PROTOCOL XSGO-CHO1

A PHASE 2 PROOF-OF-CONCEPT STUDY OF CSI-GLUCAGON™ (CONTINUOUS SUBCUTANEOUS GLUCAGON INFUSION) TO PREVENT HYPOGLYCEMIA WITH LOWER INTRAVENOUS GLUCOSE INFUSION RATES IN CHILDREN UP TO ONE YEAR OF AGE WITH CONGENITAL HYPERINSULINISM

Version 1.7
February 9, 2018

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CSI-Glucagon™ (continuous subcutaneous glucagon infusion). I have read protocol XSGO-CH01 Version 1.7 dated February 9, 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.

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Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Sponsor Contact Information

Role in Study	Name & Title	Email Address & Telephone Number
Sponsor's Study Leader & primary contact	Martin J. Cummins, VP, Drug Development	mcummins@xerispharma.com 512-498-2675 or 806-282-2120
Medical Monitor & 24-hour emergency contact	Dr. Poul Strange, Medical Consultant	Pstrange@imdcro.com 609-897-0505 x 213, fax 609-897-0555

2. SYNOPSIS

Protocol Number XSGO-CH01	
A Phase 2 Proof-of-Concept Study of CSI-Glucagon™ (continuous subcutaneous glucagon infusion) to Prevent Hypoglycemia with Lower Intravenous Glucose Infusion Rates in Children up to One Year of Age with Congenital Hyperinsulinism	
Principal Investigators:	Each participating clinical site will nominate a physician who, based on training and experience, will serve as principal investigator for that site.
IND:	123039
Project phase:	Phase 2
Compound(s):	CSI-Glucagon™ (continuous subcutaneous glucagon infusion)
Objectives:	The primary objective is to assess the efficacy of CSI-Glucagon™ delivered with an OmniPod® pump as a continuous subcutaneous (sc) glucagon infusion to prevent hypoglycemia with lower intravenous glucose infusion rates (GIRs) in patients < 1 year of age with congenital hyperinsulinism, as compared to placebo. This primary objective will be assessed by comparing the treatments for the ability to reduce baseline GIR by at least 20% within 24 hours, and at least 33% within 48 hours of the initiation of treatment. The secondary objectives include the following: • Compare average proportional GIR reduction from baseline between CSI-Glucagon™ and placebo. • Confirm the dosing algorithms for CSI-Glucagon™ delivered with an infusion pump in infants and neonates when used to lower the GIR required to maintain euglycemia (blood glucose ≥ 70 µg/dL) or extend the fasting period in patients who are on a stable drug regimen over a period of 2 days. • Compare the groups for the percentage of subjects that achieve GIR ≤ 8 mg/(kg*min) during treatment. • Compare the groups for the percentage of subjects that achieve daily total caloric intake from carbohydrate, combining oral, tube and IV sources ≤ 8 mg/(kg*min) glucose. • Assess safety of pump switch out procedures as assessed by occurrence of glucose < 50 mg/dL. • Assess safety and tolerability of glucagon delivered with the OmniPod® for up to 28 days of cumulative use.

	• Assess performance of the OmniPod®, including accuracy of dose delivery and the rate of failures/malfunctions.
Study design:	This will be a Phase 2, multi-center, randomized, placebo-controlled, double-blind trial with open-label follow-up designed to assess the efficacy of CSI-Glucagon™ delivered with an OmniPod® pump as a continuous subcutaneous glucagon infusion to prevent hypoglycemia with lower intravenous GIRs in patients < 1 year of age with congenital hypoglycemia. The study will consist of three periods: 1. A baseline stabilization phase during which concomitant therapy with glucagon, octreotide and diazoxide will be discontinued and continuous "basal" enteric feed will be held constant to the degree possible, with the only factors varying being meal size and IV GIR. Basal enteric feed will be held constant to the degree possible during the study, except for extending the fast after meal feeding when GIR = 0. 2. The first 2-day period during which randomized, blinded treatment is given and GIR adjustments are used to maintain euglycemia. 3. An open-label treatment period during which CSI-Glucagon™ may be delivered to manage glucose levels and minimize glucose infusions for a maximum of 28 days of cumulative treatment until a long-term management plan is in place.
Study locations:	Approximately 6 pediatric medical centers in the US. .
Study duration:	The total length of the study will be up to 5 weeks per patient, and total time on drug will be up to 28 days. The total time for enrollment and treatment to reach the planned interim analysis will be approximately 12 months per site.
Sample size:	This is a parallel group adaptive design with one interim analysis after 6 subjects fulfilling final protocol GIR selection criteria in each study arm have completed their post-treatment success-failure determination. Depending on the comparison of the treatment and placebo failure rates the study will either be stopped with an early claim for treatment efficacy, or continued with either 3 or 6 additional subjects per study arm so that the final comparison of failure rates will be based on 9 or 12 subjects per study arm. This final sample size will be based on the outcome of the interim analysis. The criteria for stopping early at 6 subjects per group or continuing to a final sample size of 9 or 12 subjects per group was designed so that the type 1 error is no larger than 0.025 for treatment = control failure rates at any failure rate value. The overall power for concluding that the treatment failure rate is less than control is over 98% if the placebo failure rate is at least 0.9 and the treatment rate is no more than 0.1, with early efficacy

	having a power of 66%. If the placebo failure rate is at least 0.95 and the treatment rate is no more than 0.05 then the chance for an early efficacy determination is 88%.
Subjects:	Hospitalized infant male or female patients with congenital hyperinsulinism less than 1 year of age at screening.
Inclusion Criteria:	1) Patients diagnosed with hyperinsulinism a. Biochemical; detectable insulin (i.e., ≥1 mU/L) at time of hypoglycemia (i.e. blood glucose <50 mg/dL), and/or suppressed FFA, and/or suppressed BOHB and/or glycemic response to glucagon at time of hypoglycemia *and* 2) Absolute necessity of intravenous glucose to prevent hypoglycemia as defined as attempts at weaning being unsuccessful. a. Having failed diazoxide therapy. b. Subject may be on diazoxide and/or octreotide, but these will be weaned off prior to randomization. c. Subject may be on dextrose feeds. 3) Patient may be a participant in other study protocols such as observational studies, as long as no investigational intervention has taken place within 24 hours of screening. 4) Less than 12 months of age at screening.
Exclusion Criteria:	1) Patients with history of allergy to glucagon or the excipients in Xeris' glucagon formulation. 2) Patients currently receiving, or less than 12 hours removed from IV glucagon treatment that resulted in a best achievable GIR > 8 mg/(kg*min), prior to the start of study drug. 3) Patients who are diazoxide naïve. 4) Patients within five days of starting diazoxide. 5) Patients on steroids at doses larger than 20 mg/m^2/day (hydrocortisone equivalent). 6) Patients with sepsis. 7) Patients on Alpha or beta agonists for blood pressure support. 8) Patient received an investigational drug or a study drug within 5 half-lives of drug. 9) Weight less than or equal to 2.3 kg/5.0 lbs 10) Subjects with a history of pancreatectomy and a GIR < 8 mg/(kg*min)

	after weaning of all concomitant therapies.
Brief outline of treatments:	Methods: **Period 1. Baseline** Day -1: Octreotide and diazoxide will be safely withdrawn. Continuous "basal" enteric feed will be held constant unless when GIR=0. Subjects will consume meals as needed and GIR will be adjusted to achieve pre-meal glucose minimally above 70 mg/dL. Determine minimal stable GIR required to keep glucose >70mg/dL by weaning the IV glucose Q3H pre-feeds (or Q3H if on continuous feeds). During all study periods, point-of-care (POC) blood glucose will be monitored by use of the Nova StatStrip® Hospital Glucose Measuring System, ACCU-CHEK Inform II, or an equivalent system. As per standard care practices, blood glucose will be checked every 3 hours at a minimum, or more frequently at the discretion of the PI as the clinical situation dictates. Wean IV fluids as follows: • if POC glucose is >70 mg/dL (3.3 mmol/L) and < 90 mg/dL (5 mmol/L), reduce the GIR 1 mg/kg/min and check blood glucose in 3 hours. • if POC glucose is >90 mg/dL (5 mmol/L) and <120 mg/dL (6.7 mmol/L), reduce the GIR by 2 mg/kg/min and check blood glucose in 1 hour. • if POC glucose is >120 mg/dL (6.7 mmol/L), reduce GIR by 3 mg/kg/min and check the blood glucose in 1 hour. • If GIR is unable to be reduced because glucose level is <70mg/dL (3.9 mmol/L), increase GIR by 2 mg/kg/min and check blood glucose in 1 hour. • If glucose is <50 mg/dL (2.8 mmol/L), give 200 mg/kg dextrose by IV push, increase GIR by 2 mg/kg/min, and check blood glucose in 30 minutes. More frequent, or smaller, GIR changes may be done at the investigator's discretion should the clinical condition so require. The average of the GIR levels after the initial 2 hours will be considered as the baseline GIR. Should time of day scheduling make transition to the randomized period 2difficult, the investigator has discretion to keep the subject at a "safe" GIR, which is higher than the minimal rate determined during weaning, until transition to period 2 can be achieved without risk of protocol deviations. The identified baseline GIR must be achieved twice within ±20% before proceeding to period 2.

Period 2. Randomized Treatment

Day 0:

- Insert CGMS (Dexcom® G4 Platinum) and calibrate per manufacturer. The CGM will be used for rapid alerts, which will trigger POC assessments of blood glucose that will be used to guide clinical decisions. At the investigator's discretion, this may be inserted during Period 1.
- Obtain randomization and OmniPod® containing randomized treatment.
- When CGM has stabilized (minimally 2 hours) and is reporting glucose values, draw blood for plasma insulin and glucagon levels and immunogenicity testing prior to application of the OmniPod® pump.
- Photograph the site of approximate cannula insertion prior to application of the patch pump.
- Using the appropriate syringe (see Section 9.3.3), the treatment dispenser should load a fresh OmniPod® pump with 1 mL CSI-Glucagon™ solution (5 mg/mL concentration) or placebo as per the randomization scheme, and provide the loaded pump to study staff.
- Study staff will weigh the loaded pump to the nearest whole mg (see Appendix 2), and then apply the OmniPod® pump containing CSI-Glucagon™ solution or placebo to the abdomen of the subject (see Section 9.1).
- Use the PDM to instruct the pump to insert the cannula and ensure deployment as follows:
    - Listen for an audible "click."
    - Confirm pink slide insert has moved into the window on the surface of the pump, indicating deployment.
    - Use the clear window on one end of the pump to view the inserted cannula.
- Once cannula deployment is confirmed, set basal rate at 5 µg/kg/hr (t=0).
- Monitor POC glucose every hour for the first three hours after study drug start and every 3 hours thereafter; or more frequently if the CGM shows glucose trending towards <70 mg/dL (3.9mmol/L) or >200 mg/dL (11.1mmol/L).
- Adjust IV fluids as per period 1 with the following additions:
    - if POC glucose is >70 mg/dL (3.3 mmol/L) and GIR=0, introduce and/or extend the fast after meal feeding as long as

possible, while maintaining POC glucose > 70 mg/dL.

- If GIR cannot be reduced because glucose level is <70mg/dL (3.9 mmol/L), restore continuous enteric feeding if that has been suspended, or both increase GIR by 2 mg/kg/min and increase study drug infusion rate by 5 µg/kg/hr (up to a maximum of 20 µg/kg/hr) and check blood glucose in 1 hour.
- If glucose is <50 mg/dL (2.8 mmol/L), give 200 mg/kg dextrose by IV push, increase GIR by 2 mg/kg/min, increase study drug infusion rate by 5 µg/kg/hr (up to a maximum of 20 µg/kg/hr) and check blood glucose in 30 minutes.

- At 12 hours after initial start of study drug, if GIR has not been reduced by < 20% from the baseline value determined in Period 1:
  - Remove and weigh the pump and replace it with a new one and a fresh supply of the same, blinded study drug at the same flow rate setting as the previous pump.
  - Monitor POC glucose over the next 12 hours, adjust GIR using the same rules as above for making IV fluid adjustments in the interim.

Day 1:

At 24 hours after the start of study drug, if average GIR has been reduced by < 20% from the baseline value determined in Period 1, complete the following procedures:

- Draw blood for plasma insulin and glucagon levels as well as CBC and CMP.
- Remove and weigh the OmniPod® pump (Appendix 2) and:
  - Photograph the application site, paying particular attention to the cannula insertion site.
  - Assess site for edema and erythema using the Draize scale. Any Draize scores >0 should be followed to resolution, including a follow-up photograph.
- Proceed to Period 3 (see 10.2.3).

If GIR has been reduced by ≥ 20% from the baseline value determined in Period 1, complete the following procedures:

- Continue to adjust the GIR during day 1 as per day 0.
- If IV glucose is weaned off, introduce and/or extend the fast after meal feeding as long as possible while maintaining POC glucose > 70 mg/dL.
- Should the plasma glucose continue to rise, the study drug infusion

rate may be reduced by 2.5 µg/kg/hr every 6 hours, as long as the pre-feed blood glucose can be maintained >70 mg/dL (3.3 mmol/L)

At 48 hours after the initial start of blinded study drug, complete the following procedures:

- Draw blood for plasma insulin and glucagon levels as well as CBC and CMP.
- Remove the OmniPod® pump and weigh it to the nearest whole mg.
- Photograph the application site and assess for edema and erythema using the Draize scale, with particular attention to the cannula insertion site.

Period 3. Open-label Treatment

Note: For subjects not meeting the criteria for response at 24 hours, the open-label period will begin after 24 hours of blinded study drug. For subjects meeting the criteria for response at 24 hours, the open-label period will begin after 48 hours of blinded study drug.

At the start of day open-label treatment:

- Using the same procedures for loading and weighing the pump, and confirming cannula deployment as detailed for Day 0, place a new OmniPod® pump containing CSI-Glucagon™ solution (5 mg/mL concentration) and run for 4 hours.
- Basal rate should initially be set at 5 µg/kg/hr with hourly POC glucose measurements and fluid adjustments as per Period 2.
- At 4 hours, remove and the OmniPod® pump and:
    - Photograph the application site, paying particular attention to the cannula insertion site.
    - Assess site for edema and erythema using the Draize scale. Any Draize scores >0 should be followed to resolution, including a follow-up photograph.
- Determine whether, in the investigator's assessment, continued treatment is helpful for clinical care.
    - If yes, and open-label treatment will be continuing, perform "real-world" pump change-out procedure (see Section 9.3.3).
    - If no, and open label treatment is ending, remove CGM and draw blood for immunogenicity testing, plasma insulin and glucagon levels as well as CBC and CMP. Do not perform the "real-world" pump change-out procedure in this case.
- If yes, therapy may continue, including intermittently should procedures, e.g., PET scan, require temporary discontinuation, for up to a cumulative 28 days of glucagon exposure.

	○ A new OmniPod® pump containing CSI-Glucagon™ solution should be placed at least every 72 hours. The procedures for loading and weighing the pump and confirming successful cannula deployment should be followed each time a new pump is placed. ○ Each time a pump it replaced, determine safety of pump switch out procedures as assessed by occurrence of blood glucose < 50 mg/dL. ○ Each time a pump is removed, including at final termination of therapy, it should be weighed to the nearest whole mg, and the placement site should be photographed and assessed with Draize scales. ○ At least 2 hours prior to each planned pump change, confirm the CGM sensor is working and place another as needed. ○ Every 7 days during treatment, dosing will be adjusted as applicable based on current subject body weight. ○ Every 2 weeks during treatment, draw a 1 mL blood sample for immunogenicity testing. • Each time study treatment is paused, and when treatment ends, draw blood for immunogenicity testing, plasma glucagon and insulin levels as well as CBC and CMP, resume IV fluids at pre-study rate and then manage glucose as per standard procedures. **Period 4, Post-treatment Immunogenicity Testing** • At 28 ±14 days after the last dose of study drug, the subject should have blood drawn for immunogenicity testing. This blood draw can be done at a local hospital, laboratory or clinic, or by home health care professional if subject is not able to return to the clinical site due to travel considerations.
Bio-statistical Considerations:	For each subject, the average GIR will be computed for periods 1 (baseline) and 2 (treatment) by determining the area under the curve of GIR excluding the first 2 hours versus time and then dividing by the time duration for each of the periods excluding the first 2 hours, using the last 24 hours for each period, or if less than 24 hours is available, the available data, excluding the first 2 hours. The primary comparison of treatment and placebo will be based on a success-failure determination (see Section 5.1). The primary comparison will be based on the observed treatment and placebo failure rates, using subjects having enough information from periods 1 and 2 to determine success or failure. This is a parallel group adaptive design with one interim analysis after 6 subjects in each study arm have completed their success-failure determination. If, at the interim analysis, the observed treatment failure rate

is lower than placebo so that the one-tailed p value is less than or equal to 0.0124 (Fisher's exact test, hypergeometric distribution based on the total number of observed failures) then the study will be stopped due to early demonstration of treatment efficacy.

If this interim hypergeometric one-tailed p value is greater than 0.0124 but less than or equal to 0.05, then the study will continue and an additional 3 more subjects per study arm will be randomized. If this interim one-tailed p value exceeds 0.05 then the study will continue, and an additional 6 subjects will be randomized. The final analysis will be based on the observed treatment and placebo failure rates using all subjects with a success-failure determination. If, at the final analysis, the observed treatment failure rate is lower than placebo so that the one-tailed hypergeometric p value is less than or equal to 0.04 then treatment efficacy will be established

The actual type 1 errors are smaller than the efficacy criteria would suggest because of the small sample sizes and the use of Fisher's exact test. From Monte-Carlo simulations the overall type 1 error for this design is bounded above by 0.016 for null hypothesis treatment = placebo failure rates at any failure rate using the above criteria.

Secondary analyses will include baseline adjusted analyses of the natural logarithm of GIR to obtain confidence bounds on ratio of treatment to placebo mean GIR. Other secondary endpoints will consider the average GIR over the last 24 hours during period 2. The chance that this final rate is less than 8 mg/kg/min will be estimated and compared. Also, the cumulative glucose infusion will be combined with the total enteric feeding for the last 24 hours. The chance that this combined value is less than or equal to 8 mg/kg/min will be estimated and compared.

Pharmacokinetic (PK) data of steady state glucagon concentrations following continuous subcutaneous infusion will be analyzed descriptively.

Safety analysis: all subjects who have received at least one dose of study medication will be included. Safety data will be presented in tabular and/or graphical format and summarized descriptively. For continuous data, change from baseline will be analyzed using analysis of covariance. The proportion of study participants experiencing a particular AE will be compared by group (dose) using Fisher’s Exact Test.

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

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

AE	Adverse Event
ALT	Alanine Aminotransferase
AAT	Aspartate Aminotransferase
BHOB	Beta-hydroxybutyrate
BP	Blood Pressure
CRF	Case Report Form
CSI	Continuous Subcutaneous Infusion
CZ®	Daikyo Crystal Zenith®
DMSO	Dimethyl sulfoxide
DSMB	Data and Safety Monitoring Board
FFA	Free Fatty Acids
GCP	Good Clinical Practice
GIR	Glucose Infusion Rate
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
iv	Intravenous
kg	Kilogram

L	Liters
LSLV	Last Subject Last Visit
MDR	Medical Device Report
mg	Milligram
mcg	Microgram
min	Minute
PK	Pharmacokinetic
rDNA	Recombinant
SAE	Serious Adverse Event
SC	Subcutaneous

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective of this study is to determine if CSI-Glucagon™ delivered with an OmniPod® pump to subjects with congenital hyperinsulinism can lower the GIR required to maintain euglycemia (blood glucose ≥ 70 mg/dL) over 2 days. The endpoint will be assessed by comparing the rate of treatment failure between placebo and glucagon during the blinded, randomized portion of the study. Treatment failure is defined as <20% GIR reduction at 24 hours or <33% GIR reduction at 48 hours from baseline GIR determined prior to randomization.

5.2. Secondary Objectives

The secondary objectives are to:

1. Compare average proportional GIR reduction from baseline between CSI-Glucagon™ and placebo.
2. Compare the percentage of subjects in each group that achieve GIR≤ 8 mg/(kg*min) during treatment.
3. Compare the percentage of subjects in each group that achieve daily total caloric intake from carbohydrate, combining oral, tube and IV sources ≤ equivalent to 8 mg/(kg*min) glucose.
4. Describe the proportion of subjects in each group that discontinue IV glucose infusion as well as the proportion of subjects that discontinue continuous naso-gastric feeds (ability of patient to fast for 3 hrs.).
5. Compare proportional time < 70 mg/dL as well as proportional time in euglycemia (≥70 mg/dL and < 180 mg/dL) from CGM assessments.
6. Compare device performance between the groups, including:
   - weight-based estimate of dose volume delivery
   - infusion site leakage
   - device failures/malfunctions
7. Assess safety of pump switch out procedure as assessed by occurrence of glucose < 50 mg/dL by continuous glucose monitoring.
8. Evaluate the safety and tolerability of CSI-Glucagon™ administered from an OmniPod® pump by assessing the following endpoints:
   - Incidence of adverse events (AEs) and serious adverse events (SAEs)
   - Laboratory safety variables
   - Physical examination
   - Vital signs

- Local tolerability: Erythema and/or edema formation at site of infusion assessed using the Draize scale

6. BACKGROUND AND RATIONALE

6.1. Indication

The proposed indication for CSI-Glucagon™ (continuous subcutaneous glucagon infusion) is for prevention of severe, chronic hypoglycemia related to congenital hyperinsulinism.

6.1.1. Background

Congenital hyperinsulinism (CHI) is the result of at least ten different genetic defects that result in dysregulated insulin secretion. It is the most frequent cause of severe, persistent hypoglycemia in neonates and children [1, 2]. CHI is characterized by inappropriate secretion of insulin resulting in hypoketotic hypoglycemia. If left untreated, CHI may lead to mild to severe forms of neurological damage in 30-40% of affected individuals. Surgical treatment (95-98% pancreatectomy) of patients with the diffuse form of CHI leads to diabetes mellitus in some 95% individuals by 14 years of age [3].

In CHI, the histologic abnormalities in pancreatic structure are heterogeneous, but can be grouped into the following two broad categories:

- Focal adenomatous hyperplasia
- Diffuse abnormality of the islets

In the focal form, the histologically abnormal beta cells are limited to 1 or more focal areas, whereas in the diffuse form, the β-cell abnormality is distributed throughout the pancreas. In focal CHI, a specific area of the pancreas is affected. Around 40 to 50 per cent of infants with persistent CHI will have the focal form [4].

Diffuse CHI affects the entire pancreas. It can be inherited in a recessive or dominant manner or can occur sporadically.

The management of diffuse and focal disease is different. Focal disease can now be cured if the lesions are located accurately and removed completely. However, diffuse disease will often require removal of almost the entire pancreas, if the patient does not respond to medical management. Medical management tools include continuous IV dextrose infusion or gastronomy tube feeding. In addition to diazoxide, which is an FDA approved treatment for CHI, a number of medications are used off-label including octreotide and glucagon [1].

6.1.2. Rationale

Xeris Pharmaceuticals has developed a proprietary form of glucagon that is stable in a non-aqueous form at room temperature and can be injected subcutaneously. CSI-Glucagon™ (continuous subcutaneous glucagon infusion) utilizes Xeris' biocompatible, non-aqueous peptide reformulation technology to ultimately create a concentrated, low volume, stable liquid glucagon formulation, pre-mixed and pre-loaded into a vial. Preclinical studies have demonstrated equivalent pharmacology of the Xeris glucagon formulation to aqueous-reconstituted glucagon formulations.

Xeris' soluble glucagon has been safely evaluated for treatment of severe hypoglycemia in adults in a Phase 2 safety/PK/PD study that compared 0.5 and 1 mg doses of Xeris (G-Pen™) to Eli Lilly glucagon. In addition, micro doses of the same Xeris formulation, G-Pump™ (glucagon infusion) designed for use in insulin pumps, such as the OmniPod®, have been safely evaluated along with aqueous-reconstituted Novo GlucaGen® in a Phase 2a safety/PK/PD study, in advance of its use for outpatient treatment with artificial pancreas devices. Summary results of this recently completed study are reported in Section 6.4.

Further, mini doses of the same formulation have been safely administered in a Phase 2a PK/PD study, and are currently being evaluated in an outpatient Phase 2a study in adults with type 1 diabetes, for management of mild to moderate hypoglycemia.

In 2008 Mohnike et al. reported a retrospective study of nine CHI patients treated with SC glucagon (aqueous-reconstituted Novo GlucaGen® or an experimental long-acting glucagon). It showed SC glucagon infusion could reduce or eliminate glucose infusion, and reduce or eliminate octreotide use, when SC glucagon was continued in 3 children for up to 4 years without further symptomatic hypoglycemia, convulsions or unconsciousness. Most importantly, near complete pancreatectomies or resurgeries were avoided in 5 of 9 children [5].

The proposed use of soluble glucagon to manage severe, persistent hypoglycemia related to hyperinsulinism builds on Xeris' experience in delivering soluble glucagon with an OmniPod® for management of hypoglycemia in patients with type 1 diabetes, and will explore the use of soluble glucagon delivered as a *continuous basal infusion* for medical management of severe, persistent hypoglycemia that occurs in neonates and children with congenital hyperinsulinism. Availability of CSI-Glucagon™ for medical management of CHI may lead to a significant reduction of near total pancreatectomies, subsequent insulin dependence in adolescent years and overall reduction in the incidence of severe hypoglycemia in this patient population and the attendant permanent neurologic damage and substantive burden of care in families with CHI patients.

6.2. Nonclinical Pharmacology and Toxicology Experience with Glucagon

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 [6]. Glucagon 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 [7, 8]. Xeris' drug substance is produced by solid-phase peptide synthesis (SPPS), which also conserves the glucagon peptide sequence. 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.

6.3. Nonclinical Pharmacology and Toxicology Experience with CSI-Glucagon™

6.3.1. Nonclinical Pharmacology

Information on the nonclinical pharmacology, pharmacokinetics and toxicology of CSI-Glucagon™ (continuous subcutaneous glucagon infusion) is referenced to Xeris' current Investigator's Brochure.

6.3.2. Description and Composition of Drug Product

Synthetic glucagon is the drug substance in CSI-Glucagon™. CGMP grade glucagon is manufactured, packaged and released by Bachem AG (Bubendorf, Switzerland), conforms with USP standards, and has a Type II DMF filed with the FDA. CSI-Glucagon™ is a sterile subcutaneous injectable non-aqueous formulation supplied in 2 mL Crystal Zenith® pre-filled cyclic olefin polymer vials with Flurotec® coated stoppers. Each 200 µl of CSI-Glucagon™ formulation delivers 1 mg of glucagon, with trehalose and DMSO as the only excipients. The drug product is stored at controlled room temperature (20-25°C) prior to use.

6.4. Clinical Experience with Glucagon

6.4.1. Clinical Experience with Approved Glucagon Products

Glucagon has a long history of medical use in the US, and is currently marketed by Eli Lilly & Co. as Glucagon for 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. Prior to the current recombinant products, animal-sourced glucagon was marketed. The Agency first approved glucagon for use in humans in 1960.

Of relevance to the proposed indication in infants up to 1 year of age, animal derived glucagon was delivered via IM and IV routes to neonates at doses up to 100 µg/kg with no apparent adverse effects [9].

Published information on the safety, efficacy, immunogenicity and post-marketing surveillance of Lilly glucagon as rescue therapy for severe hypoglycemia is referenced to Xeris' current Investigator's Brochure.

6.4.2. Clinical Experience with Approved Glucagon Products used Off-label to Treat Congenital Hyperinsulinism

Mohnike et al. reported a retrospective review of nine (9) CHI patient cases where continuous subcutaneous (SC) glucagon (reconstituted Novo GlucaGen®) was used as a treatment option (1 - 3 mg/day), with or without concomitant octreotide [5]. The objectives of using continuous SC glucagon were to:

- Stabilize blood glucose levels for several weeks without the use of high-volume dextrose infusions administered via a central catheter, which often causes bloating, and
- Avoid pancreatectomy or resurgeries (further reduction of pancreatic tissue) in patients with diffuse CHI.

The clinical outcomes of using continuous SC glucagon to treat CHI patients in this retrospective review were reported as follows:

- Central glucose infusions were reduced significantly or eliminated in all 9 children;
- SC glucagon was continued in 3 children for 1-4 years without further symptomatic hypoglycemia, convulsions or unconsciousness;
- Glucagon treatment was initiated to manage recurrent hypoglycemia after subtotal pancreatectomy in 2 of 9 children;
- Pancreatectomy or subsequent resurgeries (to remove additional pancreatic tissue and further reduce insulin output) were avoided in 5 of the 9 children;
- Octreotide daily dose was reduced to 8-15 µg/kg/day – considerably lower than if it were given alone, without glucagon (15-60 µg/kg/day), which is an important outcome given octreotide's adverse side effects;
- An experimental, stabilized glucagon (glucagon Technospheres™ suspension) was IRB approved and used successfully in 3 children;
- The value of a stable glucagon solution in treating hypoglycemia in CHI patients was demonstrated, even though development of the Technospheres™ stabilized glucagon was not continued.

Thus, significant clinical support exists for basal glucagon administration as a significant enhancement in the prevention of severe, persistent hypoglycemia in patients with CHI. In the inpatient setting, continuous subcutaneous glucagon infusion via an OmniPod® infusion pump would be preferable to high-volume dextrose or glucose infusion via a central catheter. This is because dextrose infusion rates are often so high they can cause fluid overload, especially in patients with diffuse disease. Moreover, IV infusion of dextrose is not sustainable in an outpatient setting. Therefore, to move a patient out of the inpatient setting requires surgery to insert a gastronomy tube (G-tube) to enable administration of continuous dextrose or feedings for a prolonged period of time. G-tube feeding is not a patient or caregiver-friendly medical management tool, and often the tube insertion site can become infected.

Both of the clinicians who aided Xeris in the design of this study, one of whom will be participating as an investigator, have experience using IV glucagon to stabilize CHI patients prior to surgery. Over 10 years of clinical use, approximately 100 CHI patients have been administered IV doses of glucagon, generally about 1 mg/day, for up to 25 days without significant adverse effects observed [10]. Among the approximately 43 cases with evaluable data, a mean reduction from baseline in GIR of roughly 50% has been observed. According to these clinical experts, IV line blockages due to fibrillation of reconstituted aqueous glucagon have been a frequent problem.

In a more recent study [11], a dose of 2.5-5 µg/kg/hr of glucagon administered by the IV route resulted in significant increases in blood glucose concentration in children with hyperinsulinemic hypoglycemia. In particular, a dose of 5 µg/kg/hr was positively and significantly correlated with blood glucose concentration, so this has been selected as the starting dose for the current study.

In addition to administration of glucagon to CHI patients via continuous subcutaneous infusion [5], infusion pumps have been used to safely and effectively deliver insulin to patients with neonatal diabetes. In a review of 18 years of clinical practice, a French endocrinologist reported using continuous subcutaneous insulin infusion (CSII) in 17 newborns with neonatal diabetes on

a transient (n=8) or permanent basis [12]. In all but one case, CSII was initiated in the first 1-2 months of life and continued 2 months to 1.7 years in transient cases and up to age 13 in a permanent case. CSII was reported to be free from side effects and to be more effective at managing blood glucose, compared to frequent daily injections.

6.4.3. Clinical Experience with XeriSol™ Glucagon

Information on the clinical trials completed to date in healthy normal volunteers and patients with type 1 diabetes given injections or bolus doses via subcutaneous infusion pump of the same glucagon formulation as CSI-Glucagon™ is referenced to Xeris' current Investigator's Brochure.

6.4.4. Clinical Pharmacology

For a summary of clinical pharmacology data with glucagon, reference can be made to both the Eli Lilly & Co. Glucagon Injection [rDNA origin], and Novo Nordisk GlucaGen® (glucagon [rDNA origin] for injection) approved labeling and published literature.

7. STUDY DESIGN

7.1. Study Overview

This will be a Phase 2, multi-center, randomized, placebo-controlled, double-blind parallel group study with open-label follow-up designed to evaluate the efficacy of CSI-Glucagon™ for the prevention of hypoglycemia with lower IV glucose infusion rates when delivered subcutaneously to patients up to 1 year of age with congenital hyperinsulinism, using an OmniPod® infusion pump. CSI-Glucagon™ is expected to provide a better inpatient treatment option compared to the current standard of care.

The study will consist of three phases:

1. Baseline Phase: First is a baseline stabilization phase during which concomitant therapy with glucagon, octreotide and diazoxide will be safely weaned and continuous "basal" enteric feed will be held constant to the degree possible, with the only factors varying being meal size and IV GIR adjusted by a set plasma glucose measurement driven algorithm that stays unchanged throughout the end of period 3 and, thus, applies equally to both treatment groups. Basal enteric feeding will be held constant to the degree possible until the third phase of the study, except for extending the fast after meal feeding when the GIR is tapered off.
2. Blinded, Randomized Treatment Phase: Following the stabilization phase, subjects will be randomly assigned to blinded treatment with either glucagon or placebo, which will be delivered for up to 2 days with an OmniPod® pump with the controller set to a starting basal rate of 5 µg/kg/hr and GIR adjustments used to maintain euglycemia. After 48 hours of blinded treatment, all subjects will transition to open-label treatment in period 3.
    a. At 24 hours, if GIR reduction from baseline is < 20%, subjects will be transitioned early to open-label drug.
3. Open-label Treatment Phase: The third study period will involve an initial assessment of the safety of a pump switch out, followed by use of CSI-Glucagon™ to manage glucose with minimal glucose infusions for a maximum of 28 days of cumulative exposure until a long-term management plan is in place. All subjects, even those meeting the criteria for treatment failure during phase 2, whether they received placebo or CSI-Glucagon™, will be eligible for the open-label treatment phase as long as such treatment is deemed to be beneficial in the judgement of the attending investigator.

Following the end of study treatment, IV fluids at pre-study rate will be resumed and glucose levels will be managed per standard protocol.

7.2. Interruption and Termination of Dosing

Dosing may be paused at an investigator's discretion for any serious adverse event (SAE) which occurs in a patient receiving treatment until causality is fully assessed by the Investigator (see Section 12.6). Dosing will be discontinued if the SAE is determined to be probably drug-related, but otherwise may continue (or resume) at the discretion of the investigator if Sponsor is in agreement.

Dosing will be terminated for any subject experiencing a serious device-related injury (see Section 12.14. For subjects experiencing a device failure or non-serious device-related injury, dosing may continue at the discretion of the investigator if the Sponsor is in agreement.

If study drug is to be terminated due to an SAE or serious device-related injury, dosing may be tapered off, rather than halted abruptly, at the investigator's discretion, so appropriate adjustments to GIR and/or alternative therapy for hypoglycemia can be initiated.

If possible, dosing should continue uninterrupted during the study, but interruption is permissible if necessary for the care of the patient e.g., a PET scan. Dosing should be resumed as soon as possible, following the same GIR weaning schedule as at initiation.

8. ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

8.1. Inclusion Criteria

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

1. Patients diagnosed with hyperinsulinism:
    a. Biochemical; detectable insulin (i.e., ≥1 mU/L) at time of hypoglycemia (i.e. blood glucose <50mg/dL), and/or suppressed free fatty acids (FFA), and/or suppressed beta-hydroxybutyrate (BOHB) and/or glycemic response to glucagon at time of hypoglycemia.
2. Absolute necessity of intravenous glucose to prevent hypoglycemia:
    a. Having failed diazoxide therapy as defined by inadequacy of 5 days maximum dose of diazoxide to eliminate the need for IV glucose, not necessarily that diazoxide has no effect.
    b. May be on diazoxide and/or octreotide, but these drugs will be weaned off prior to randomization.
    c. May be on dextrose feeds.
3. Patient may be a participant in other study protocols such as observational studies, as long as no investigational intervention has taken place within 24 hrs or 5 half-lives of a drug prior to screening.
4. Less than 12 months of age at screening.

8.2. Exclusion Criteria

1. Patients with history of allergy to glucagon or the excipients in Xeris' glucagon formulation.
2. Patients currently receiving, or less than 12 hours removed from IV glucagon treatment that resulted in a best achievable GIR > 8 mg/(kg*min) prior to the start of study drug.
3. Patients who are diazoxide naïve.
4. Patients within five days of starting diazoxide.
5. Patients on steroids at doses larger than 20 mg/m^2/day (hydrocortisone equivalent).
6. Patients with sepsis.
7. Patients on alpha or beta agonists for blood pressure support.
8. Patients who received an investigational drug or a study drug within 5 half-lives of drug.
9. Patients with body weight less than or equal to 2.3 kg/5.0 lbs.
10. Patients with a history of pancreatectomy and a IV GIR < 8 mg/(kg*min) after weaning of all concomitant therapies.

8.3. Randomization Criteria

Randomization will occur at the end of period 1 of the study through a centralized web-based system. Subjects will be randomized until the requirements of the interim analysis are achieved (see Section 13.4), at which point randomization will be halted, pending the outcome of the analysis.

9. STUDY TREATMENTS

9.1. Allocation to Treatment

Subjects will be enrolled until 12 evaluable patients fulfilling all final protocol GIR selection criteria complete period 2 of the study across all investigational sites, at which point an interim analysis will be conducted. The randomization will be adaptive with a minimization procedure to balance glucose infusion rate at baseline and non-evaluable patients and subjects not fulfilling all final protocol GIR selection criteria will be replaced. The final sample size is tentatively projected at 24, but may adapt based on the planned interim analysis (see Section 13.4).

Each subject will receive a basal subcutaneous infusion from an OmniPod® infusion pump placed on the anterior abdomen, 5-10 cm away from the umbilicus as per manufacturer's directions. Based on the prior experience of the investigators in treating CH patients with glucagon, the starting basal infusion rate for the subjects will be set at 5 µg/kg/hr, but this can be adjusted as necessary for a particular subject based on the GIR determined in period 1.

9.2. Blinding

Blinding will be achieved through the availability of an indistinguishable placebo.

9.3. Drug Supplies

9.3.1. 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 stabilizing excipients. 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.

The placebo comparator to be used in this study is the vehicle for CSI-Glucagon™. It contains no glucagon, but otherwise has the same composition and is indistinguishable in appearance from the test product.

The CSI-Glucagon™ and matching placebo are packaged, labeled and distributed for Xeris under cGMP by MRI Global (Kansas City, MO).

For use during blinded Period 2, sites will be provided with a supply of active and placebo product packaged in identical vials with the same blinded label on each. A separate set of unblinded vials of active product will be supplied for use during open-label Period 3.

9.3.2. 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.

9.3.3. Preparation, Dispensing and Administration

- CSI-Glucagon™ and vehicle will be supplied as 1 mL of non-aqueous solution in plastic Crystal Zenith (CZ) 2 mL vials. Each vial of CSI-Glucagon™ will be used to fill a single OmniPod® pump.
- CSI-Glucagon™ will be transferred to the OmniPod® using the kitted syringe and needle. Alternatively, a DMSO-compatible B Braun Injekt F® Low Waste Syringe 1 mL (supplied by Xeris) may be used along with the fill needle supplied by the pump manufacturer. 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.

To maintain blinding during the randomized portion of the trial (Period 2), study medications will be blinded. The investigator will have the ability to unblind should such be necessary for the care of the subject in an emergency situation. During the open-label portion of the study (Period 3), study drug may be dispensed by any appropriately trained member of the study staff. During Period 3, dosing will be adjusted every 7 days as applicable based on the current body weight of the subject. During either period, the OmniPod® pump may be loaded with study drug by the pharmacist or other appropriately trained study staff.

The OmniPod® pump placement and study procedures will be performed by qualified/trained site staff who have read the OmniPod® Instructions for Use and following Table 3 for conversion of required glucagon flow rate to OmniPod® basal settings for pumping insulin.

Table 3: OmniPod® Controller Settings

Treatment	Desired Basal Rate	OmniPod® Setting	OmniPod® Setting (4 kg infant)
CSI-Glucagon™	2.5 µg/kg/hr	Infant weight in kg * 0.05 U/hr	0.2 U/hr
	5 µg/kg/hr	Infant weight in kg * 0.1 U/hr	0.4 U/hr
	10 µg/kg/hr	Infant weight in kg * 0.2 U/hr	0.8 U/hr
	15 µg/kg/hr	Infant weight in kg * 0.3 U/hr	1.2 U/hr
	20 µg/kg/hr	Infant weight in kg * 0.4 U/hr	1.6 U/hr

During Period 2 (blinded treatment), each OmniPod® will be used for a maximum of 48 hours. During period 3 (open-label), each OmniPod® will be used for up to 3 days, and will then be exchanged for a fresh pump. Before placement and after use each, each OmniPod will be weighed to the nearest whole mg (see Appendix 2).

During the first pump switch-out during Period 3 (i.e., after the initial 4 hours), the new OmniPod® will be placed on the subject but not immediately activated. To evaluate changes in blood glucose during "real-world" use conditions, the existing pump will be deactivated and

removed, and blood glucose will be assessed. After 5 minutes, blood glucose will be repeated, and then the new pump will be activated.

9.3.4. Device Reliability

A secondary objective of the study is to assess reliability of the OmniPod® infusion pump. This will be accomplished by performing weight-based estimates of dose volume delivery and noting episodes of significant infusion site leakage, device failures, malfunctions or occlusions.

Unless operational considerations at a site preclude it, all OmniPod® infusion pumps should be weighed before and after use, following the procedure outlined in Appendix 2. Given the short duration, the pump used for the 4-hour "switch out" at the beginning of Period 3 is excluded from this requirement.

If operational considerations make a site unable to weigh OmniPod® pumps, information on delivery volume obtained from the PDM should be captured in the EDC each time a pump is removed from a subject.

9.3.5. Drug Storage and Drug Accountability

Unless notified otherwise by the Sponsor, all supplied CSI-Glucagon™ and control vials are to be stored at controlled room temperature between 20°C to 25°C (68° to 77°F), and 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, on an on-going basis by the Xeris or its representative. Any deviations in the storage conditions must be documented (including minimum and maximum temperature excursions, as well as estimate of total duration 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, including OmniPods, and will return unused products to Xeris at the end of the study, following directions from Xeris.

9.4. Concomitant Medications

During the screening process, information regarding concomitant medications, such as diazoxide or octreotide, prescribed by the referring physician must be documented. Medications taken within 4 weeks of Screening will be documented on the concomitant medication log. Any changes to a subject's concomitant medication regimen during the study will also be documented on the concomitant medication log.

10. STUDY PROCEDURES

10.1. Screening Visit

Subjects will be screened to confirm they meet the selection criteria for the study. The investigator or study team member will obtain informed consent from each subject's parent/guardian in accordance with the procedures described below (see Section 16.3).

All subjects will be in-patients. Those less than 1 month of age or with unstable condition will be in the neonatal intensive care unit. As such, vital signs will be monitored continuously via cardiorespiratory monitoring. All enteric feedings will consist of FDA-approved, hospital-issued infant formula or breast milk provided by the mothers.

Subjects will undergo the following procedures to confirm they meet eligibility criteria for this study:

- Review medical history and medications
- Length and weight
- Blood pressure and pulse
- Physical examination
- Venous blood draws for tests as outlined in the Schedule of Activities (Table 5)
- Assessment of inclusion/exclusion criteria by Study investigator

10.2. Treatment and Evaluation Phase

Subsequent to qualification for the study and receipt of parental consent, the following procedures will be completed:

10.2.1. Period 1: Baseline GIR (Day -1)

During this baseline phase, IV glucagon, octreotide and diazoxide will be safely withdrawn prior to randomization of study drug on Day 0. Continuous "basal" enteric feed will be held constant during all study periods unless GIR=0. Subjects will consume meals as needed and GIR will be adjusted to achieve glucose minimally above 70 mg/dL.

Determine minimal GIR required to keep glucose >70mg/dL, by weaning the IV glucose Q3H pre-feeds (or Q3H if on continuous feeds). During all study periods, point-of-care (POC) blood glucose will be monitored by each site's standard practice, which will involve use of the Nova StatStrip® Hospital Glucose Measuring System, ACCU-CHEK Inform II, or an equivalent system. At the discretion of the PI, the CGM specified for Period 2 (see 10.2.2) may be placed during Period 1. As per standard care practices, blood glucose will be checked every 3 hours at a minimum, or more frequently at the discretion of the PI as the clinical situation dictates.

- Wean IV fluids as follows:
  a. if POC glucose is >70 mg/dL (3.3 mmol/L) and < 90 mg/dL(5 mmol/L), reduce the GIR 1 mg/kg/min and check blood glucose in 3 hours.

b. if POC glucose is >90 mg/dL (5 mmol/L) and <120 mg/dL (6.7 mmol/L), reduce the GIR by 2 mg/kg/min and check blood glucose in 1 hour.
c. if POC glucose is >120 mg/dL (6.7 mmol/L), reduce GIR by 3 mg/kg/min and check blood glucose in 1 hour.

Note: the intent of the weaning procedure is to achieve minimal GIR at which POC glucose drops just below 70 mg/dL. Once POC glucose < 70 mg/dL has been achieved at least twice, the subject can transition to Period 2. If operational considerations preclude an immediate transition, the GIR will be returned to the previous "safe" level that maintained POC glucose > 70 mg/dL until the subject can be randomized. The "baseline" GIR will be the average GIR during the weaning procedure, minus the first two hours, and excluding the post-weaning period of "safe" GIR, if applicable.

- If GIR cannot be reduced because glucose level is <70 mg/dL (3.9 mmol/L), increase GIR by 2 mg/kg/min and check blood glucose in 1 hour.
- If glucose is <50 mg/dL (2.8 mmol/L), give 200 mg/kg dextrose by IV push, increase GIR by 2 mg/kg/min, and check blood glucose in 30 minutes.

The identified GIR must be achieved twice within ±20% during before proceeding to period 2.

More frequent or smaller GIR changes may be done at the investigator's discretion should the clinical condition so require.

10.2.2. Period 2: Blinded, Randomized Treatment (Days 0-1)

Once baseline GIR has been established in Period 1, the following procedures will be completed, including initiation of blinded study treatment.

Day 0

1. If not inserted during Period 1, insert CGM (Dexcom® G4 Platinum) and calibrate per manufacturer. Stabilize for a minimum of 2 hours and confirm CGM is reporting glucose values before proceeding to step 2.

   {Note: The CGM will be used for rapid alerts, which will trigger POC assessments of blood glucose that will be used to guide clinical decisions.}

2. Draw blood for plasma insulin and glucagon levels and immunogenicity testing (as listed in Table 5), prior to application of the OmniPod® pump.
3. Photograph the site of approximate cannula insertion prior to application of the OmniPod® pump.
4. Using the appropriate syringe (see Section 9.3.3), load a fresh OmniPod® pump with 1 mL CSI-Glucagon™ solution (5 mg/mL concentration) or placebo as per the randomization scheme.
5. Study staff will weigh the loaded pump to the nearest whole mg (see Appendix 2), and then apply the OmniPod® pump to the abdomen of the subject (see Section 9.1).
6. Use the PDM to instruct the pump to insert the cannula and ensure deployment as follows:

- Listen for an audible "click."
- Confirm pink slide insert has moved into the window on the surface of the pump, indicating deployment.
- Use the clear window on one end of the pump to view the inserted cannula.

7. Once cannula deployment is confirmed, set basal rate at 5 µg/kg/hr. Record time of starting the pump; this is t=0.
8. Monitor POC glucose every hour for the first three hours after study drug start and every 3 hours thereafter; or more frequently if the CGM shows glucose falling <70 mg/dL (3.9 mmol/L) or rising above >200 mg/dL (11.1 mmol/L). Additionally, the trajectory of change in plasma glucose concentration based on the two most recent POC measurements should be used to adjust the frequency of glucose monitoring as needed to prevent plasma glucose <70 mg/dL (3.9 mmol/L) or >200 mg/dL (11.1 mmol/L).
9. Adjust IV fluids as per period 1 with the following additions:
   a. If POC glucose is >70 mg/dL (3.9 mmol/L) and GIR=0, introduce and/or extend the fasting period after meal feeding as long as possible, while maintaining POC glucose > 70 mg/dL.
   b. If GIR cannot be reduced because glucose level is < 70 mg/dL (3.9 mmol/L), **restore continuous enteric feeding if that has been suspended,** or increase glucose infusion rate by 2 mg/kg/min and **increase study drug infusion rate by 5 µg/kg/hour (to a maximum of 20 µg/kg/hr) and** check blood glucose in 1 hour.
10. If glucose is <50 mg/dL (2.8 mmol/L), give 200 mg/kg dextrose by IV push, increase GIR by 2 mg/kg/min, **increase study drug infusion rate by 5 µg/kg/hour (to a maximum of 20 µg/kg/hr)** and check blood glucose in 30 minutes.At 12 hours after start of study drug, determine average GIR since the start of blinded therapy, excluding the first 2 hours. If average "on treatment" GIR has been reduced by < 20% from the baseline value determined in Period 1, take the following actions:
    a. Remove the pump and weigh it.
    b. Replace the pump with a new one at the same flow rate setting as the previous pump and a fresh supply of the same blinded study drug.
    c. Monitor POC glucose over the next 12 hours, adjusting GIR using the same rules as above for making IV fluid adjustments in the interim.

    {Note: This same procedure should be followed if the pump alarms or if there is an acute deterioration in an otherwise stable subject, indicating a possible occlusion.}

Day 1

At 24 hours after the initial start of study drug, determine average GIR since the start of blinded therapy, excluding the first 2 hours. Then compare the "on treatment" GIR to the baseline value determined in Period 1 and calculate the percentage change. Depending on percentage change in GIR, follow the procedures under either item 1 or item 2.

1. At 24 hours if average GIR has been reduced by < 20% from the baseline value determined in Period 1, complete the following procedures:

a. Draw blood for plasma insulin and glucagon levels as well as CBC and CMP.
b. Remove and weigh the OmniPod® pump (Appendix 2) and:
    a. Photograph the application site, paying particular attention to the cannula insertion site.
    - Assess site for edema and erythema using the Draize scale. Any Draize scores >0 should be followed to resolution, including a follow-up photograph.
c. Proceed to Period 3 (see 10.2.3).

2. At 24 hours if average GIR has been reduced by ≥ 20% from the baseline value determined in Period 1, complete the following procedures:

    a. Continue to adjust the GIR during day 1 as per day 0.
    If GIR=0, continuous enteric feeding has been completely weaned, and plasma glucose continues to rise, reduce study drug infusion rate by 2.5 µg/kg/hr every 6 hours to a minimum of 2.5 µg/kg/hr, as long as the pre-meal blood glucose is >70 mg/dL (3.9 mmol/L).

    At approximately 48 hours from the start of the first blinded study treatment, complete the following:

    b. Draw blood for insulin and glucagon levels as well as CBC and CMP.
    c. Remove the OmniPod® pump, weigh it, and photograph the application site, paying particular attention to the cannula insertion site.
    d. Assess site for edema and erythema using the Draize scale. Any Draize scores > 0 should be followed to resolution, including a follow-up photograph.
    e. Proceed to Period 3 (see 10.2.3).

10.2.3. Period 3: Open-label Treatment

After 24 hours of the initial start of study drug, subjects with a reduction in average GIR <20% at 24 hours will be assigned to open-label CSI-Glucagon™.

After 48 hours of the initial start of study drug, subjects with a reduction in average GIR ≥20% at 24 hours will be assigned to open-label CSI-Glucagon™.

After a subject is assigned to open-label CSI-Glucagon™, the following procedures will be performed.

Note: If continuous enteric feed was reduced in period 2 and increased feeding is necessary by the algorithm, the same rate as established during period 1 should be the target, and any additional demands will be covered with the IV GIR.

Period 3:

At the start of open-label treatment:

1. Photograph the site of approximate cannula insertion prior to application of a new OmniPod® pump.
2. Using the same procedures for loading and weighing the pump, and confirming cannula deployment as detailed for Day 0, apply a new OmniPod® pump containing CSI-

Glucagon™ (5 mg/mL), instruct the pump to insert the cannula and set basal rate of 5 µg/kg/hr. Record time of starting the pump; this is t=0.

3. Adjust IV fluids as per the Day 1 procedures.
4. At 4 hours, remove the OmniPod® pump and:
    a. Photograph the application site, paying particular attention to the cannula insertion site.
    b. Assess site for edema and erythema using the Draize scale. Any Draize scores > 0 should be followed to resolution, including a follow-up photograph.
5. The investigator should provide an assessment as to whether continued treatment would be helpful for clinical care.
    a. If yes, and open-label treatment will be continuing, perform "real-world" pump change-out procedure (see Section 9.3.3).
    b. If no, and open label treatment is ending, remove CGM and draw blood for immunogenicity testing, plasma insulin and glucagon levels as well as CBC, and CMP. Do not perform the "real-world" pump change-out procedure in this case.
6. If CSI-Glucagon™ treatment is considered helpful for clinical care, therapy may continue, including intermittently should procedures, e.g., PET scan, require temporary discontinuation, for up to a cumulative 28-day glucagon exposure.
    a. Using the same procedures for loading and weighing the pump, and confirming cannula deployment as detailed for Day 0, a new OmniPod® pump containing CSI-Glucagon™ solution should be placed immediately and again at least every 72 hours, including any time the pump alarms due to an occlusion.
    b. Each time a pump is replaced, the safety of pump switch out procedures should be as assessed by occurrence of blood glucose < 50 mg/dL.
    c. Each time a pump is removed, including at final termination of therapy, the pump should be weighed, and the placement site should be photographed and assessed with Draize scales and any reactions followed to resolution.
    d. POC glucose will be assessed every three hours; or more frequently if the CGM shows glucose falling <70 mg/dL (3.9 mmol/L) or rising above >200 mg/dL (11.1 mmol/L). Additionally, the trajectory of change in plasma glucose concentration based on the two most recent POC measurements should be used to adjust the frequency of glucose monitoring as needed to prevent plasma glucose <70 mg/dL (3.9 mmol/L) or >200 mg/dL (11.1 mmol/L).
    e. CGM will be utilized for rapid alerts, which will trigger POC assessments of blood glucose that will be used to guide clinical decisions. At least 2 hours prior to each planned pump change, confirm the CGM sensor is working and place another as needed.
    f. Every 2 weeks during treatment, draw blood for immunogenicity testing.
7. Whenever CSI-Glucagon™ treatment is temporarily paused and when treatment ends:
    a. Draw blood for CBC, CMP, immunogenicity testing and plasma insulin and glucagon.
    b. Perform physical exam and measure height and weight.

c. Resume IV fluids at pre-study rate and manage glucose as per standard procedures.

10.2.4. Period 4, Post-treatment Immunogenicity Testing

At 28±14 days after receiving the last dose of glucagon in the study, subjects should have blood drawn for immunogenicity testing. Preferably, this will be done at the study site. If travel or other considerations preclude the subject returning to the study site, the blood draw may be performed at a local hospital, laboratory or clinic, or by home health care professional. In this case, the plasma sample will be sent directly to the central lab for testing. Xeris or its designee will coordinate with the site and the subject to facilitate collection, processing and shipping of this blood sample.

10.3. Subject Withdrawal

Subjects may withdraw from the study at any time at the parent/guardian's request or they may be withdrawn any time at the discretion of the investigator or sponsor, for safety, behavioral or administrative reasons. In any circumstance, every effort should be made to document the subject's outcome, if possible. Information regarding the reason for not completing the study will be recorded on the appropriate case report forms. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs. It will be documented whether or not each subject completed the clinical 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 examination should be scheduled soon after the decision to withdraw is made. The following assessments should be completed if possible at this examination:

- Update any changes to medical history and concomitant medications.
- Perform physical examination and measure height and weight.
- Collect blood pressure and pulse rate measurements.
- Obtain blood samples as outlined in Schedule of Activities

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

Table 4: Schedule of Assessments and Procedures

Assessment	Screening	Period 1: Baseline GIR	Period 2: Randomized treatment		Period 3: Open-Label Treatment		Period 4: Post-Treatment
		Day -1	Day 0	Day 1	Day 2	Q3D	
Informed consent	x	—	—	—	—	—	
Demographic data	x	—	—	—	—	—	
Medical history	x	—	—	—	—	—	
Concomitant medications	x	x[a]	x[a]	x[a]	x[a]	x[a]	
Review eligibility	x	—	—	—	—	—	
Physical exam & weight	x	—	—	—	—	x[b]	
Vital signs (CRM)	x	x	x	x	x	x	
Hematology (CBC)	x[c]	—	—	—	x[f]	x[b]	
Clinical chemistry (CMP)	x[c]	—	—	—	x[f]	x[b]	
Blood glucose (POC)	x	x	x	x	x	x	
Immunogenicity	—	—	x	—	—	x[d]	x[g]
Plasma glucagon/insulin	—	—	x	x	x	—	
Wean diazoxide and octreotide	—	x	—	—	—	—	
Adjust GIR (and continuous enteric feed) when GIR=0	—	x	x	x	x	x	
Insert new CGM sensor	—	—	x	—	—	x[e]	
Photograph planned insertion site; weigh & place new OmniPod®	—	—	x	—	x[f]	x	
Remove & weigh OmniPod®; photograph and assess site with Draize scales	—	—	—	x	@ 4 hrs	x	
Adverse events	—	—	x	x	x	x	

[a] Update as applicable.
[b] Complete only when treatment ends or pauses.
[c] Normal clinical care samples drawn within 7 days of the intended start of Period 2 will satisfy this requirement.
[d] To be drawn every 2 weeks during open-label treatment, Day 14 and 28 (if applicable), whenever treatment is paused, and at the end of open-label treatment.
[e] Weekly or as needed.
[f] Will be performed on Day 1 if subject is a treatment failure and is switched to open-label treatment at 24 hours.
[g] To be drawn at 28 ±14 days post-glucagon treatment.

11. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time 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 collections, every effort must be made to obtain these samples at the same clock time each day. Blood collections and other study procedures should be performed at the time periods specified in the Schedule of Activities. With the exception of blood samples for determination of plasma glucagon, and insulin concentrations and immunogenicity testing, all biological samples will be assayed at onsite clinical laboratories. Procedures for the proper processing, storage and shipment of samples to offsite laboratories will be provided to all investigators prior to the start of the study.

11.1. Blood Volume

There will be 3 PK blood samples of about 2.0 mL each drawn over the first 3 days of treatment, plus a 1 mL sample for immunogenicity testing at the start of treatment. Hematology and chemistry panels will be collected at Screening, at the end of blinded treatment and at the end of open-label treatment. Testing performed as part of routine care may be used to satisfy the Screening requirement for hematology and chemistry. The amount of blood drawn on any particular day for study-specific procedures will not exceed 5% of estimated blood volume based on the weight of the subject (Table 5). All subjects exposed to CSI-Glucagon™ will have additional 1 mL blood samples for immunogenicity testing collected at 14 and 28 days of open-label treatment (if applicable), whenever treatment is paused, at the end of open-label treatment, and again at 28 ±14 days following the last dose.

Table 5: Volume of Blood Collections for Study-Specific Testing

	Sample Type	Hematology	Chemistry	Immunogenicity*	PK (insulin and glucagon)**	Total (mL)
Volume/Day	Screen	1***	1***	-	-	2
	Period 2, Day 0	-	-	1	2	3
	Period 2, Day 1 non-responders	1	1	-	2	4
	Period 2, Day 2 responders	1	1	-	2	4
	Period 3, Day 14 (if applicable)	-	-	1	-	1
	Period 3, Day 28 (if applicable)	-	-	1	-	1
	Period 3 Pauses/End	1	1	1	2	5
	Post Treatment****	-	-	1	-	1

*Note: Testing will be repeated whenever CSI-Glucagon™ treatment is temporarily paused, when treatment ends and at 28±14 days following the last dose of CSI-Glucagon™.
**Note: POC glucose samples are not reflected in this table, given the small volume of blood that is needed (~1.2 µl/sample) for plasma glucose measurements at bedside.
*** If not performed within 7 days of the start of study treatment as part of routine clinical care.
****At 28±14 days after the study treatment ends.

11.2. Clinical Laboratory Tests

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

Table 6: Clinical and Safety-related Laboratory Tests to be Performed

Hematology	Chemistry	Central Laboratory
WBC count	Glucose	Glucagon levels
RBC count	Creatinine	Insulin levels
Hemoglobin	Sodium	Immunogenicity
Hematocrit	Chloride	
Platelet count	Bicarbonate	
	Potassium	
	Calcium	
	Albumin	
	Alkaline Phosphatase	
	AST/SGOT	
	ALT/SGPT	

The local clinical laboratory at each site will perform all testing specified in Table 6 with the exception of Central Laboratory tests (i.e., plasma glucagon and insulin and immunogenicity testing). The investigator must maintain, on file, written evidence that the clinical laboratory to be used is certified under the Clinical Laboratory Improvement Act or equivalent certification (depending on local regulations). Further, the investigator must provide Xeris Pharmaceuticals or its agent with a copy of the certification, the range of normal values, the effective dates for the ranges, and the units of measurement for all laboratory tests requested in the protocol. If any of the laboratory measurements will be transformed and/or categorized in any way, a description of the procedures(s) used should be included. Xeris Pharmaceuticals or its agent must receive these documents before the shipment of clinical supplies.

One central analytical lab will analyze the glucagon and insulin samples, and another the anti-glucagon samples collected in this study. The procedures for preparing, storing and shipping these samples to the central analytical labs will be provided to each investigator prior to commencement of the study.

11.3. Vital Signs

Heart rate and respiration will be measured continuously by cardiorespiratory monitoring. These items along with BP and body temperature will be recorded in the CRF once daily at approximately the same time of day from Screening to the end of study treatment.

11.4. Photographs

Digital photographs of study drug infusion sites will be taken at the following times:

- Prior to the application of each OmniPod® pump, photograph the site of approximate cannula insertion.
- Upon removal of each OmniPod® pump, photograph the application site, paying particular attention to the cannula insertion site.

- For any insertion sites with Erythema or Edema scores >0 (Draize scale), follow-up photographs should be taken to document resolution.

Photographs should be time/date stamped and labeled with the subject ID number and stored on a secure, access-restricted computer. Care should be taken not to include the subject's face or other identifying information in the photographs.

12. SAFETY AND ADVERSE EVENT (AE) REPORTING

12.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be reported. 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 (see Section 12.4) requiring immediate notification to Xeris Pharmaceuticals (see Section 12.9). For all AEs, follow-up by the investigator is required until the event resolves or stabilizes at a level acceptable to the investigator to consider it closed, and Xeris Pharmaceuticals should concur with that assessment.

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

12.2. Reporting Period

For all AEs, the reporting period to Xeris Pharmaceuticals begins from the time informed consent is obtained through the last administration of the investigational product.

12.3. 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, and/or
- Test result is considered to be an AE by the investigator or Sponsor.

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

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

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

12.4. Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence at any dose which:

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

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in hospitalization or death. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent an 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. All SAEs are reportable to the Sponsor within 24 hrs. of first awareness of the event by an investigator (see Section 12.9)

12.5. Severity Assessment

The investigator will use the adjectives mild, moderate or severe to describe the maximum intensity of each AE. These intensity grades are defined as follows in Table 7 .

Table 7: Adverse Effects Assessment

MILD	Does not interfere with subject's usual function
MODERATE	Interferes to some extent (<50%) with subject's usual function
SEVERE	Interferes significantly (≥50%) with subject's usual function

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

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

12.6. Causality Assessment

The investigator will use the following question when assessing causality of an adverse event to study drug, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? ‘‘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. Regardless of causality, all SAEs are immediately reportable to the Sponsor (see Section 12.9).

12.7. Withdrawal Due to Adverse Events

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

12.8. Eliciting Adverse Event Information and Reporting

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

12.9. Serious Adverse Event Reporting Requirements

If an SAE occurs, Xeris Pharmaceuticals is to be notified within 24 hrs. of awareness of the event by the investigator, regardless of the investigator’s determination of causality. In particular, if the SAE is fatal or life-threatening, notification to Xeris Pharmaceuticals must be informed as soon as possible, 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., an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hrs. after learning such event and document the time of first awareness of the AE.

A death occurring during the study, during the per-protocol follow-up period, or within 4 weeks 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 reports must be confirmed promptly either by email or overnight courier.

12.10. Non-Serious Adverse Event Reporting Requirements

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

12.11. Sponsor Reporting Requirements to Regulatory Authorities

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

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

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

12.12. Pregnancy

This is not applicable since all subjects are under 1 year of age.

12.13. Subject Monitoring

Subjects will be monitored for AEs throughout the study by the study unit staff. The principal investigator or designated sub-investigator will be on site for initial pump placement and for the subsequent 4 hours. The principal investigator or designated sub-investigator will also be on call for the remainder of the study. As necessary, a physician will administer treatment for any AEs.

Safety parameters, including laboratory results, will be assessed by the principal investigator or his delegate using the site's criteria for clinical laboratory 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.

12.14. Medical Device Reports

A reportable medical device report (MDR) is one for which there is a reasonable possibility that a device has or may have caused or contributed to a death or serious injury.

Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:

(1) Failure;

(2) Malfunction;

(3) Improper or inadequate design;

(4) Manufacture;

(5) Labeling; or

(6) User error.

Serious injury means an injury or illness that:

(1) Is life-threatening,

(2) Results in permanent impairment of a body function or permanent damage to a body structure, or

(3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

All reportable MDRs will be reported to Xeris within 24 hours of an investigator's first awareness of the event. For all reportable MDRs, within 10 working days of becoming aware of the event, the investigator will complete Med Watch Form FDA 3500A for submission to FDA, in the case of a device-related death, or to the device manufacturer, in the case of a device-related serious injury.

13. DATA ANALYSIS AND STATISTICAL METHODS

13.1. Sample Size Determination

This is a parallel group adaptive design with one interim analysis after 6 subjects in each study arm have completed their post-treatment success-failure determination. Depending on the comparison of the treatment and placebo failure rates, the study will either be stopped with an early claim for treatment efficacy, or continued with either 3 or 6 additional subjects per study arm so that the final comparison of failure rates will be based on 9 or 12 subjects per study arm. The final sample size will be based on the outcome of the interim analysis.

The criteria for stopping early at 6 subjects per group or continuing to a final sample size of 9 or 12 subjects per group was designed so that the type 1 error is no larger than 0.025 for treatment = control failure rates at any failure rate. The overall power for concluding that the treatment failure rate is less than control is over 98% if the placebo failure rate is at least 0.9 and the treatment rate is no more than 0.1, with early efficacy having a power of 66%. If the placebo failure rate is at least 0.95 and the treatment failure rate is no more than 0.05 then the chance for an early efficacy determination is 88%.

Power and type 1 error levels were computed using Monte Carlo simulations of the study, 10,000 replications for each determination (R, version 3.1.2).

13.2. Statistical Analyses

The pharmacodynamic endpoints will be derived from the individual glucose infusion rates (GIRs).

Primary and secondary efficacy analyses will be performed using two cohorts of subjects:

- Primary cohort defined as all subjects fulfilling final protocol GIR selection criteria having average GIR assessments at periods 1, 2.
- Per-Protocol cohort defined as subjects from the Primary cohort having no major protocol violations.

The primary endpoint will be based on the Primary cohort. The safety analyses will use the Safety cohort defined as all subjects receiving either of the treatment regimens.

13.2.1. Primary Endpoint (Pharmacodynamic)

For each subject, the average GIR will be computed for periods 1 (baseline), 2 (treatment) by determining the area under the curve of GIR excluding the first 2 hours versus time and then dividing by the time duration for each of the periods excluding the first 2 hours using the last 24 hours for each period, or if less than 24 hours is available, the available data excluding the first 2 hours.

The primary comparison of treatment and placebo will be based on a success-failure determination (see Section 5.1).

This is a parallel group, adaptive design with one interim analysis after 6 subjects in each study arm have completed their success-failure determination. If, at the interim analysis, the observed

treatment failure rate is lower than placebo so that the one-tailed p value is less than or equal to 0.0124 (Fisher's exact test, hypergeometric distribution based on the total number of failures) then the study will be stopped due to early treatment efficacy.

If this interim one-tailed p value is greater than 0.0124 but less than or equal to 0.05, then the study will continue and an additional 3 more subjects per study arm will be randomized. If this interim one-tailed p value exceeds 0.05 then the study will continue, and an additional 6 more subjects will be randomized. The final analysis will be based on the observed treatment and placebo failure rates using all subjects with a success-failure determination. If, at the final analysis, the observed treatment failure rate is lower than placebo so that the one-tailed p value is less than or equal to 0.04 (hypergeometric distribution) then treatment efficacy will be established.

The actual type 1 errors are smaller than the efficacy criteria would suggest because of the small sample sizes and the use of Fisher's exact test. From Monte-Carlo simulations the overall type 1 error for this design is bounded above by 0.016 for null hypothesis treatment = placebo failure rates at ay failure rate using the above criteria. The type 1 error achieves its maximum at treatment = placebo = 0.5, and for this design the maximum is 0.016 as estimated by 10,000 Monte Carlo replications of the design.

13.2.2. Secondary Endpoints (Pharmacodynamic)

Secondary analyses will include baseline adjusted analyses of the natural logarithm of GIR to obtain confidence bounds on ratio of treatment to placebo mean GIR.

Other important secondary endpoints will consider the average GIR over the last 24 hours during period 2. The chance that this final rate is less than 8 mg/kg/min will be estimated and compared. Also, the cumulative glucose infusion will be combined with the total enteric feeding for the last 24 hours. The chance that this combined value is less than or equal to the daily equivalent of 8 mg/kg/min will be estimated and compared.

Furthermore, the following secondary endpoints will be described:

- Discontinuation of feeds with ability to fast for 3 hours
- Discontinuation of Gastrostomy tube (G tube) of glucose infusion

13.2.3. Pharmacokinetics

Pharmacokinetic (PK) data of steady state glucagon concentrations following continuous subcutaneous infusion will be analyzed descriptively.

13.2.4. Device Performance

The following endpoints related to device performance will be analyzed descriptively.

- Comparison of target vs. a weight-based estimate of dose volume delivery
- Infusion site leakage
- Occlusions
- Device failures/malfunctions

13.2.5. Safety/Tolerability

Safety/tolerability endpoints to be analyzed by treatment period will include:

- Adverse events (AEs)
- Laboratory safety variables
- Physical examination
- Body weight
- Vital signs
- Local tolerability

13.2.5.1. Adverse events:

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

13.2.5.2. Laboratory safety assessments:

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

13.2.5.3. Physical examination:

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

13.2.5.4. Vital signs:

Vital signs will be summarized by descriptive statistics.

13.2.5.5. Local Tolerability

The incidences of erythema and edema will be analyzed with a McNemar's test.

13.3. Subgroup Analysis

No subgroup analysis is planned for this study.

13.4. Interim Analysis

An unblinded interim analysis will be conducted after the 6th subject in each study arm has completed period 2. The objectives of this interim analysis are to:

1. Stop the study early for overwhelming evidence of early efficacy, as defined above in Section 13.2.1.

2. Continue the study enrolling either 3 or 6 additional subjects per study arm depending on the outcome of the interim analysis (see Section 13.2.1)

The unblinded statistician not related to the conduct of the study will perform this interim analysis according to a DSMB charter that will define the analysis details and the communications between the unblinded statistician, the DSMB, and the sponsor.

14. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

15. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS

15.1. Case Report Forms/Electronic Data Record

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

The investigator has the responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that these are accurate, authentic, attributable, complete, consistent, legible, contemporaneous, enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained in the CRFs is true.

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

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

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

15.2. Records Retention

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

15.3. Monitoring

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

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

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

15.4. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will have oversight of this study. The DSMB is an expert advisory group of physicians who function as a review committee independent from the Sponsor, and who function to ensure the safety of subjects enrolled in the study. DSMB members will meet periodically, without the Sponsor or study team members present, to review and discuss cumulative safety and efficacy data.

After the review of each Data Report has been completed, the DSMB Chairperson will provide the official DSMB recommendation to Sponsor regarding the appropriateness of continuing the study, from a safety perspective, as well as any other recommendations relevant to study conduct and/or patient safety.

The operating procedures of the DSMB are based on and are in compliance with the Food and Drug Administration's "Guidance for Clinical Trial Sponsors [on the] Establishment and Operation of Clinical Trial Data Monitoring Committees" (March 2006, OMB Control Number: 0910-0581) and with the European Medicines Agency's "Guideline on Data Monitoring Committees" (January 2006, EMEA/CHMP/EWP/5872/03 Corr).

15.5. Audits and Inspections

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

The investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

16. ETHICAL CONSIDERATIONS

16.1. Conduct

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

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

16.2. Institutional Review Board (IRB)

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

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

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

16.3. Subject Information and Consent

Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained from the parent/guardian. For patients who are considered potentially eligible for the study based on case history, the study protocol will be discussed with the parent/guardian by a study investigator and clinic coordinator. The parent/guardian will be

given the Informed Consent Form to read. The parent/guardian will be encouraged to discuss the study with family members and their personal physician(s) before deciding whether to participate in the study. If the parent/guardian agrees to have the child participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the parent/guardian and another copy will be added to the participant's chart or retained by the center research staff. The signed informed consent document must be available for verification by the study monitors at all times.

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

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and Xeris Pharmaceuticals before use.

16.4. Subject Recruitment

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

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

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

17. DEFINITION OF END OF TRIAL

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

18. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

18.1. Protocol Modifications and Deviations

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

18.2. Study Termination

The study may be prematurely terminated at any time because of a regulatory authority decision, change in opinion of the IRB, safety problems, or at the discretion of Xeris Pharmaceuticals or the principal investigator. Circumstances that may warrant premature study termination at a one or more clinic sites or overall 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
- 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 remove all participating subjects from ongoing study treatment 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 in a timely manner.

19. PUBLICATION OF STUDY RESULTS

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

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21. APPENDICES

APPENDIX 1. DRAIZE SCALE

- Draize Scale for Erythema and Edema: to be used for physical examination abnormalities at the infusion site.
- Investigative Site Instructions: The infusion site should be examined after removal of the OmniPod® pump and recorded on the case report form.
- For any infusion site with an Erythema or Edema Formation score > 0, follow-up examinations should be performed until scores equal 0.

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

APPENDIX 2. OMNIPOD® WEIGHING PROCEDURES

The following procedures will be followed to load and weigh the OmniPod® pump.

1. Remove pod from original sealed plastic cover and set cover aside.
2. Load pod as per protocol:
    a. If placebo group, load with 1 mL vehicle, using the kitted needle and syringe
    b. If active group, load with 1 mL glucagon, using a 1 mL Injekt-F syringe and kitted needle
3. Using PDM, prime pod.
    a. A small amount of fluid may collect under/around the needle shield; blot and discard.
4. Place pod back into the original opened plastic cover and place in Ziploc baggie labeled with the subject's study ID number.
    a. Add a fresh sterile gauze pad to the baggie.
5. Weigh baggie and record weight to nearest whole mg.
6. Take PDM and baggie containing pod with original opened plastic cover and dry gauze pad to NICU.
7. Remove the needle shield and blot any pooled liquid using the gauze pad.
8. Place pod on patient as per protocol.
9. Place adhesive backing, needle shield, used gauze pad and original opened plastic cover back into the baggie and return it to Pharmacy.
10. When it is time to remove pod, retrieve plastic baggie from Pharmacy.
11. Deactivate and remove pod and place in plastic baggie and return baggie to Pharmacy with PDM.
12. Pharmacy will weigh plastic baggie, containing used pod, needle shield, adhesive backing and used gauze pad, and record weight to nearest whole mg.
13. Pharmacy will record reading from PDM regarding the amount of drug infused since priming.

Note: Per the manufacturer, the maximum allowable time between Pod priming and activation is 1 hour.