASED by 1-30mg/dl or INCREASED by any amount** • Adjust rate in **current** algorithm per BG	**IF BG decreased by more than 50 mg/dL** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard, move **left** to ¼ Standard (Low) Algorithm and adjust rate per BG. • Check BG in 15 minutes if decrease was over 100 mg/dL. **If BG decreased by 25 – 50 mg/dL** • Adjust rate in **current** algorithm per BG **If BG increased by any amount, remained the same or decreased by less than 25 mg/dL** Step 1. Remain in **current** algorithm and adjust rate per BG. Step 2. If **after** remaining in **current** algorithm and next BG check continues to increase by any amount or decrease by less than 25 mg/dL, move **right** one algorithm Step 3. Check BG at next time point per protocol, and restart at step 1 if appropriate.

Table 4: Recommended Euglycemia Maintenance IV Insulin Infusion Rate Algorithms

BG mg/dL	# 1/8 units/hr (ml/hr)*	# 1/4 units/hr (ml/hr)*	# 1/2 units/hr (ml/hr)*	# 1 Standard units/hr (ml/hr)*	# 2 units/hr (ml/hr)*	# 3 units/hr (ml/hr)*	# 4 units/hr (ml/hr)*	# 5 units/hr (ml/hr)*	# 6 units/hr (ml/hr)*
80-90	0.1 (0.5)*	0.2 (1)	0.3 (1.5)	0.5 (2.5)	0.6 (3)	0.8 (4)	1.0 (5)	1.2 (6)	1.4 (7)
90 - 120	0.2 (1)	0.3 (1.5)	0.5 (2.5)	0.7 (3.5)	0.8 (4)	1.0 (5)	1.2 (6)	1.4 (7)	1.6 (8)
121-160	0.3 (1.5)	0.4 (2)	0.7 (3.5)	0.9 (4.5)	1.1 (5.5)	1.2 (6)	1.4 (7)	1.6 (8)	1.8 (9)
161-180	0.4 (2)	0.5 (2.5)	1 (5)	1.1 (5.5)	1.3 (6.5)	1.5 (7.5)	1.7 (8.5)	1.9 (9.5)	2.1 10.5
181-220	0.5 (2.5)	0.6 (3)	1.2 (6)	1.3 (6.5)	1.5 (7.5)	1.7 (8.5)	1.9 (9.5)	2.1 (10.5	2.3 11.5)
221-260	0.6 (3)	0.8 (4)	1.5 (7.5)	1.7 (8.5)	1.9 (9.5)	2.1 (10.5	2.3 (11.5	2.5 (12.5	2.7 (13.5
261-300	0.8 (4)	1 (5)	2 (10)	2.2 (11)	2.4 (12)	2.6 (13)	2.8 (14)	3.0 (15)	3.2 (16)
Over 300	1 (5)	1.3 (6.5)	2.5 (12.5	2.8 (14)	3.0 (15)	3.2 (16)	3.4 (17)	3.6 (18)	4.0 (20)

*When using 100 units of regular insulin per 500ml of saline, the pump infusion rates in parentheses apply.

9.4. Hypoglycemia Induction Procedure

After the data are checked and PG confirmed to have been within range the visit proceeds. If the PG is < 70 mg/dL or > 200 mg/dL, the subject must be rescheduled.

The hypoglycemia induction procedures have to be initiated in the morning defined as 6 A.M. to 12 P.M. Subjects should have both arms cannulated one for infusion and one for sampling. Separate infusion pumps for insulin and glucose should be ready to begin the procedure. Subjects should remain blinded to their PG levels throughout this procedure.

The venous sampling arm should be kept warm in a heated hand box throughout the treatment procedure, in order to achieve “arterialized” samples. The subject’s hand should be monitored at least twice an hour to assure it remains warm during the hypoglycemia induction procedure, and if it turns cool appropriate measures take to keep it warm.

The periods of the procedure and what is adjusted are outlined in Table 5.

Table 5: Hypoglycemia Induction Overview

Period Reference	Measured PG (mg/dl)			Minimum Time	Insulin infusion		Glucose infusion
	Target	+/-	Range		Insulin infusion rate	Adjustments	Glucose infusion rate
Overnight stabilization	100	20	80-120		Euglycemia algorithm	Yes	0, but ready
Baseline stabilization	100	10	90-110	60 min.	20 mU/(BSA*min)	Change only if insufficient	As needed for stabilization
Start induction 1st step	70				20 mU/(BSA*min)	Change only if insufficient	Decrease to drop PG at a rate of ≈1 mg/(dl*min)
Induction 1st step	70				20 mU/(BSA*min)	Change only if insufficient	Increase when PG nears target
70 mg/dl stabilization	70	5	65-75	30 min.	20 mU/(BSA*min)	Change only if insufficient	As needed for stabilization
Start induction 2nd step	70				20 mU/(BSA*min)	Change only if insufficient	Decrease to drop PG at a rate of ≈1 mg/(dl*min)
Induction 2st step	50				20 mU/(BSA*min)	Change only if insufficient	Increase when PG nears target
50 mg/dl stabilization	50	5	45-55	30 min.	20 mU/(BSA*min)	Change only if insufficient	As needed for stabilization
Normalization	100		80-140		0	No	As needed until PG> 70 mg/dl

9.4.1. Baseline Stabilization with Constant Insulin Infusion Rate

1. After the baseline procedures are complete the insulin infusion rate is set at 20 mU/(BSA*min). The rate should be kept constant until the hypoglycemia procedure is over unless it proves insufficient. The BSA is calculated using the formula $BSA=0.007184*W^{0.425}*H^{0.725}$ where 'W' is weight measured in kg and 'H' is height measured in cm [Du Bois].
2. Based on PG measurement every 5 minutes the glucose infusion rate (GIR) is adjusted to maintain plasma glucose within in the 90-110 mg/dL range with a target of 100 mg/dL.
3. Time 0 begins at the first PG reading within the range of 90-110 mg/dL.
4. The PG will be measured every 5 minutes for sixty minutes:
    a. If > 2 of 12 PG measurements are not within the specified range, the sixty minute stabilization period will restart.
        - This baseline stabilization must be completed within 120 minutes.
    b. If no more than 2 of 12 PG readings are outside the range, subject will continue to step Hypoglycemia induction, 1st step.
    c. Plasma Glucose and assessment of hypoglycemia symptoms will be measured as a baseline
    d. Hypoglycemia symptoms will be assessed every ten minutes while subject is above 70 mg/dL
    e. Two sets of baseline counter regulatory hormone blood samples are drawn 10 minutes apart once the sixty minutes are met (e.g. 60 and 70 minutes)

9.4.2. Hypoglycemia Induction, 1st Step

1. The GIR will be decreased with the goal of achieving a PG change rate of – 1 mg/(dL*min) to achieve the target of 70 mg/dL.
2. At every PG measurement the estimated time to the 70 mg/dL target will be assessed and the GIR adjusted accordingly.
    - Hypoglycemia symptoms will be assessed every five minutes when subject is below 70 mg/dL

9.4.3. 70 mg/dL Stabilization

1. The GIR will be adjusted to maintain the target 70 mg/dL ± 5 mg/dl guided by PG measurements every 5 minutes.
2. Should PG briefly be lower than target range, the steps may be prolonged.
3. When the plasma glucose has been maintained at 70 mg/dL ± 5 mg/dl, for a minimum of 30 minutes and the described data collection procedures completed. Then the next phase may begin.

9.4.4. Hypoglycemia Induction and Stabilization, 2nd Step

1. The GIR will be decreased with the goal of achieving a PG change rate of – 1 mg/(dl*min) to achieve the target of 50 mg/dL but no greater than 54 mg/dL.
2. The PG will be measured every 5 minutes for thirty minutes:
    a. If 1 PG measurement is greater than 54 mg/dL during the thirty minutes; the 2nd step will re-start, per investigator discretion.
3. At every PG measurement the estimated time to the 50 mg/dL target will be assessed and the GIR adjusted accordingly.
    a. Plasma Glucose and assessment of hypoglycemia symptoms will be measured and assessed every 5 minutes.

4. When the plasma glucose at 50 mg/dL has been maintained for a minimum of 30 continuous minutes, two sets of blood samples for assessment of counter regulatory hormones will be drawn 10 minutes apart (e.g. 30 and 40 minutes).

9.4.5. Normalization to Euglycemia

1. When the plasma glucose at 50 mg/dL has been maintained for a minimum of 30 minutes and the described data collection procedures completed, the IV insulin infusion will be stopped and the IV glucose infusion will continue.
    a. Plasma Glucose and assessment of hypoglycemia symptoms will be measured and assessed every 5 minutes until subject's PG is ≥ 70mg/dL
    b. Plasma Glucose and assessment of hypoglycemia symptoms will be measured and assessed every 10 minutes until subject's PG is between 90-110 mg/dL or the subject reaches Euglycemia.
2. When PG is >70 mg/dL, the IV glucose infusion is stopped.
3. The subject will be offered a standardized meal. Euglycemia is confirmed in this recovery period.
4. The subject may be discharged when deemed medically stable by the investigator, per CRU criteria.
5. The subject's outpatient insulin dosing will be resumed to their baseline setting, after discharge from the CRU.

9.5. Visit Structure

A schedule of assessments for this study is provided below in Table 6. All visits should occur relative to the randomization which is day zero.

9.5.1. Visit 1 - Screening (Day up to 25 days + 5)

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 14.3. Subject Information and Consent. Assessment of inclusion/exclusion criteria by a study investigator, including a review of the subject's medical history.

1. Demographic data collection
2. Concomitant medication review
3. Recording of the subject's insulin correction factor (i.e., the reduction in blood glucose in mg/dL per 1 unit of insulin taken).
4. Assessment of vital signs, including measurement of BP, after a 5-minute seated rest.
5. Physical examination, excluding breast, pelvic and genitourinary exams.
    - Measurement of height and weight
6. Performance of a 12-lead ECG (after subject has completed a 10-minute supine rest.)
7. Urine pregnancy test for women of childbearing potential.

8. Rapid Urine drug screen.
9. Collection of venous blood for the following tests as outlined in the Schedule of Activities: hemoglobin A1C, complete blood count (without differential), complete metabolic panel (CMP), screening for HIV, HBV and HCV (Table 8), and immunogenicity testing.
10. The subject will complete the Gold Scale
11. The subject will be asked if he/she has a smartphone for the logging, and if not order a smartphone for subject use during the study.
12. The subject will be instructed to continue their usual diabetes management.
13. Once laboratory results are obtained and a final determination of eligibility is made, subject will be contacted to schedule visit 2 for initiation CGM baseline assessment.

    ** If a subject is outside of the screening window, the laboratory assessments will need to be repeated before enrollment.

9.5.2. Visit 2 (Day -7) Initiation of Baseline CGM Assessment and Diary Data Collection

The subject will arrive at the clinic and the following procedures will be completed:

1. Eligibility review
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. Review Adverse Events
4. The subject will receive and be trained in the use of the glucose meter and strips for use in the study during the CGM data collections periods.
5. The study personnel will assist the subject with downloading the iPRO mylog App and creating the appropriate account to allow synchronization with the CGM data.
    a. Each site is provided with their specific clinic i.d. from the sponsor
6. The subject will have the blinded iPRO2 CGM device assigned, inserted and initiated according to the manufacturer's instructions. The iPRO2 device ID will be logged for later entry into the eCRF.
7. The importance of using the study glucose meter no less than 12 hours apart will be emphasized for the subject.
    a. Subjects must perform blood glucose readings at a minimum of twice per twenty-four hour period.
8. The subject's clinical practice glucose, insulin, diary and pump data, if applicable, leading up to the visit will be reviewed and any dose adjustments as required will be made.
    a. An Insulin Diary will be provided to the subject to collect the following, daily:

- Total daily dose
- Total Daily Bolus
- Basal Rate

9. Schedule the subject's next visit and provide the following reminder:
    a. Subject should not administer any long acting insulin dose after dinner the day before the induction procedure.
    b. Sensors will only hold 7 days of data. Should a subject receive an alert from the iPro app, S/He should contact the site for guidance.

9.5.3. Visit 3 (Day 1) Start of Treatment Phase

The subject will arrive to the clinic at about 6-9 am for the planned randomization. The subject will fast after midnight until the end of the hypoglycemia procedure the subsequent day.

The following procedures will be completed:

1. Eligibility Review
2. The subject's CGM, electronic diary, and insulin utilization data will be collected/uploaded to the electronic data capture (EDC).
3. Assessment will be made whether the CGM baseline data meet the criteria of minimum 6 days are recorded using the CGM device. The clinic will be notified within 30 minutes from time of subject data upload as follows:
    a. If the data do not meet the above criteria, the subject is inserted with another CGM for renewed baseline of CGM period. The visit is rescheduled for a week later and the subject is sent home with instructions for another baseline attempt. Should the second baseline period not yield eligible CGM data, the subject will stop further participation in the procedures.
    b. If the data meets criteria, the visit proceeds.

The following procedures will be carried out once CGM data is confirmed. This includes a confirmation that the subject did not have a hypoglycemic event, < 70 mg/dL during the 8 hours prior to the induction.

4. A new CGM sensor will be inserted.
5. The subject will be asked of any changes in concomitant medications since their last visit and this will be documented in the CRF.
6. The subject will fill out the Gold Score about hypoglycemia awareness.
7. Urine pregnancy test for women of childbearing potential.
8. The subject will be reminded to refrain from using his or her own insulin until the hypoglycemia induction procedure the following day is complete. However, the subject will withhold their long acting insulin.

9. The Insulin Diary will be collected from the previous visit and a new diary given to the subject to collect the following, daily:
    - Total daily dose
    - Total Daily Bolus
    - Basal Rate
10. IV lines are inserted in both upper extremities. One side will be used for both IV insulin infusion and IV glucose infusion. The other side will be used for venous sampling during the clamp procedure.
11. Collection of venous blood for the following tests as outlined in the Schedule of Activities:
    - CBC/CMP
    - Plasma glucagon (PK) prior to Omnipod placement
12. Plasma glucose is measured using a laboratory quality instrument, e.g. the YSI 2300 or 2900 that will be used for the clamping procedure.
13. Insulin infusion should begin after the baseline venous blood samples are obtained. An IV glucose infusion should be started concomitantly.
14. Assessment of vital signs, including measurement of BP, after a 5-minute seated rest
15. The 100 mg/dL baseline prior to hypoglycemia induction will be assessed for adequacy or initiated as described in section 9.4.1.
    a. When the baseline has been deemed adequate for at least 60 minutes two sets of blood samples for assessment of counter regulatory hormones will be drawn 10 minutes apart and processed.
16. The hypoglycemia induction including PG determination and hypoglycemia symptoms assessments (Appendix 2) will be executed as described in sections 9.4.2 to 9.4.5.
17. When hypoglycemia at 50 mg/dL has been held for 30 minutes, two sets of blood samples for assessment of counter regulatory hormones will be drawn 10 minutes apart and processed.
18. Treatment allocation and dispensing: The subject will be randomized as described in section 8.4, investigational product and Omnipods for the subject will be retrieved from storage.
19. When PG is >70 mg/dL in the normalization phase (section 9.4.6) the subject will be instructed in the filling and deployment of the OmniPod.
20. The study personnel will ensure the Omnipod flow rate is correctly set per protocol.
21. The subject will fill and deploy the first Omnipod under the observation of study personnel, insert and initiate the device as part of the training so that the subject can do this at home 2-3 days later.
22. The subject will be supplied with sufficient investigational product, Omnipods, and other study materials until the next weekly visit. The subject's training will include instructions to prepare a new Omnipod with the study drug for insertion, every 2-3 days.
23. Each time a new OmniPod is started local tolerability will be assessed as follows:

a. Subjects will complete a Visual Analog (VAS) questionnaire regarding infusion site discomfort (Appendix 3) at **10±5** minutes, at **30±5** minutes and again at **180±5** minutes following the injection of study drug.

b. Subjects will complete an Injection Site Discomfort Description and Duration Questionnaire at **10±5** minutes post-dosing. If discomfort is ongoing at 10 minutes post-dosing, the questionnaire will be completed again before the subject leaves the clinic to document the final duration.

24. When the normalization procedure is complete and the subject is medically stable for discharge, the next CRU visit, to replenish supplies, will be scheduled. The subject will be reminded to keep his or her iPROmylog diary, bring used and unused Omnipods and investigational product vials back at the next visit.

9.5.4. Visit 4 – Safety check (Day 7±2)

This visit can occur at any time of day as is least cumbersome for subject and clinic scheduling. The following will occur.

1. AEs since the last visit will be recorded.
2. Concomitant medication review.
3. Subject data including CGM, insulin utilization, electronic diary data will be uploaded to the MedTronic iPRO2 platform.
4. The subject's Omnipod will be removed.
5. The investigator or sub-investigator will use the modified Draize scales (Appendix 4) to assess erythema and edema formation at the injection site at 10±5 minutes following removal of the Omnipod. Any injection site with a score > 0 for either erythema or edema at 10 minutes post-dosing will be re-evaluated for both at 60±5 minutes post-dosing. If any scores remain > 1 at the 60-minute evaluation, the subject may leave the clinic but will be instructed to contact study staff if the condition fails to resolve.
6. Investigational Product and Omnipod accountability will be performed
7. The subject will load and initiate a new Omnipod with investigational product.
8. The subject will be given investigational product and Omnipods to cover time to next visit and will be instructed to exchange the Omnipod every 2-3 days.
9. Each time a new OmniPod is started local tolerability will be assessed as follows:
    - Subjects will complete a Visual Analog (VAS) questionnaire regarding infusion site discomfort (Appendix 3) at 10±5 minutes, at 30±5 minutes and again at 180±5 minutes following the injection of study drug.
    - Subjects will complete an Injection Site Discomfort Description and Duration Questionnaire (Appendix 4) at 10±5 minutes post-dosing. If discomfort is ongoing at 10 minutes post-dosing, the questionnaire will be completed again before the subject leaves the clinic to document the final duration.
10. The next visit will be scheduled
11. The subject will be reminded to keep his or her iPROmylog diary, bring used and unused Omnipods and investigational product vials back at the next visit

9.5.5. Visits 5 (Day 14±2)

Visit procedures are identical to Visit 4 listed in section 9.5.4.

9.5.6. Visit 6 (Day 21±1)

Visit procedures are identical to Visit 5 listed in section 9.5.4.

Additionally, the Insulin Diary will be given to the subject to collect the following, daily:

- Total Daily Dose
- Total Daily Bolus

- Basal Rate

9.5.7. Visit 7 (Day 28±1)

The subject will fast after midnight the night before and arrive to the clinic at about 6-9 am the day of the planned hypoglycemia induction procedure. They will fast until the end of the hypoglycemia induction procedure the subsequent day. The subject will undergo the Hypoglycemia Induction Procedure as described in Section 9.4

1. AEs since the last visit will be recorded.
2. Concomitant medication review.
3. Assessment of vital signs, including measurement of BP, after a 5-minute seated rest
4. Physical examination, excluding breast, pelvic and genitourinary exams.
    - Measurement of height and weight
5. Performance of a 12-lead ECG (after subject has completed a 10-minute supine rest.)
6. Urine pregnancy test for women of childbearing potential.
7. Rapid urine drug screen.
8. The subject will have the following samples drawn:
    - CBC/CMP
    - Plasma glucagon (PK) before the Omnipod is removed
    - Immunogenicity sample
9. The subject's glucose, insulin, diary and pump data, if applicable, since the last visit will be reviewed. Subject data will be uploaded to the Medtronic Carelink Portal.
10. The Insulin Diary will be collected from the previous visit
11. The subject will complete the Gold Scale
12. The subject's Omnipod will be removed. Drug and Omnipod accountability will be completed.
13. The investigator will use the modified Draize scales (Appendix 5) to assess erythema and edema formation at the injection site at 10±5 minutes following removal of the Omnipod. Any injection site with a score > 0 for either erythema or edema at 10 minutes post-dosing will be re-evaluated for both at 60±5 minutes post-dosing. If any scores remain > 1 at the 60-minute evaluation, the subject may leave the clinic but will be instructed to contact study staff if the condition fails to resolve.
14. The subject will be reminded to refrain from using his or her own insulin until the hypoglycemia induction procedure is complete.
15. IV lines are inserted in both upper extremities for IV insulin and glucose infusion, and for venous sampling.
16. Plasma glucose is measured using a laboratory quality instrument, e.g. the YSI 2300 or 2900 that will be used for the clamping procedure.

17. Plasma Glucose will be maintained in the 80-120 mg/dL range until as described in section 9.4.
18. The subject will undergo the hypoglycemia induction procedure and normalization to euglycemia, per Section 9.4.
19. At the end of the treatment visit, the subject will discontinue use of the iPRO2mylog.
20. For the rest of the study, the subject will continue their standard of care for diabetes management. Study drug and devices are no longer used.

9.5.9. Visit 8 (Week 12±1 week)

CGM Resumption for 3-Month Follow Up

This visit can occur at any time of day as is least cumbersome for subject and clinic scheduling. The following will occur.

1. Concomitant Medication Review
2. AEs since the last visit will be recorded.
3. The subject's dedicated blood glucose meter and iPRO2 recorder will be retrieved from storage and the subject will resume use as well as the iPRO2mylog diary with the insertion of a new CGM sensor.
4. The subject will be given a supply of BGM strips until the next visit a week later, to verify calibration of the CGM.
5. The Insulin Diary will be given to the subject to collect the following, daily:
    - Total Daily Dose
    - Total Daily Bolus
    - Basal Rate
6. The next visit will be scheduled.

9.5.10. Visit 9 (Week 13±1 Week) 3-Month Follow Up

The subject will arrive to the clinic at about 6-9 am the day of the planned hypoglycemia induction procedure. The subjects will undergo this inpatient CRU visit.

1. AEs since the last visit will be recorded.
2. Concomitant medication review.
3. Assessment of vital signs, including measurement of BP, after a 5-minute seated rest
4. Urine pregnancy test for women of childbearing potential.
5. The subject will be reminded to refrain from using his or her own insulin until the hypoglycemia induction procedure is complete.
6. The subject will complete the Gold Scale

7. Subject data including CGM, insulin utilization, electronic diary data will be uploaded to the MedTronic iPRO2 platform.
8. The Insulin Diary will be collected from the previous visit.
9. IV lines are inserted in both upper extremities for IV insulin and glucose infusion, and for venous sampling.
10. Plasma glucose is measured using a laboratory quality instrument, e.g. the YSI 2300 or 2900 that will be used for the clamping procedure.
11. Plasma Glucose will be maintained in the 80-120 mg/dL range as described in section 9.4.
12. The subject will undergo the hypoglycemia induction procedure and normalization to euglycemia, per Section 9.4
13. The subject will have the following sample drawn:
    - Immunogenicity Sample

9.5.11. Visit 10 (Week 25±1 Week)

CGM Resumption for 6-Month Follow Up

The visit procedures are identical to those on Visit 8 week 12 as described in section 9.5.8.

9.5.12. Visit 11 (Week 26±1 Week)

6-Month Follow Up and Completion of Study

The visit procedures are identical to those on Visit 9 as described in section 9.5.9 with the additions that the following is performed:

1. A physical examination, excluding breast, pelvic and genitourinary exams.
2. The subject will have the following samples drawn:
    - CBC/CMP
3. Final discharge of the subject from the study.

9.6. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject to determine the reason(s) why the subject failed to return for the scheduled visit, and to reschedule the missed visit. In all circumstances, every effort should be made to document subject outcome. Information regarding the reason for not completing the study will be recorded in the CRF. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, and follow-up with the subject

regarding any unresolved AEs. It will be documented whether each subject completed the study. Any subject who receives at least one treatment dose of study medication will be included in the safety analysis.

If a decision by the investigator or sponsor is made to withdraw a subject, a final visit should be scheduled soon after the decision to withdraw is made. The subject will be asked to return to site for the assessments listed in Section 9.5.11.

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 6: Schedule of Assessments

Assessment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening Day 25+ 5	**CGM Placement Day -7**	**Baseline Day 1**	**Safety Check Day 7±1**	**CGM Placement Day 14±1**	**CGM Placement Day 21±1**	**Treatment End Day 27-28±1**	**CGM Placement 12±1 weeks**	**3-Month F-up +13±1 weeks**	**CGM Placement 25±1 weeks**	**6-Month F-up 26±1 weeks**
Informed consent	X										
Demographic data	X										
Concomitant medications	X		X	X	X	X	X	X	X	X	X
Eligibility review	X	X	X								
Vital signs	X		X				X		X		X
Physical exam [a]	X						X				X
ECG	X						X				
Urine pregnancy test	X		X				X		X		X
Rapid urine drug screen	X						X				
CBC/CMP	X		X				X				X
HbA1c	X										
Subject glucose testing data review and insulin dose adjustment		X	X	X	X	X	X				
Randomization			X								

Assessment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening Day -- 25±5	**CGM Placement Day -7**	**Baseline Day 1**	**Safety Check Day 7±1**	**CGM Placement Day 14±1**	**CGM Placement Day 21±1**	**Treatment End Day 27-28±1**	**CGM Placement 12±1 weeks**	**3-Month F-up 13±1 weeks**	**CGM Placement 25±1 weeks**	**6-Month F-up 26±1 weeks**
Hypoglycemia induction			X				X		X		X
Plasma glucose (YSI)[b]			X				X		X		X
Hormone levels[c]			X[d]				X[d]		X		X
Gold scale & Hypoglycemia symptom questionnaire	X[e]		X				X		X		X
Blood samples for immunogenicity testing	X				X		X		X		X
Insert new CGM		X	X	X	X	X		X		X	
Retrieve prior CGM			X	X	X	X	X		X		X
Account for and Dispense vials & OmniPods			X	X	X	X	X[f]				
Subject questionnaire for InjectionSite Discomfort			X	X							

Assessment	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screening Day -- 25±5	CGM Placement Day -7	Baseline Day 1	Safety Check Day 7±1	CGM Placement Day 14±1	CGM Placement Day 21±1	Treatment End Day 27-28±1	CGM Placement 12±1 weeks	3-Month F-up 13±1 weeks	CGM Placement V6 +25±1 weeks	6-Month F-up 26±1 weeks
Draize scales				X			X				
Subject Insulin Diary[g]		X	X[h]			X	X[h]	X	X[h]	X	X[h]
Review AE		X	X	X	X	X	X	X	X	X	X

[a] Excluding breast and pelvic/genitourinary exam.
[b] Every 5 minutes during hypoglycemia induction
[c] Norepinephrine, glucagon, cortisol and growth hormone 10 minutes apart when PG is at 100 mg/dl and 50 mg/dl, 4 times total per hypoglycemia procedure.
[d] For glucagon prior to hypoglycemia induction at baseline day -1 and before the removing of the Omnipod at day 27.
[e] Only the Gold Scale is administered at screening
[f] Accounting only, no dispensing.
[g] Subject Insulin Diary will be provided to the subject to collect the following: Total Daily Dose, Total Daily Bolus, Total Basal.
[h] Subject Insulin Diary is only collected from the subject

10. ASSESSMENTS

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

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

10.1. Estimated Blood Volume Drawn through Time

At each hypoglycemia induction there will be approximately 50 blood samples for PG determination of about 2cc each Additional sample requirements are shown in (Table 7). The largest blood volume drawn over any 3-month period is < 350 ml (less than 24 tablespoons).

Table 7: Frequency and Volume of Blood Collections

Assay	Sample Volume (mL)	Screening	V3	V7	V9	V11	Total (mL)
Plasma Glucose (YSI)*	2		50	50	50	50	400
Serum Ethanol	5	1					5
Chemistry (14 gen chem. incl. ALT, AST, bilirubin, albumin)	7.5	1	1	1		1	30
C-peptide, serum	2.5	1					2.5
Hematology (Hemoglobin, Hematocrit, Platelet Count, MPV, RDW, RBC Count, WBC Count, MCV, MCH, MCHC, - no differential)	3.5	1	1	1		1	14
HbA1c (included in hematology)		1					0

Assay	Sample Volume (mL)	Screening	V3	V7	V9	V11	Total (mL)
Hormone levels: Cortisol, Norepinephrine, Growth hormone	2		4	4	4	4	32
Hormone levels: Plasma epinephrine	4		4	4	4	4	64
Glucagon	8.5		4	5	4	4	144.5
Immunogenicity (Anti-glucagon antibody)	3.5	1		1	1	1	14
Total/Visit (mL)		22	169	181	161.5	172.5	706

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

10.2. Clinical Laboratory Tests

The tests outlined in Table 8 will be performed at the specified time points described in the Schedule of Activities.

Table 8: Clinical and Safety Related Laboratory Tests Performed at Site

Hematology	**CMP/Metabolic**	**Urine**
WBC count	Ca^{++}	β-hCG[a]
RBC count	Random Glucose	Drug screen[b]
Hemoglobin	Albumin	
Hematocrit	Na^{+}	
Platelet count	K^{+}	
MPV	Total Protein	
RDW	Bicarbonate	
MCV	Chloride	
MCH	BUN	
MCHC	Creatinine	
(no differential)	Alkaline Phosphatase	
	AST/SGOT	
	ALT/SGPT	
	Bilirubin	

Hormones	**Immunogenicity**	**Laboratory**
Growth Cortisol Epinephrine Norepinephrine Glucagon	Anti-glucagon-antibody	HbA1c C-peptide HIVab HCVab HBsAg

[a] Female participants of childbearing potential require a negative pregnancy test at Screening. Pregnancy testing will be repeated at the last treatment visit.
[b] Drug screening performed at Screening and the 2 Treatment Visits will include: cocaine, THC, opiates, benzodiazepines, and amphetamines. Except as noted below, inclusion in the study requires all tests to be negative at screening with the exception of THC, which will be noted, but will not be considered exclusionary.

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

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

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

A central analytical lab will analyze the PK samples collected in this study. The procedures for preparing, storing and shipping PK samples to the analytical lab are discussed. To the extent possible based on storage limitations at the sites, PK samples will be batched so as to reduce the overall number of shipments. The main and back-up PK samples (i.e., Aliquots 1 and 2) for a particular subject should never be included in the same shipment.

During treatment visits, PG levels will be measured using a bedside rapid glucose analyzer (e.g. YSI 2300 or 2900). At each time point specified in Section9.5, 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 PG 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.

10.3. Electrocardiogram (12-lead ECG)

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

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

10.4. Blood Pressure and Heart Rate

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

BP and heart rate will be measured in the sitting position with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. The dominant arm will be used throughout the study. The subject should be rested for at least 5 min. before the BP is obtained. SAFETY AND ADVERSE EVENT (AE) REPORTING

10.5. Definition of an Adverse Event

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

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

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

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

- Test result is considered to be an AE by the investigator or Sponsor.

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

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

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

10.6. Reporting Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be reported with two exceptions. Since it is being experimentally induced in this study, hypoglycemia will not be considered an AE in this study unless the event meets one of the definitions of an SAE (see Section 10.8). Injection site reactions will not be considered an AE unless a skin reaction or pain requires medical intervention.

For all AEs, the investigator must pursue and attempt to obtain information adequate to determine the outcome of the AE and to assess whether it meets the FDA criteria for classification as an SAE, requiring immediate notification to Xeris Pharmaceuticals. For AEs with a causal relationship to the investigational product, follow-up by the investigator is required until the event resolves or stabilizes at a level acceptable to the investigator to consider it closed, and Xeris Pharmaceuticals should concur with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, the Sponsor may escalate any non-serious adverse event that is determined to be serious (according to the FDA definitions of 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.

10.7. Reporting Period

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

10.8. Serious Adverse Events

An SAE is any untoward medical occurrence which:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or extends hospitalization.
- Results in persistent or significant disability.
- Is another important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in hospitalization or death. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent a SAE outcome, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions which do not result in hospitalization.

10.9. Severity Assessment

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

Table 9: AE Severity Assessment

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

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

10.10. Causality Assessment

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

10.11. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, and recorded on the appropriate CRF. When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements (see Section 10.13).

10.12. 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 10.13.

10.13. Serious Adverse Event Reporting Requirements

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

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (e.g., a study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of the event and document the time of first awareness of the AE.

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

10.14. Non-Serious Adverse Event Reporting Requirements

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

10.15. AE Reporting Requirements to Regulatory Authorities

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

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

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

10.16. Pregnancy

The active pharmaceutical product in Xeris Pharmaceuticals' glucagon formulation is glucagon, which is in Pregnancy Category B. Female subjects able to become pregnant will be tested (rapid, urine) for pregnancy at the Screening visit. Any subject found to be pregnant at the Screening visit (Visit 1) will not be randomized into the study. Pregnancy testing will be repeated prior to each induced hypoglycemia procedure (i.e., Visits 3, 7, 9 and 11). 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, nor will induced hypoglycemia procedures be performed. 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.

10.17. Subject Monitoring

Subjects will be monitored for AEs throughout the study by the study staff. The principal investigator or designated sub-investigator will be on site for drug administration initiation and during hypoglycemia induction procedures. 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/her 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.

11. DATA ANALYSIS AND STATISTICAL METHODS

Descriptive and inferential statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. For some data that may be presented as continuous variables, there may be scientific reasons to present that data in constructed categories as well (e.g., BMI). Reasons for the categories will be described in the Clinical Study Report (CSR). Graphical displays may be presented for selected results.

A stand-alone Statistical Analysis Plan (SAP) will be written to describe in detail all statistical analyses planned for the study. It will be accompanied by mock Tables, Figures, and Listings. The SAP will be finalized and approved by signature and dates prior to database lock. The SAP will take precedence over the protocol for details about the statistical analyses for the study. In addition to the SAP, other graphical representations of the results may be produced after review of the data (post hoc).

Verbatim terms recorded for medical history conditions and adverse events will be mapped to a System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and all prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

11.1. Efficacy

The primary aim of the study is to evaluate change from baseline of plasma epinephrine concentration during induced hypoglycemia with PG <50 mg/dl between placebo and CSGI after 4 weeks of blinded treatment. The null hypothesis to be tested is there is no difference in the change from baseline to 4 weeks between the two groups for plasma epinephrine concentration during induced hypoglycemia with PG<50 mg/dl. Two-group t-test will be implemented for each hypothesis test.

11.1.1. Closed Hierarchical Hypothesis Tests

The analysis of the primary endpoint will be performed using a hierarchical hypothesis test in which an alpha of 5% will be preserved for each test. Testing will be employed in the following order:

- CSGI (combined groups) versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)
- CSGI high dose versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)
- CSGI low dose versus Placebo (if statistically significant <0.05, then the next hypothesis test will be conducted)
- CSGI high dose versus CSGI low dose

Sensitivity analysis of the primary efficacy outcome in the PP population will be conducted where:

- All subjects who are lost to follow-up or have missing outcome data will be considered to have a favorable outcome in each of the treatment groups.
- Subjects who are lost to follow-up or have a missing primary endpoint at Day 27 in the high or low dose group will be considered to have an unfavorable outcome whereas in the placebo group will be considered to have a favorable outcome
- Subjects who have a missing outcome data will be excluded from the analysis

11.1.2. Analysis Populations

Three analysis populations are planned for the study:

Intent-to-treat Population (ITT or All Randomized): All subjects randomized into the study. The ITT population will be analyzed according to the treatment group to which subjects were randomized.

Per-Protocol Population (PP Population): Subjects in the ITT population who receive at least 90% of study treatment through Day 27, including use of a concomitant medication or other therapy that could confound the assessment of efficacy.

Safety Population

All enrolled subjects who received at least one study treatment application. Unless otherwise stated, the safety population will be the default analysis population for all safety analyses. Analyses of safety will be performed based on treatment received, even if different from treatment group to which subjects were randomized.

11.1.3. Sample Size Calculation:

The primary hypothesis is to evaluate change from baseline to 4 weeks of plasma epinephrine concentration after 30 minutes of induced hypoglycemia with plasma glucose <50mg/dL between treatment groups. Sample size is based on a closed hierarchical hypothesis test as described above in section 13.1.1.

Using this method, an alpha of 5% will be preserved for each hypothesis test where the next ordered test will only be conducted if statistical significance is achieved for that hypothesis. Final calculations are based on 80% power and an alpha of 5%, to demonstrate a plasma epinephrine increase compared to placebo of 1.5 nmol/l given and SD of 1.34 nmol/l at an induced PG of 50 mg/dl. Sixteen subjects per treatment group (CSGI high dose, CSGI low dose, and placebo) are required based on the minimum sample size estimate for a comparison.

11.2. Pharmacokinetic and Pharmacodynamic Analyses

The pharmacokinetic endpoint of steady state glucagon concentration will be derived from the individual plasma glucagon assessments. The pharmacodynamic endpoints will be derived from the glucose infusion rates, the plasma sample hormone analyses, and the CGM data.

11.2.1. Pharmacokinetic Secondary Endpoints:

Change from baseline in serum glucagon steady state across the treatment groups will be analyzed descriptively.

11.2.2. Pharmacodynamic Secondary Endpoints:

The secondary endpoints cumulative glucose infusion to maintain glucose at 50 mg/dl for the first 30 minutes, other counter regulatory hormones, and CGM derived variables will be analyzed by mixed model analysis.

Other endpoints will be analyzed descriptive with inferential testing being performed should the descriptive data indicate differences of clinical importance between the groups.

11.3. Safety Analysis

All safety analyses will be performed using the safety analysis population.

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

- Adverse events and serious adverse events (Screening to Final Visit)
- Laboratory safety variables (Screening to Final Visit)
- Physical examination (Screening to Final Visit)
- Vital signs (Screening to Final Visit)
- Body weight (Screening to Final Visit)
- ECG (Screening to Final Visit)
- Local tolerability, including:
    - Subjective injection site discomfort as reported by subjects using a 100-mm VAS and ordinal pain scales (Appendix 3).
    - Erythema and or edema formation at site of injection assessed using the Draize scale (Appendix 4).

11.3.1. Adverse events:

All AEs will be reviewed by the Medical Monitor once they are coded using the Medical Dictionary for Regulatory Activities (MedDRA). A summary table indicating the number and the percentage of subjects having at least one AE will be made by SOC and preferred term.

11.3.2. Laboratory safety assessments:

Laboratory values (biochemistry and hematology) will be flagged if outside the normal range. A listing of abnormal values will be presented in listings. The individual values will be listed indicating values outside normal range. Laboratory assessments will be summarized for Screening and end of study.

11.3.3. Physical examination:

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

11.3.4. Vital signs and body weight:

Vital signs will be summarized by descriptive statistics. Change from baseline will be presented.

11.3.5. ECG:

12-lead electrocardiogram (ECG) will be performed at baseline and at end of treatment (Visit 7). ECG results will be reviewed by the principal investigator for clinically notable abnormalities. The safety analysis for ECG measurements and outliers will be described based on the investigator assessments.

11.3.6. Local Tolerability:

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

11.4. Subgroup Analysis

No subgroup analyses are planned.

11.5. Interim Analyses

There are no planned statistical interim analyses.

However, the primary endpoint analysis at Day 27 will be executed when the last subject data for this the visit has been completed and monitored. Primary endpoint analysis results will only be unblinded at the treatment group level (CSGI high dose. CSGI low dose, and placebo) and individual treatment assignments will remain blinded until the end of the study and the database locked. Study investigators, study staff, subjects and the sponsor will remain blinded to individual treatment group assignments.

12. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

13. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS

13.1. Case Report Forms/Electronic Data Record

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

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

In most cases, the source documents are the hospital's or physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Xeris Pharmaceuticals and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document

13.2. Record Retention

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

13.3. Monitoring

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

The Xeris Pharmaceuticals' designated representative (the monitor or auditor) will contact the investigator and conduct regular visits to the clinical site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterpretable data will be resolved in coordination with the investigator.

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

13.4. Audits and Inspections

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

14. ETHICAL CONSIDERATIONS

14.1. Conduct

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

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

14.2. Institutional Review Board (IRB)

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

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

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

14.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. Subject names, address, date of birth and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Xeris Pharmaceuticals to de-identify the study subject. In the

case of data transfer, Xeris Pharmaceuticals will maintain confidentiality and protection of subject personal data.

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

14.4. Subject Recruitment

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

14.5. Reporting of Safety Issues and Serious Breaches of the Protocol

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

15. DEFINITION OF END OF TRIAL

Last Subject Last Visit (LSLV) for each site is defined as the date the last subject at that site completes the 6-month follow-up visit (Visit 11).

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16. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

16.1. Protocol Modifications and Deviations

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

16.2. Study Termination

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB, safety problems, or at the discretion of Xeris Pharmaceuticals or the principal investigator. Circumstances that may warrant premature study termination include, but are not limited, to the following:

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

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

17. PUBLICATION OF STUDY RESULTS

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

18. REFERENCES

American Diabetes Association (ADA) Workgroup on Hypoglycemia: Defining and reporting hypoglycemia in diabetes. Diabetes Care 28:1245–1249, 2005

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 356:1842–1852, 2007.

Skrivarhaug T, Bangstad H-J, Stene LC, Sandvik L, Hanssen KF, Joner G: Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 49:298 –305, 2006.

U.K. Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50:1140 –1147, 2007.

McLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. Diabet. Med. 1993. 10: 238-245.

Centers for Disease Control (CDC) and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011

Close Concerns, Inc. Market Survey (2,808 respondents). 2010.

Glucagon™ (glucagon for injection [rDNA origin]) Prescribing Information. Eli Lilly and Company, revised February 2005

Glucagen® (glucagon [rDNA origin] for injection) Prescribing Information. Novo Nordisk, Inc. revised December 2011.

Jelinek LJ, Lok S, Rosenberg GB, Smith RA, Grant FJ, Biggs S, Bensch PA, Kuijper JL, Sheppard PO, Sprecher CA, et al. Expression cloning and signaling properties of the rat glucagon receptor. Science. 1993 Mar 12; 259(5101): 1614-6.

Wakelam MJ, Murphy GJ, Hruby VJ, Houslay MD. Activation of two signal-transduction systems in hepatocytes by glucagon. Nature. 1986 Sep 4-10; 323(6083): 68-71.

FDA CDER #1. Glucagon (glucagon hydrochloride). NDA No. 01-2122. Eli Lilly and Company, Indianapolis, IN, November 14, 1960.

Eistrup, C., Hjortkjæ, R. K., Pickersgill, N., Virgo, D. M. and Woolley, A. P. A. H. (1993), Glucagon Produced by Recombinant DNA Technology: Repeated Dose Toxicity Studies, Intravenous Administration to CD Rats and Beagle Dogs for Four Weeks. Pharmacology & Toxicology, 73: 103–108.

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

Du Bois D, Du Bois EF (Jun 1916). "A formula to estimate the approximate surface area if height and weight be known". Archives of Internal Medicine. 17 (6): 863–71.

APPENDICES

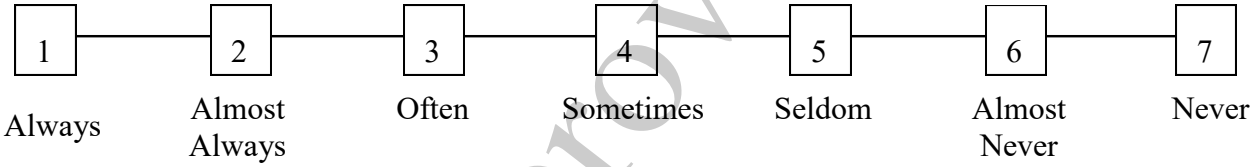
APPENDIX 1. GOLD SCORE

Investigative Site Instructions: The subject should complete the gold scale questionnaire at the start of screening and each treatment phase in visits 3, 7, 9 and 11.

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 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 and 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?



APPENDIX 2. HYPOGLYCEMIA SYMPTOM QUESTIONNAIRE

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

- When the plasma glucose has been stable at 70+/-5 mg/dL for 20 minutes, a hypoglycemia symptom questionnaire administered, which will be repeated after 10 minutes
- Every 5 minutes the hypoglycemic questionnaire will be administered while the subject PG is <70 mg/dL
- Subjects should remain blinded to their PG levels throughout the treatment visit.

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 3. 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 **10±5** minutes, at **30±5** minutes and again at **180±5** minutes following the injection of study drug. The subject completes the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort according to the instructions below. The goal is for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion.

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

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

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

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

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

No Discomfort — Worst Possible Discomfort

APPENDIX 4.

Delivery Site Discomfort Description and Duration Questionnaire

Study Personnel Instructions: All questions should be completed by the subject at **10±5** minutes following the delivery of study drug. The goal is for the subject to report if they had any discomfort and if there was discomfort, the qualitative nature and duration of discomfort associated with the delivery of study drug, ignoring any transient pain associated with the pump placement.

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 all questions below.

1. Did you have any discomfort when the pump administered the study drug?_____Yes ____No

If yes,

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

_____Pain (e.g., throbbing, soreness, muscle ache)
_____Itching
_____Tingling, twitching or numbness
_____Irritation (e.g., burning, stinging)
_____Other (specify) :
_____

1b. About how long after the study drug administration did the discomfort start? (please enter a number) _____*minutes*

1c. In total, how long did the discomfort last? (please enter a number): _____*minutes*

APPENDIX 5. 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 Omnipod site.
- The injection site should be examined for formation of both erythema and edema and results recorded in the Case Report Form. Evaluations of the injection site should be performed at 10 ± 5 and 60 ± 5 minutes post-treatment.

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	**Slight edema** (edges of area well defined by definite raising)	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

Document Approvals

Approved Date: 10/8/2019, PRO-19-00084 Version 4

Approval Task Verdict: Approve	Kimberly Alegado, (kalegado@xerispharma.com) Quality Approval 08-Oct-2019 14:50:28 GMT+0000

QA Approval Task Verdict: Approve	Ashley Gregory, (agregory@xerispharma.com) Quality Assurance Approval 08-Oct-2019 14:51:26 GMT+0000