CLINICAL STUDY PROTOCOL

A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Parallel Study to Evaluate Glucagon RTU (Glucagon Injection) Compared to Standard of Care for the Prevention of Exercise-Induced Hypoglycemia During Regular Aerobic Exercise in Adults with Type 1 Diabetes

Protocol Number:	XSMP-204
CTA Number:	222108
Phase:	2
Study Drug:	GLUCAGON Ready-to-Use (Glucagon Injection)
Sponsor:	Xeris Pharmaceuticals, Inc 180 North LaSalle Street, Suite 1600 Chicago, IL 60601
Medical Monitor:	Khaled Junaidi, MD
Date of Protocol:	Version 4.0, 6/20/2019 Version 3.0, 25 Feb 2019
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Xeris Pharmaceuticals (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing the study.

1. TABLE OF CONTENTS

PROCEDURES IN CASE OF EMERGENCY

Role in Study	Name & Title	Email Address & Telephone Number
Sponsor's Study Leader & primary contact	Julie Murphy, MSHS Clinical Project Manager	jmurphy@xerispharma.com (312) 736-1255 (direct) (312) 841-9478 (cell)
Medical Monitor & 24-hour emergency contact	M. Khaled Junaidi, MD, Medical Director, Clinical Research	kjunaidi@xerispharma.com (312) 517-1461 (direct) (815) 593-2218 (cell)
Reporting of Investigational Product concerns, including device failures	Xeris Medical Affairs Department	Safety-XSMP204@xerispharma.com (630) 915-5885 (815) 593-2218

PROTOCOL AMENDMENT HISTORY

Summary of Changes From Version 3.0

Affected Section(s)	Summary of Revisions Made	Rationale
Title page	Updated to add GCP and Confidentiality statements	Consistency with other protocol
Protocol Amendment History	Add a list of changes since Version 3.0	Correctness
Signature page	Revised to include all functional areas	Correctness
Section 2	Revised grammar, punctuation, spelling; added safety endpoints, revised study schema and Schedule of Assessments	Correctness
Section 3	Updated abbreviations	Correctness
Section 4	Updated editorial items (grammar, punctuation, spelling)	Correctness
Section 5	Separated Objectives and Endpoints, which had been in the same section	Correctness
Section 6	Editorial corrections; updated the definition of End of Study	Correctness
Section 8	Moved all information related to treatment of subjects to Section 8 from Section 9	Correctness
Section 9	Added a section that describes all assessments	Completeness
Section 10	Corrected missing elements from study procedures	Completeness
Section 11	Corrected language in the description of withdrawal of a subject	Correctness
Section 12	Editorial corrections	Completeness
Section 13.1.3	Added missing information	Completeness
Section 14	Added references	Completeness
Appendices	Updated with references (sources), and corrected procedures	Completeness

Summary of Changes from Version 2.0 to 3.0

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout the protocol	Administrative clarifications located throughout the protocol	To correct pagination and version number inconsistencies
Schedule of Assessments	Added Adverse Event Assessment to screening visit	To add consistency throughout protocol
Schedule of Assessments / 9.3.1.	Added the use of Polar Beat H10 heart rate sensor to both CRC exercise sessions.	Site will be using this to monitor subject heart rate during exercise sessions.
Table 3	Removed exploratory endpoint: "Proportion of time with 80% max heart rate during exercise sessions."	This endpoint is no longer applicable as 80% is a target heart rate, but not required, during exercise sessions.
8.1	Inclusion criteria #4: Updated inclusion criteria to include pmol/L equivalent of ng/mL for random C-peptide.	The local lab will report this value using pmol/L.
11.4.4	Revised wording for start time of collection of adverse events from starting "at Visit 2" to "from time of consent"	To add consistency throughout protocol.
N/A	Clarification to Summary of Changes from Version 1.0 to 2.0: Removed Urinalysis from schedule of assessments and body of protocol	Urinalysis was inadvertently added to protocol 1.0 and subsequently removed as this does not impact safety.
10.3.1	Removed verbiage regarding short-term excursions	The current stability data supports controlled room temperature storage only.

Summary of Changes from Version 1.0 to 2.0

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout the protocol	Administrative clarifications located throughout the protocol	To clarify specific points and address inconsistencies
Schedule of Assessments	Removed Urinalysis from schedule of assessments and body of protocol	Data from this procedure will not be analyzed
Appendix 6	Injection Site Discomfort Description and Duration Questionnaire has been added	Originally left as a stand-alone document but has now been added to the appendix for consistency.

XERIS PHARMACEUTICALS SIGNATURE PAGE

A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Parallel Study to Evaluate Glucagon RTU (Glucagon Injection) Compared to Standard of Care for the Prevention of Exercise-Induced Hypoglycemia During Regular Aerobic Exercise in Adults with Type 1 Diabetes

Version 4.0
6/20/2019

Medical Director:	See attached electronic signature page
	Khaled Junaidi, MD Medical Director, Clinical Research Xeris Pharmaceuticals, Inc.
Clinical Operations:	See attached electronic signature page
	Martin J. Cummins, BS Vice President, Clinical Development Xeris Pharmaceuticals, Inc
Regulatory:	See attached electronic signature page
	Aziz Alam, MS Senior Director, Regulatory Affairs Xeris Pharmaceuticals, Inc
Biostatistics and Data Management	See attached electronic signature page
	Nicole Close, PhD Head of Biostatistics and Clinical Data Management Xeris Pharmaceuticals, Inc.
Director Quality Assurance:	See attached electronic signature page
	Ed Drower, MS Director of Good Clinical Practices Xeris Pharmaceuticals, Inc

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The Principle Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from Xeris Pharmaceuticals, Inc., and documented approval from the Research Ethics Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. PROTOCOL SUMMARY

2.1. Synopsis

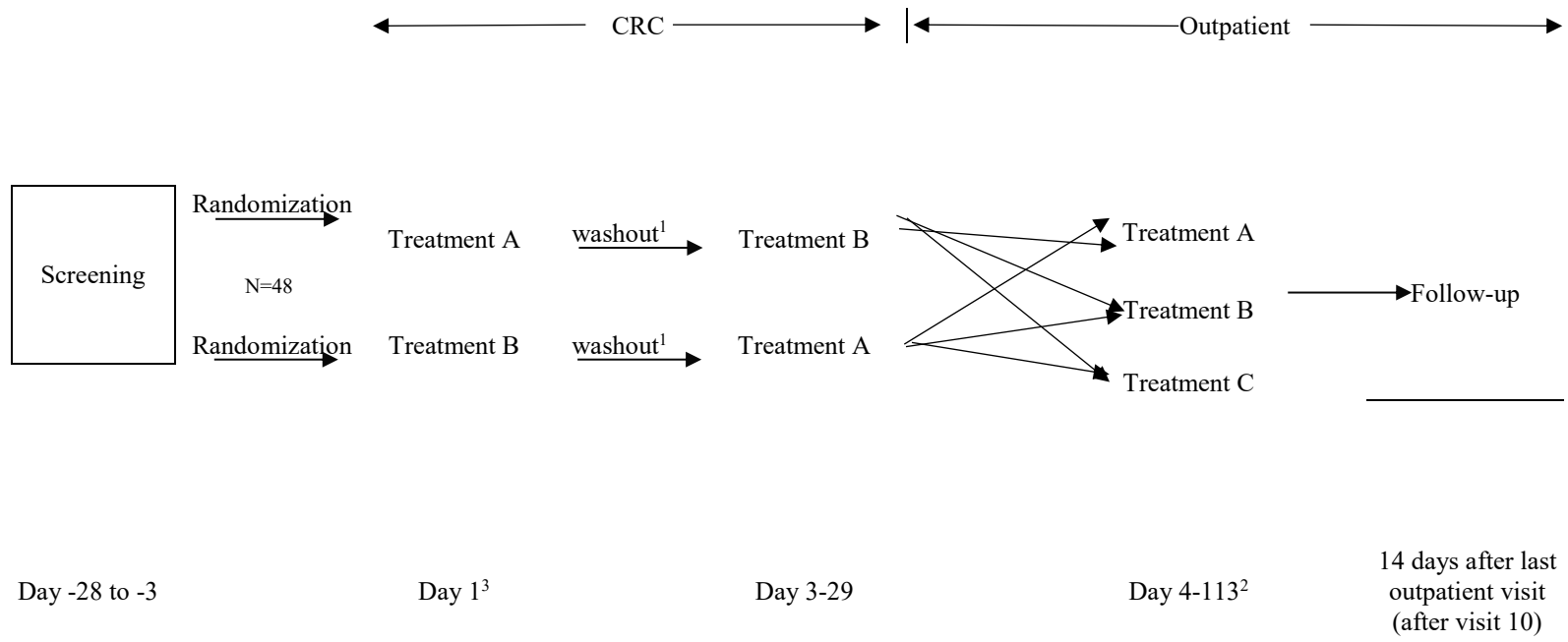
Title	A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Parallel Study To Evaluate Glucagon RTU (Glucagon Injection) Compared To Standard Of Care For The Prevention Of Exercise-Induced Hypoglycemia During Regular Aerobic Exercise In Adults With Type 1 Diabetes.
Study Description	This study is a randomized, placebo-controlled, double-blind, two-treatment, two- period, crossover comparison in a clinical research center (CRC) setting followed by a randomized, placebo-controlled, double-blind, 2-arm parallel comparison with a third open-label arm in the Outpatient Phase. The purpose of the study is to evaluate the preliminary efficacy of Glucagon Ready-to-Use (RTU) to prevent exercise-induced hypoglycemia in adults with Type 1 diabetes mellitus (T1D) who perform regular, moderate-to-high intensity, aerobic exercise of at least 45 minutes duration in an inpatient setting and at least 30 minutes duration in the outpatient setting, and who receive daily insulin treatment via a subcutaneous infusion pump and to monitor safety in this population. During the CRC Phase, each subject will undergo two, 45-minute morning aerobic exercise sessions. Subjects will be randomized to receive the first treatment at Visit 3 and crossed over to the second treatment at Visit 4. All CRC exercise sessions will take place in the morning, following an overnight fast. At 5 minutes prior to each exercise session, subjects will reduce their basal rate of insulin infusion by 50% and maintain this reduction for the duration of exercise. Immediately after making the basal rate insulin reduction, subjects will self-administer one of the following randomly assigned interventions: 1. Placebo (vehicle) 2. Glucagon RTU During the 12-week Outpatient Phase, subjects will be assigned randomly in a 1:1:1 ratio to 1 of the following interventions to self-administer prior to moderate-to-high intensity aerobic exercise sessions lasting at least 30 minutes: 1. A 50% reduction in basal rate insulin 5 minutes before exercise + pre-exercise injection of placebo (blinded) 2. A 50% reduction in basal rate insulin 5 minutes before exercise + pre-exercise injection of Glucagon RTU (blinded) 3. No reduction in basal rate insulin + pre-exercise injection of Glucagon RTU (open-label)
Objectives	**Primary Objective:** To evaluate if the subcutaneous (SC) administration of Glucagon RTU (Glucagon Injection) just before exercise, with or without a 50% reduction in basal rate insulin, compared to a 50% basal rate insulin reduction alone, prevents the occurrence of hypoglycemia (ie, blood glucose ≤70 mg/dL; 3.89 mmol/L) measured by blood glucose meter (BGM) during and after

	moderate-to-high intensity aerobic exercise by adult subjects with T1D in an outpatient setting.
	Secondary Objectives: 1. To evaluate how Glucagon RTU (Glucagon Injection) contributes to prevention of hypoglycemia during exercise and post-exercise recovery. 2. To evaluate the effect of Glucagon RTU (Glucagon Injection) on insulin utilization during 12 weeks of out-patient exercise. 3. To evaluate the effect of Glucagon RTU (Glucagon Injection) on patient-reported outcomes (PROs) of: Barriers to Physical Activity Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS) and Hypoglycemia Confidence Scale (HCS) after 12 weeks of outpatient exercise.
Endpoints	**Primary Endpoint:** Incidence of hypoglycemia (ie, blood glucose ≤70 mg/dL; 3.89 mmol/L) associated with an exercise session across 12 weeks of outpatient treatment as measured by blood glucose measurements (BGM). **Key Secondary Endpoints:** 1. Glucose levels below target range, measured by unblinded CGM (inpatient and outpatient), defined as both time (in minutes) and mean decremental area over the curve ($AUC_{(0\text{-}300\ min)}$ in minutes*mg/dL) during exercise: • Below range, as defined by interstitial glucose (IG) ≤ 70 mg/dL (3.89 mmol/L) • Below range, as defined by IG between 54 to - 70 mg/dL (3 – 3.89 mmol/L) • Below range, as defined by IG < 54 mg/dL (3 mmol/L) • Proportional time (percentage time within hypoglycemia IG ≤ 70 mg/dL (3.89 mmol/L) and clinically significant hypoglycemia IG < 54 mg/dL (3 mmol/L)) 2. Change from Baseline at the end of the Outpatient Phase in the following PROs: Barriers to Physical Activity in Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS-II), Hypoglycemic Confidence Scale (HCS). Other Secondary Endpoints • Change from Baseline at Weeks 4, 8, and 12 in insulin utilization as reported by the subject in the Outpatient Phase.
Safety Endpoints	Safety endpoints include the following: summaries of number of subjects (%) with adverse events, including serious adverse events; change from Baseline in vital signs and clinical laboratory test values; number of

	abnormal and clinically significant 12-lead ECG results. All safety parameter results will be listed.
Study Population	The study will include 48 male and female subjects in North America with Type 1 diabetes (T1D) aged 18 to 65 years at Screening, who engage in regular, moderate-to-high-intensity aerobic exercise at least 30 minutes in duration, and who receive daily insulin therapy via SC infusion pump. Approximately 100 subjects may be screened to obtain 48 randomized subjects.
Phase	2
Description of Sites/Facilities Enrolling	LMC Manna Research 1929 Bayview Avenue, Suite 107 Toronto, Ontario M4G 0A1 Canada
Principal Investigator	Ronnie Aronson, MD, FRCPC, FACE
Description of Study Intervention	Glucagon RTU is a non-aqueous, injectable liquid formulation of glucagon. Glucagon RTU consists of synthetic glucagon peptide dissolved in a DMSO diluent, with trehalose and mannitol added as stabilizing excipients. Glucagon RTU is presented in a 2-mL glass vial (1 mL fill). The placebo consists of the matching Glucagon RTU vehicle without glucagon in the same vial presentation. Both products will be administered SC around the umbilicus using a staked-needle syringe. The dose is 30 µL per injection, which delivers 150 µg of glucagon for the active formulation.
Study Duration	The estimated duration of the entire study is 8 months.
Participant Duration	Participant study duration is approximately 20 weeks (5 months). Subjects will participate in a 4-week Screening Period, a 2-week CRC Phase, 12-week Outpatient Phase, and a 2-week for the End of Study Visit.

2.2. Schema

Figure 1: Schema of Study Design



1 Single dose cross-over treatment in a CRC setting will be separated by 2 to 28 days.

2 Outpatient setting where patients are randomized to 1 of 3 parallel treatment arms.

3 Randomization into1 of 3 Treatment Arms at the beginning of the study:
Treatment A: Pump reduction of 50% in basal rate 5 minutes before exercise for the duration of exercise, plus pre-exercise placebo injection (30 µLvehicle)
Treatment B: Pump reduction of 50% in basal rate 5 minutes before exercise for the duration of exercise, plus pre-exercise Glucagon RTU injection (30 µL active - 0.15 mg)
Treatment C: No pump reduction for the duration of exercise, plus pre-exercise Glucagon RTU injection (30 µL active - 0.15 mg)

2.3. Schedule of Activities

Table 1 Schedule of Assessments and Procedures

Assessment	Visit 1	Visit 2	Visit 3[o] CRC 1	Visit 4[o] CRC 2	Visits 5 to 10 Outpatient Phase	Visit 11 Follow-up[f] /ET
	Screening Day–28 to –3	CGM Placement Day –2 to –1	Treatment Period 1 (Days 1[a,b,c])	Treatment Period 2 Day 3 to 29[d]	Treatment Period 3 Day 4 to 113[e]	
Informed consent	X					
Medical History/ Demographics	X					
Inclusion/exclusion criteria	X					
Concomitant medications (including insulin pump data)	X	X	X	X	X	X
Height, weight and physical examination	X					X
12-lead ECG	X					X
Vital signs	X		X	X	X	X
Urine pregnancy test	X		X	X	X	X
Urine drug screen	X					
Hematology	X					X
Clinical chemistry	X					X
HbA1c	X					X
Plasma Glucose	X					X
C-peptide	X					X
Immunogenicity[g]			X		X	X
CGM		X[d]	X[h]	X[h]	X[h]	X[h]
Exercise[i,o]			X	X		
BGM[k]			X	X[j]	X[j]	X[j]
Study drug administration			X	X[l]	X	
Wearable Activity Monitors (Fitbit Ionic and Polar Beat H10)			X[m]	X[m]	X[n]	X[n]
HBV, HCV, HIV Screen	X					

Assessment	Visit 1	Visit 2	Visit 3[o] CRC 1	Visit 4[o] CRC 2	Visits 5 to 10 Outpatient Phase	Visit 11 Follow-up[f] /ET
	Screening Day–28 to –3	CGM Placement Day –2 to –1	Treatment Period 1 (Days 1[a,b,c])	Treatment Period 2 Day 3 to 29[d]	Treatment Period 3 Day 4 to 113[e]	
Outpatient Study Training				X		
Diary[i]			X	X	X	X
Glucose Tabs Log			X	X	X	X
Randomization			X			
8-Hour fast	X		X	X		X
Venous blood glucose (YSI)			X	X		
BAPAD-1 Questionnaire			X			X
Draize Scale			X	X		
HFS			X			X
Hypoglycemia Confidence Scale			X			X
Injection Site Discomfort Description and Duration Questionnaire			X	X		
Adverse event review	X	X	X	X	X	X

*Visits will occur every 2 weeks during the out-patient phase. The visit window is +/- 3 days for the outpatient visits.
BAPAD-1 = Barriers to Physical Activity in Type 1 Diabetes Scale; BGM = blood glucose monitor; CRC = Clinical Research Center; CGM = continuous glucose monitor; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HFS = Hypoglycemia Fear Survey; HIV = human immunodeficiency virus; YSI = Yellow Springs Instrument

a. As long as the subject has 2 days of rest between each CRC visit.
b. Subjects will be instructed not to exercise between Visit 2 and Visit 3.
c. Questionnaires to be completed are Barriers to Physical Activity Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS) and Hypoglycemia Confidence Scale (HCS).
d. CGM will be placed approximately 24-48 hours prior to data collection at CRC Visit 2.
e. Collection timepoints ± 2 minutes are: -15 minutes, 0 minutes (just before initiation of exercise), and at 15, 30, 45, 60 and 75 minutes after initiation of exercise.
f. Follow-Up occurs 14 days after the last exercise period.
g. An immunogenicity sample will be drawn before the first dose of investigational product, every four weeks (28 days +/- 2 days) and at the End of Study visit.
h. CGM data will be downloaded.
i. During the CRC Phase of the study, subjects will perform moderate-to-high-intensity exercise of at least 45 minutes duration, with each exercise session separated by at least 2 days during the inpatient phase of the study. During the Outpatient Phase of the study, subjects will be asked to maintain a weekly exercise average of 2 to 3 sessions weekly of at least 30 minutes. Exercise data will be downloaded from the wearable device. Data include heart rate, calories burned, daily steps, floors climbed, distance covered, active minutes.
j. BGM Measurements will be performed at the following timepoints during CRC visits, ± 2 minutes:
   - -15 minutes (both YSI and BGM)
   - Time 0 (immediately before exercise) (both YSI & BGM))
   - 15 minutes (YSI only)
   - 30 minutes (both YSI & BGM)
   - 45 minutes (both YSI & BGM, end of exercise)

- 60 minutes (YSI only)
- 75 minutes (both YSI & BGM, thirty minutes after completion of exercise)

k. BGM data will be downloaded at each patient visit.
l. Investigational Product (IP) for first outpatient visit will be dispensed at the end of visit 4.
m. Subject will wear both Fitbit Ionic and Polar Beat H10 heart rate sensor during this visit.
n. Subject will wear only the Fitbit Ionic during these visits.
o. Prior to beginning the exercise session, if the subject's blood glucose is below 100 mg/dL the subject is allowed to take dextrose tabs (e.g., 2-4 tabs) to raise the blood glucose, and the blood glucose verified to be within 100-180 mg/dL (5.56 – 10 mmol/L). The number of dextrose tabs and time administered are recorded.
Prior to beginning the exercise session, if the blood glucose is >180 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 100 to 180 mg/dL.

At discretion, the investigator may reschedule the visit to occur after a minimum wait of 24 hours. The visit should be re-scheduled so it occurs within the originally defined visit window. For example, a rescheduled Visit 3 (CRC 1) should occur within 28 days of Visit 1 (Screening), while a rescheduled Visit 4 (CRC 2) should occur within 28 days of a completed Visit 3 (CRC 1)..

3. ABBREVIATIONS

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

Table 2: Abbreviations and Definition of Terms

Abbreviation/Specialist Term	Definition
AE	adverse event
ANOVA	analysis of variance
AUC	area under the concentration versus time curve
AUC_{∞}	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC_t	area under the concentration versus time curve from time 0 to the last measurable concentration (time t)
BGM	blood glucose measurement
BMI	body mass index
C_{max}	maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation expressed as a percentage
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IMP	investigational medicinal product
ITT	Intent-to-treat
LDL	low-density lipoprotein
LOQ	limit of quantification
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
OECD	Organization for Economic Cooperation and Development
OHRP	Office for Human Research Protections
QTc	corrected QT interval

Abbreviation/Specialist Term	Definition
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SD	standard deviation
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed plasma concentration
UP	Unanticipated Problems
WBC	white blood cell
WHO	World Health Organization
YSI	Yellow Springs Instrument

4. INTRODUCTION

4.1. Study Rationale

Exercise is at the cornerstone of Type 1 diabetes (T1D) management [1]. However, blood glucose stability during exercise, and for 12-24 hours afterwards, remains a major challenge [2]. Fear of hypoglycemia deters many patients from engaging in aerobic exercise [3]. For those who choose to exercise on a regular basis, hypoglycemia is a common complaint that often requires breaks in exercise sessions, sports and competition, games and training [3]. To reduce the incidence of hypoglycemia during and immediately after exercise, patients are recommended to reduce their bolus dose at the meal preceding exercise by 25-75% [4], however, this approach frequently results in pre-exercise hyperglycemia, particularly if the exercise is performed 2 hours or more after the meal [2, 4, 5]. Even exercise in the fasting state in patients on continuous subcutaneous insulin infusion (CSII) promotes a drop in glycemia if basal insulin levels are not adjusted [5].

Post-exercise hypoglycemia is also very common in T1D, with roughly 50% of young patients developing the condition about 7-11 hours after the end of vigorous afternoon exercise [8]. Further, if insulin administration is used to correct post-exercise meal-related hyperglycemia (often called rebound hyperglycemia), severe post-exercise hypoglycemia may occur which may even result in death [9]. Patients can reduce the dose of meal time insulin administered with the dinner meal after late day exercise to reduce nocturnal hypoglycemia risk [10] or lower basal insulin delivery for 6 hours at bedtime [11] to help mitigate risk, but these strategies often result in hyperglycemia [10, 11]. Although extra carbohydrate ingestion not covered by insulin administration can help prevent hypoglycemia during and after exercise [12], excessive intake defeats the ability of the patient to have a negative caloric balance, thereby limiting the capacity for patients to control their body weight.

Patients on insulin pump therapy have the flexibility to reduce basal insulin delivery in anticipation of exercise and in recovery to help guard against hypoglycemia. The International Society for Pediatric and Adolescent Diabetes guidelines recommend that basal insulin reductions should be done 60-90 minutes before the start of exercise so that circulating insulin levels are lowered by the start of the activity [13]. This task is somewhat cumbersome and unpredictable and is usually not performed correctly, even by the most educated and motivated patients. Glucose production by the liver during moderate intensity exercise is primarily facilitated by a rise in the glucagon to insulin ratio [14] and patients with T1D have a reduction in this ratio during exercise because of a relative peripheral hyperinsulinemia [14] and impaired glucagon secretion [15], it may be better to attempt to change this ratio by the administration of glucagon at the onset of exercise [16]. The recent development of a more stable form of soluble glucagon (eg, Glucagon RTU from Xeris Pharmaceuticals, Inc. [Xeris]) has given researchers and clinicians the possibility of using this product as a preventative strategy to combat exercise-associated hypoglycemia.

4.2. Background

In Protocol No. XSMP-201, a Phase 2a clinical trial, Glucagon RTU was evaluated in a dose-seeking study among 12 adults aged 18 to 50 years with T1D. The study was conducted in an inpatient clinical research center setting, and tested doses of 75, 150, and 300 µg. Subjects were

studied on 3 separate occasions using 2 independent injections of glucagon on each study day. All treatments were well tolerated, no SAEs were observed and AEs were generally mild in nature and consisted primarily of pain or a burning sensation at the injection site. Observations of edema and erythema were generally mild and transient. Nausea occurred at the high dose only, in one- third of the patients.

Glucagon injections were made both after an overnight fast and several hours later, following an injection of insulin to mimic the amount they would have taken for a 30-g carbohydrate snack. The study results showed a clear dose response with an initial response observed after 15 to 20 minutes, and the peak time of response after 30 to 45 minutes, both after an overnight fast and following insulin to induce mild hypoglycemia. In all cases, subjects responded to the 150 and 300 µg doses with an increase of plasma glucose of 40 to 100 mg/dL following an overnight fast, and a somewhat smaller increase of 40 to 60 mg/dL following insulin. The 75 µg dose resulted in a smaller rise in glucose (+30 mg/dL) in most subjects, but in no case did the glucose continue to decrease after SC glucagon administration even at that lowest dose. On the basis of these results, a dose of 150 micrograms was selected for a follow-up study for prevention of exercise-induced hypoglycemia.

Protocol No. XSMP-203 was a single-blind, randomized 4-way crossover pilot study involving 15 adult subjects with T1D, ages 18 to 64 years, using continuous subcutaneous insulin infusion (CSII) and wearing a continuous glucose monitor. At 5 minutes prior to 45-minute sessions of moderate aerobic exercise, subjects received a 150-µg dose of Glucagon RTU or performed one of 3 alternate approaches for prevention of hypoglycemia: (1) consumed 20-gm glucose tablets, (2) implemented a 50% reduction in basal rate insulin, or (3) no intervention prior to exercise (ie, untreated control).

During exercise, plasma glucose increased slightly with Glucagon RTU compared to a decrease with control and insulin reduction, and a greater increase with glucose tablets. Insulin levels were not different among sessions, while glucagon increased with Glucagon RTU. Hypoglycemia (≤70 mg/dL (3.89 mmol/L)) was experienced by 6 subjects in the control arm, 5 subjects in the insulin reduction arm, and no subjects using glucose tablets or Glucagon RTU. A total of 5 subjects experienced hyperglycemia (≥250 mg/dL) with glucose tablets and 1 with Glucagon RTU.

There were no SAEs reported in the study and no subjects discontinued prematurely. No participant reported nausea during exercise, but 2 participants reported nausea with symptoms of bloating post-exercise after receiving Glucagon RTU.

4.3. Risk/Benefit Assessment

4.3.1. Known Potential Risks

One of the main complications of glycemic control with insulin is the emergence of hypoglycemia, and the absolute or relative excess of therapeutic insulin is the primary determinant of risk. Hypoglycemia in diabetes is defined as “all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm” [5], and manifests clinically as diaphoresis, pallor, nausea, palpitations, tremor, anxiety, cognitive impairment, behavioral changes and psychomotor abnormalities, and loss of consciousness, seizure, and coma in severe

hypoglycemia. Recent reports have found that from 6 to 10% of deaths of patients with T1D are attributable to hypoglycemia [6]. The American Diabetes Association Workgroup recommends that patients with drug-treated diabetes (insulin secretagogues or insulin) become concerned about developing hypoglycemia at a plasma glucose concentration of ≤ 70 mg/dL (3.89 mmol/L) [17].

Therapy with insulin causes hypoglycemia during the course of established T1D and progressively more frequently over time in Type 2 diabetes. The U.K. Hypoglycemia Study Group reported an incidence of 110 hypoglycemic episodes per 100 patient-years in patients with T1D treated with insulin for <5 years, and an incidence of 320 episodes per 100 patient-years in those with T1D treated for >15 years [18]. People living with Type 1 diabetes suffer an average of two symptomatic hypoglycemic events per week – and a severe, temporarily disabling event approximately once a year [19]. Insulin-using people with Type 2 diabetes typically have several hypoglycemic episodes in a given year, 1-2 of these being severe episodes. There are currently approximately 1.4 million people with Type 1 diabetes and 3.8 million insulin-using people with Type 2 diabetes in the US alone [20]. On average, the total insulin-using patient population experiences about 3 million severe hypoglycemic events per year.

4.3.2. Known Potential Benefits

In response to the unmet medical need for a simple and ready-to-use glucagon for episodes of hypoglycemia, Xeris is developing a glucagon product. The Glucagon RTU (Glucagon Injection) utilizes Xeris' biocompatible, non-aqueous peptide/protein reformulation technology. This technology has allowed Xeris to create a concentrated, low volume, stable glucagon formulation, pre-mixed in a ready-to-use vial for administration by a single use syringe, and ultimately will allow development of a multi-dose pen. This creates a product with a number of advantages for the treatment of hypoglycemia:

- Ready-to-use treatment with no reconstitution required,
- Precise dosing to avoid overtreatment of low blood sugar,
- Rapid dosing due to room-temperature liquid stability, and
- Enhanced portability and availability in a multi-use format.

Current and future studies are aimed at evaluating the safety and efficacy of Glucagon RTU (Glucagon Injection) to provide patients with a better option for treatment and prevention of non-severe hypoglycemia.

5. OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

To evaluate whether the SC administration of Glucagon RTU (Glucagon Injection) just before exercise, with or without a 50% reduction in basal rate insulin, compared to a 50% basal rate insulin reduction alone, prevents the occurrence of hypoglycemia (ie, blood glucose ≤70 mg/dL; 3.89 mmol/L) measured by blood glucose meter (BGM) during and after moderate-to-high intensity aerobic exercise by adult subjects with T1D in an outpatient setting.

5.1.2. Secondary Objectives

- To evaluate how Glucagon RTU (Glucagon Injection) contributes to prevention of hypoglycemia during exercise and post- exercise recovery
- To evaluate the effect of Glucagon RTU (Glucagon Injection) on insulin utilization during exercise.
- To evaluate the effect of Glucagon RTU (Glucagon Injection) on PROs BAPAD-1, HFS-II, and HCS after 12 weeks of outpatient exercise

5.1.3. Exploratory Objectives

- To evaluate the glycemic time in range associated with exercise sessions and post-exercise
- To evaluate the impact of Glucagon RTU (Glucagon Injection) on the quantity of glucose tabs used over time during exercise sessions
- To evaluate weight loss or weight maintenance over time
- To examine food intake both before and after exercise
- To examine the effects of exercise and Glucagon RTU on overnight hypoglycemia following episodes of exercise
- To evaluate the effects of exercise and Glucagon RTU use upon changes in hemoglobin A1c
- To evaluate the intensity and duration of the frequent exercise sessions
- To evaluate overall frequency of aerobic exercise over the study period

- To evaluate effects on exercise duration and intensity as well as daily activity metrics

5.2. Endpoints

5.2.1. Primary Endpoint

The primary endpoint is the incidence of hypoglycemia (ie,, blood glucose ≤70 mg/dL; 3.89 mmol/L) associated with an exercise session across 12 weeks of outpatient treatment as measured by a blood glucose meter (BGM).

5.2.2. Key Secondary Endpoints

- Glucose levels below target range, measured by unblinded CGM (inpatient and outpatient), defined as both time (in minutes) and mean decremental area over the curve (AUC(0-300 min) in minutes*mg/dL) during exercise:
  - • Below range, as defined by interstitial glucose (IG) ≤ 70 mg/dL (≤3.89 mmol/L)
  - • Below range, as defined by IG between 54 to 70 mg/dL (3 – 3.89 mmol/L)
  - • Below range, as defined by IG < 54 mg/dL (<3 mmol/L)
  - • Proportional time (percentage time within hypoglycemia IG ≤ 70 mg/dL (3.89 mmol/L) and clinically significant hypoglycemia IG < 54 mg/dL (3 3 mmol/L))
- Insulin utilization as reported by the subject at Baseline, Weeks 4, 8, and 12 in the Outpatient Phase.
- Change from Baseline to the end of the Outpatient Phase in PROs: Barriers to Physical Activity in Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS-II), and Hypoglycemic Confidence Scale (HCS),

5.2.3. Other Secondary Endpoints

- Change from Baseline in insulin utilization as reported by the subject at Weeks 4, 8, and 12 in the Outpatient Phase.
- Exploratory EndpointsMean time and mean proportional time (%) within range, as defined by plasma glucose between 70 and 180 mg/dL (3.89 to 10 mmol/L) (CGM, 0 to 300 minutes with exercise)
- The time, proportional time (percentage), and mean incremental area under the curve (AUC) during which plasma glucose >180 mg/dL (10 mmol/L), and ($AUC_{(0- 300\ min)}$ in minutes*mg/dL) during exercise.

- The time, proportional time (percentage), and mean incremental area under the curve (AUC) during which plasma glucose >250 mg/dL (AUC(0- 5 hours) in minutes*mg/dL) during exercise.
- Incidence of overnight hypoglycemia as measured by CGM.
- Compare the glucose tablet utilization during exercise, across the 3 treatment arms.
- Compare food (carbohydrate) intake pre/post exercise across the 3 treatment arms.
- Compare the number of exercise sessions performed across the 3 treatment arms.
- Compare the number of minutes of exercise performed per week.
- Compare caloric expenditure during exercise, across 3 treatment arms.
- The change from Baseline in body weight will be measured and analyzed across the 3 treatment arms.
- Compare the number of steps taken and the distance achieved during exercise sessions across 3 treatments..
- The following assessments during exercise sessions will be captured from the wearable activity monitor: heart rate, daily steps, calories burned, distance covered, floors climbed, active minutes.
- Change from baseline in HbA1c

5.2.4. Safety Endpoints

Safety endpoints include the following: summaries of number of subjects (%) with adverse events, including serious adverse events; change from Baseline in vital signs and clinical laboratory test values; number of abnormal and clinically significant 12-lead ECG results. All safety parameter results will be listed.

6. STUDY DESIGN

6.1. Overall Design

This study is a randomized, placebo-controlled, double-blind, t2-treatment, 2-period, crossover comparison in a clinical research center (CRC) setting, followed by a randomized, placebo-controlled, double-blinded, 2-arm parallel comparison with a 3rd open-label arm in an outpatient setting to evaluate the preliminary efficacy and safety of Glucagon RTU to prevent exercise-induced hypoglycemia (EIH) in adults with Type 1 diabetes mellitus (T1D), who perform regular, moderate-to-high intensity aerobic exercise.

The CRC Stage will involve 2 daytime clinical research center (CRC, or comparable setting) exercise sessions 2 to 28 days apart, in a morning exercise session, for the following treatment assignments:

1. Insulin pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise placebo injection (30 µL vehicle), or
2. Insulin pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise Glucagon RTU (30 µL active - 0.15 mg).

At investigator discretion, the insulin pump rate can be reduced overnight based on the subject's medical history for the duration of the study.

BGM assessments (Yellow Springs Instrument [YSI] readings) during CRC visits will be at -15, 0, 30, 45, and 75 minutes from the start of exercise. Subjects will also wear unblinded CGM during both the CRC and Outpatient Stages of the study.

The Outpatient Stage will be 12 weeks in duration, during which subjects will be randomized to 1 of 3 parallel treatment arms, 2 of which are double-blinded, and 1 is open-label.

Subjects will receive:

1. Insulin pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise placebo injection (30 µL vehicle), or
2. Insulin Pump reduction (50% reduction in basal rate five minutes before exercise, for the duration of the exercise), and pre-exercise Glucagon RTU (30 µL active - 0.15 mg), or
3. Pre-exercise Glucagon RTU (30 µL active - 0.15 mg) without pump changes.

Subjects will measure blood glucose using BGM at -15 and 0 minutes (ie, just before exercise) to establish a baseline, and after 30 minutes of exercise, 30 minutes post-exercise, and at the end of exercise (if greater than 30 minutes). Subjects will wear an unblinded CGM during the conduct of the study.

6.2. Justification for Dose

Mild to moderate hypoglycemia is common in individuals with T1D. Many individuals, particularly those under tight control, experience glucose levels ≤70 mg/dL (3.89 mmol/L) on a

daily or near-daily basis. When hypoglycemia is identified - either by measuring the glucose level or by symptoms, standard treatment consists of oral carbohydrate intake. This approach is generally successful in preventing more severe hypoglycemia and raising blood glucose concentrations. However, hyperglycemia often results and it can be difficult to quickly regain good control. In addition, the carbohydrate intake can make weight control challenging. Case reports have suggested that it may be more appealing to use small doses of glucagon to proactively raise the glucose level, avoiding the caloric value of the carbohydrate intake.

Although not labeled for use in situations other than severe hypoglycemia, small doses of glucagon have been shown to be particularly useful when an individual with T1D is unable to eat (e.g., young children who refuse or individuals with gastroenteritis or other illnesses). Haymond et al., reported that administration of glucagon by the subcutaneous route at a dose of 10 micrograms per year of age up to 150 micrograms was sufficient to increase the plasma glucose transiently (over 60 to 90 minutes) by 60 to 80 mg/dL and that repeated doses could be used for a subsequent mild hypoglycemic event without a worsening of nausea or vomiting [13]. This finding was confirmed in a report on the use of mini-dose glucagon in a pediatric practice in Australia, at a summer camp for children with diabetes, and in the inpatient setting [14, 15, 16]. While it is known that some individuals with T1D have successfully used mini-dose glucagon, little is known about frequency of use and response to treatment in an outpatient setting.

6.3. End of Study Definition

The end of the study is defined as the last visit date for the last subject in the study.

7. STUDY POPULATION

7.1. Inclusion Criteria

1. Clinical diagnosis of presumed autoimmune type 1 diabetes, receiving daily insulin via continuous subcutaneous insulin infusion.
2. Age 18 to < 65 years.
3. Duration of type 1 diabetes ≥ 2 years.
4. Random C-peptide < 0.6 ng/mL (< 198 pmol/L).
5. Using insulin therapy by continuous subcutaneous insulin infusion pump for at least 6 months.
6. History of exercise-related hypoglycemia.
7. Performs aerobic exercise regularly (2-3 times per week), and desires to exercise per ADA guidelines (150 minutes per week). Examples of aerobic exercise include powerwalking, hiking, running/jogging, cycling, swimming, cross country skiing, and aerobic fitness classes.
8. Will abstain from the use of non-insulin diabetes therapies such as SGLT-2s, GLP-1s, and metformin for the duration of the study.
9. Subject must be willing to adhere to the protocol requirements for the duration of the study.
10. Subject has provided informed consent as evidenced by a signed/dated informed consent form completed before any trial-related activities occur.

7.2. Exclusion Criteria

1. Frequently experience hyperglycemia with exercise, in the clinical judgement of the investigator.
2. Pregnant and/ or Nursing: For female subjects of childbearing potential, there is a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study, and for at least 1 week after the last dose of study drug. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence. Note, there are no requirements for male subjects.
3. One or more severe hypoglycemic episodes in the past 12 months (as defined by an episode that required third party assistance for treatment).
4. Uses inhaled insulin.
5. HbA1c > 9.0% at Screening.
6. Renal insufficiency (serum creatinine greater than 3 mg/dL (0.17 mmol/L)).
7. Serum ALT or AST equal to or greater than 3 times the upper limit of normal.

8. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3 mg/dL (0.17 mmol/L); or serum bilirubin greater than 2 mg/dL (0.11 mmol/L).
9. Hematocrit of less than or equal to 30%.
10. Mean of triplicate BP readings at Screening where SBP <90 or >150 mm Hg, or DBP <50 or >100 mm Hg.
11. Clinically significant ECG abnormalities.
12. Use of > 2.0 U/kg total insulin dose per day.
13. Inadequate bilateral venous access in both arms.
14. Congestive heart failure, NYHA class III or IV.
15. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers.
16. Major surgical operation within 90 days prior to screening, or planned surgical operation during the study.
17. History of seizure disorders.
18. Current bleeding disorder, treatment with warfarin or any anticoagulants, or platelet count below 50,000.
19. History of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
20. History of insulinoma.
21. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients(DMSO, mannitol, & trehalose) in the investigational formulation.
22. History of glycogen storage disease.
23. Subject tests positive for HIV, HCV or active HBV infection (HBsAg+) at Screening.
24. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
25. Active substance or alcohol abuse, in the opinion of the investigator. Subjects reporting active marijuana use or testing positive for THC via rapid urine test will be allowed to participate in the study at the discretion of the investigator.
26. Participation in other studies involving administration of an investigational therapeutic agent (drug or device) within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and during participation in the current study.
27. Any reason the investigator deems exclusionary.

7.3. Lifestyle Considerations

Not applicable.

7.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized. A minimal set of screen failure information is required (demographics, inclusion/exclusion criteria, adverse event, protocol deviation, and date of screen failure) to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Screen failures may be rescreened after a 30-day waiting period, at the discretion of the Investigator. Approximately 100 subjects may be screened to obtain 48 randomized subjects.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

A description of the study drug is presented in Table 2.

Table 2: Investigational Product, Comparator, and Rescue Medication

	Investigational Product	Comparator	Rescue Medication	
Product Name:	Glucagon RTU (Glucagon Injection	Placebo	Glucose Tablets	Glucagon for Injection®
Dosage Form:	Injectable	Injectable	Tablets	Injectable
Unit Dose	150 µg	150 µg	16g (4 tabs, 4 g/tab)	1 mg (1 unit)
Route of Administration	Injection	Injection	Oral	Injection
Physical Description	Supplied in 2.0 mL Crystal Zenith®cyclic olefin polymer vials with Flurotec® coated rubber stoppers	Placebo to match	Supplied commercially; 50 4-gm glucose tablets per bottle	The kit contains 1 IU of glucagon, a diluent syringe containing 12 mg/mL of glycerin, Water for Injection, and hydrochloric acid
Manufacturer	Pyramid Laboratories Inc. Costa Mesa, CA, USA	Pyramid Laboratories, Inc. Costa Mesa, CA, USA	Dex4 Glucose Tablets by AMG Medical, Montreal, QC, Canada	Eli Lilly, Indianapolis, IN, USA

8.2. Storage

Glucagon RTU (Glucagon Injection) should be stored at controlled room temperature 20° to 25°C (68° to 77°F).

Outpatient storage information will be provided in the Instructions for Use (i.e., Investigation Product Instruction Manual).

8.3. Study Drug Administration

The 30-unit (300 µL) Covidien Monoject syringe (29 G × ½ ” needle) will be used with the Glucagon RTU (Glucagon Injection) formulation and matching placebo. The study drug dosage is 30µL (150 µg of glucagon or matching volume of vehicle).

Each dose will be from a new, single-use vial of Glucagon RTU (Glucagon Injection).

Prior to beginning the exercise session, if the subject’s blood glucose is below 100 mg/dL the subject is allowed to take dextrose tabs (e.g., 2-4 tabs) per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered dextrose tabs and the subject’s glucose level should be within the range of 100 to 180 mg/dL

Prior to beginning the exercise session, if the blood glucose is >180 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject’s glucose level should be within the range of 100 to 180 mg/dL.

At discretion, the investigator may reschedule the visit to occur after a minimum wait of 24 hours. The visit should be re-scheduled so it occurs within the originally defined visit window. For example, a rescheduled Visit 3 (CRC 1) should occur within 28 days of Visit 1 (Screening), while a rescheduled Visit 4 (CRC 2) should occur within 28 days of a completed Visit 3 (CRC 1).

8.4. Treatment Compliance

Treatment compliance measures both the exercise performed and the study drug administered.

During the CRC Phase of the study, subjects will perform moderate-to-high-intensity exercise of at least 45 minutes duration, with each exercise session separated by at least 2 days during the inpatient phase of the study.

During the Outpatient Phase of the study, subjects will be asked to maintain a weekly exercise average of 2 to 3 sessions weekly of at least 30 minutes.

Subjects should self-administer assigned study drug for all qualified exercise sessions. Adherence to study drug will be evaluated via the study diary.

8.5. Measures to Minimize Bias: Randomization and Blinding

The study statistician will create the randomization schedule for the study. The randomization assignment for the participant will be conducted once at the time of enrollment with confirmation of subject eligibility. The CRC assignments will be by random assignment during the first session to either Glucagon RTU or placebo. At the second session , the participant will be crossed over to the other treatment assignment. At the completion of the CRC visits, the subject

will then have the treatment assignment applied for the parallel group study. The randomization schedule methodology for the Outpatient setting is by permuted random block to 1 of 3 treatment assignments in a 1:1:1 ratio.

1. A 50% reduction in basal insulin rate 5 minutes before exercise + pre-exercise injection of placebo (blinded)

2. A 50% reduction in basal insulin rate 5 minutes before exercise + pre-exercise injection of Glucagon RTU (blinded)

3. No reduction in basal insulin rate + pre-exercise injection of Glucagon RTU (open label)

The cross-over study is blinded to the extent possible since all participants will receive both Glucagon RTU and placebo. All staff, participants and study team members will know that the participant will receive both study treatments during the CRC sessions. During the outpatient study, two of the treatments will be blinded to the study staff, participants and Sponsor. One arm of the study will be open-label. It is imperative for the study staff to remain blinded to treatment assignment prior to randomization and during the study treatment periods as not to bias the outcome.

Glucagon RTU and placebo will be prepared and administered so that each will be indistinguishable from the other.

8.6. Unblinding

Blinding of study treatment is critical to the integrity of this clinical trial. It is expected that in the vast majority of cases, AEs can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual subject's treatment assignment is considered critical to the subject's management, the treating physician may unblind the treatment assignment. The investigator should contact the responsible Medical Director to discuss the subject and circumstances requiring the unblinding. The blind will be broken only for the specific subject under discussion. The Sponsor will remain blinded to the treatment assignment. Every effort will be made to restrict knowledge of the treatment assignment to the investigator only.

8.7. Concomitant Therapy

All therapies (prescriptions and over-the-counter medications) other than the study drugs administered from informed consent until the last study visit must be recorded in the source documents and in the concomitant therapy section of the eCRF (name of the drug, dosage, route and dates of administration).

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

The use of oral, transdermal, implantable, and injectable hormonal contraceptives is to be recorded in the source documents and in the concomitant therapy section of the eCRF.

8.7.1. Rescue Medicine

8.7.1.1. Oral Glucose Tablets

Standard of care for patients with symptoms of hypoglycemia and confirmed (BGM) blood glucose ≤70 mg/dL (3.89 mmol/L) is to take 16g (4 tabs, 4 g/tab) of glucose tabs, or per standard of care, and repeat the 16-g carbohydrate serving every 15 minutes until blood glucose is >70 mg/dL (3.89 mmol/L).

8.7.1.2. Glucose Emergency Kit

Subjects should be trained to administer a glucagon emergency kit should the subject experience severe hypoglycemia that requires external assistance.

9. ASSESSMENTS

9.1. Efficacy Assessments

9.1.1. Wearable Fitness Tracker (Fitbit Ionic)

At Visit 2, subjects will be fitted with a wearable fitness tracker. The Fitbit Ionic® is a wearable fitness tracker that is worn on the wrist. The Fitbit Ionic provides training workouts and monitors heart rate. The fitness tracker will be worn by each subject in this study to monitor the level of exercise intensity, and also to measure the 30-minute time periods at which subjects will measure their blood glucose. Data can be downloaded via Bluetooth to a central location.

9.1.2. Polar Beat H10 Heart Rate Sensor

The Polar Beat H10 Heart Rate Sensor will be provided to the subject at Visit 2 and is worn during Visit 3 and Visit 4 for accurate measurement of heart rate. It is not provided to the subject for use outside of the clinic.

9.1.3. Continuous Glucose Monitoring

A continuous glucose monitoring device (Dexcom® G5 Continuous Glucose Meter) will be placed on the subject and calibrated at Visit 2. It will be used to collect interstitial glucose measurements on a continuous basis.

9.1.4. Barriers to Physical Activity Diabetes (Type 1) Questionnaire

The Barriers to Physical Activity in Diabetes (Type 1) (BAPAD-1) is a 12-question instrument to assess the likelihood that a subject with T1D will exercise within the next 6 months; it is completed by the subject for the first time at Visit 3 and is also completed at the Follow-up Visit. Subjects are asked the question: “Indicate the likelihood that each of these items would keep you from practicing regular physical activity during the next 6 months?” and they are to respond by rating the 12 responses with a “1” (unlikely) to “7” (extremely likely). The higher the score, the less likely the subject is to engage in exercise.

9.1.5. Hypoglycemia Fear Survey II

The Hypoglycemia Fear Survey II (HFS-II) is a 33-item questionnaire, with 15 questions addressing actions the subject may take to avoid low blood glucose, and the remaining questions addressing fears the subject may have about low blood glucose. Responses range from a score of 0 (never) to 4 (almost always). The higher the score, the greater the subject’s fear of hypoglycemia. The HFS-II is completed at Visit 3 and the Follow-up Visit.

9.1.6. Hypoglycemia Confidence Scale

The Hypoglycemia Confidence Scale (HCS) is a 9-item questionnaire that assesses the subject’s confidence about safety regarding hypoglycemia. The questionnaire has 4 responses possible for

each question, ranging from "not confident at all" to "very confident. The HCS is completed at Visit 3 and the Follow-up Visit.

9.1.7. Modified Draize Scale

The Modified Draize Scale is used by the study site personnel to assess the degree of erythema and edema cause by the study drug injection. Each term (erythema and edema) has 5 choices of grades of the reaction, from "slight erythema/edema" to "severe erythema/edema". The study site personnel is to mark the choice that best represents the degree of erythema/edema observed at the injection site. The Modified Draize Scale is completed at Visits 3 and 4.

9.1.8. Injection Site Discomfort Description and Duration Questionnaire

The Injection Site Discomfort Description and Duration Questionnaire is a 3-question instrument that assesses a subject's level of discomfort and its duration post-injection. There are 5 responses for each of the the first 2 questions, which address the level of discomfort and the duration of the discomfort, respectively, for each injection . For the 3rd question, the total time for the duration of discomfort is to be provided. The Injection Site Discomfort and Duration Questionnaire is to be completed at Visits 3 and 4.

9.2. Pharmacokinetic/Pharmacodynamic Assessments

9.2.1. Immunogenicity Testing

An immunogenicity sample will be drawn before the first dose of investigational product, every 4 weeks (28 days +/- 2 days) and at the End of Study visit (Visit 3, Visit 5, Visit 7, Visit 9, and Visit 11 [Follow-up Visit]).

9.3. Safety Assessments

Safety assessments include the following: collection of adverse events, including serious adverse events, measurement of vital signs, clinical laboratory tests, 12-lead ECGs, and physical examinations, including measurement of weight.

9.3.1. Adverse Events and Serious Adverse Events

9.3.1.1. Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal result of diagnostic procedures, including clinical laboratory test abnormalities.

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be reported with the following exception. Hypoglycemia will not be considered an AE in this study unless the event is severe hypoglycemia with a BG reading ≤ 54 mg/dL (3 mmol/L), requires third-party assistance, or if the event meets one of the definitions of an SAE.

9.3.1.2. Definition of Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death.
- is life-threatening, i.e., the subject was at risk of death at the time of the event (e.g., ventricular fibrillation and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization. Hospitalization refers to an overnight admission into hospital for the purpose of investigating and/or treating the AE. Hospitalization for an elective procedure, or routinely scheduled treatment for a pre-existing condition that has not worsened, is not an SAE.
- results in persistent or significant disability/incapacity, i.e., causing substantial disruption of the subject's ability to conduct normal life.
- is a congenital anomaly/birth defect.
- is medically significant, i.e., may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject's health or may require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

9.3.1.3. Classification of an Adverse Event

9.3.1.3.1. Severity of Event

The Investigator or delegate will use the adjectives "mild," "moderate," or "severe" to describe the maximum intensity of the AE. These intensity grades are defined as follows in Table 3 .

Table 3 AE Severity Assessment

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

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

9.3.1.3.2. Relationship to Study Intervention

The Investigator will use the following question when assessing causality between an AE and the study drug, where an affirmative answer designates the event as a suspected adverse reaction: "Is there a reasonable possibility that the drug caused the event?" A ''reasonable possibility'' means that there is evidence to suggest a causal relationship between the drug and the AE. The Investigator's assessment of causality must be provided for all AEs and recorded in the source documentation. The degree of certainty about causality will be graded using the categories below:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.3.1.3.3. Expectedness

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied. Expectedness refers to the awareness of AEs previously observed. The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.3.1.4. Time Period and Frequency for Event Assessment and Follow-up

Adverse events will be assessed starting from time of consent through up to 14-21 days after the last dose of study drug (Follow-up Visit). The timing of event assessments is detailed in the Schedule of Activities (Table 1bookmark7).

All adverse events will be followed until resolution or the subject is medically stable.

9.3.1.5. Adverse Event Reporting

The Investigator or delegate 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. All AEs (including SAEs) occurring during the clinical investigation must be documented in the source documents and on the AE forms of the eCRF.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the AE to the study drugs in the source documents and on the AE forms of the eCRF. All measures required for AE management must be recorded in the source documents and reported according to Sponsor's instructions.

9.3.1.6. Serious Adverse Event Reporting

All SAEs independent of the circumstances or suspected cause must be reported on a Serious Adverse Event Form by the Principal Investigator to the Sponsor within 24 hours of their knowledge of the event, preferably by fax (1-312-276-4497) or by e-mail (kjunaidi@xerispharma.com or Safety-XSMP204@xerispharma.com).

The SAE form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

Follow-up and outcomes should be reported for all subjects who experience an SAE.

It is critical that the information provided on the Serious Adverse Event Form matches the information recorded in the source documents and on the (e)CRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to the Sponsor until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

9.3.2. Events of Special Interest

Not applicable.

9.3.3. Reporting of Pregnancy

All initial reports of pregnancy in subjects must be reported to the Sponsor by the Investigator or delegate within 24 hours of his/her knowledge of the event using a Pregnancy Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

9.4. Unanticipated Problems

9.4.1. Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

10. STUDY PROCEDURES

A schedule of activities for this study is provided below in Section Section 10.1-Section 10.3 bookmark27(screening and CRC Stage) and Section 10.4 (Outpatient Stage).

10.1. Visit 1 – Screening (Day -28 to -3)

Prior to completing any screening activities, the investigator or study team member will obtain informed consent from each subject.

A Screening visit must be completed at least 3 days (to allow for receipt of blood test results), and no more than 28 days prior to the anticipated date of the first treatment visit (Day 1). The following evaluations will be completed during the screening visit:

1. Assessment of inclusion/exclusion criteria by a study investigator, including a review of the subject's medical history, and demographics.
2. Review of concomitant medications.
3. Physical exam, including measurement of height and weight (no shoes, lightly clothed), but excluding genital/pelvic exams.
4. 12-lead ECG after subject has completed a minimum 5-minute supine rest.
5. Vital signs measurements, including measurements of temperature, respiration rate, heart rate, and BP, after a 5-minute seated rest.
6. Urine pregnancy test for women of childbearing potential and discussion about study requirements regarding contraception.
7. Sample collection for urinary drug screen.
8. Collection of venous blood for complete blood count (without differential), serum chemistry, and screening for HIV, HBV, and HCV.
9. A fasting blood sample (minimum 8 hours) will be taken for measurement of plasma glucose, HbA1c, and C-peptide.
10. Assessment of baseline AEs.

Once laboratory results are obtained and a final determination of eligibility is made, subjects will be contacted to schedule the CGM Placement Visit.

10.2. Visit 2 – CGM Placement (Day -2 to -1)

1. Concomitant Medication Review.
2. CGM Placement.
    a. The CGM will be placed 24 to 48 hours prior to data collection on CRC visit 3 and Visit 4 and the subject will be trained on calibration procedures.

3. A wearable activity monitor, Fitbit Ionic, will be provided to the subject for use during the study. The wearable activity monitor will be set up and training will be provided to the subject.
4. Adverse Event Review.

10.3. CRC Phase

10.3.1. Visit 3 – Treatment 1 (Day 1) / Visit 4 Treatment 2 (Day 3-29) Clinic Arrival

1. Subjects will arrive to clinic in the morning, after an overnight fast of at least 8 hours.
    - Subjects may proceed with exercise if BG is 100-180 mg/dL (5.56 – 10 mmol/L), as measured by the blood glucose meter.
        - If the subject's blood glucose is below 100 mg/dL the subject is allowed to take dextrose tabs (e.g., 2-4 tabs) per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 30 minutes should have passed from the last dose of administered dextrose tabs and the subject's glucose level should be within the range of 100 to 180 mg/dL
        - Prior to beginning the exercise session, if the blood glucose is >180 mg/dL after repeat test, then the investigator may treat with an intravenous (IV) bolus dose of regular insulin, per discretion, to bring the subject into the required blood glucose range. Before initiating study treatment, at least 40 minutes should have passed from the last dose of administered insulin and the subject's glucose level should be within the range of 100 to 180 mg/dL
        - If the subject's blood glucose cannot be optimized to 80 to 150 mg/dL within 2 hours, then the visit should be rescheduled after a minimum 24 hour wait, per investigator's discretion.
        - At discretion, the investigator may reschedule the visit to occur after a minimum wait of 24 hours. The visit should be re-scheduled so it occurs within the originally defined visit window. For example, a rescheduled Visit 3 (CRC 1) should occur within 28 days of Visit 1 (Screening), while a rescheduled Visit 4 (CRC 2) should occur within 28 days of a completed Visit 3 (CRC 1).
2. It will be confirmed that the CGM placed at Visit 2 is active and that the subject has followed calibration instructions.
3. Concomitant medications will be assessed.
4. Vital signs measurements, including measurements of temperature, respiration rate, heart rate, and BP, after a 5-minute seated rest.
5. Urine pregnancy test for women of childbearing potential.

6. Blood sample for immunogenicity testing (Only performed at Visit 3).
7. The wearable activity monitor will be worn by the subject during each exercise session.
   - Subject will wear both the Fitbit® Ionic and Polar Beat H10 heart rate sensor provided by the site during these visits.
8. Questionnaires/Forms will be filled out: Barriers to Physical Activity Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS) and Hypoglycemia Confidence Scale (HCS). These questionnaires are only administered at Visit 3/ Treatment 1.
9. The subject will be randomized for this study. (This only occurs at Visit 3/ Treatment 1).
10. Starting at 5 minutes prior to exercise:
    a. The subject will reduce the basal infusion rate of insulin by 50%.
    b. Study Medication will be administered based upon randomization assignment.
11. Subject will then complete an exercise session (See Appendix 1bookmark99).
    a. Heart rate will be monitored via the Fitbit Ionic device and Polar Beat H10 heart rate sensor during these exercise sessions.
    b. During the exercise session, the subject is to drink carbohydrate free liquids only (e.g., Powerade Zero or comparable product) and will be provided with glucose/dextrose tabs to use as needed.
    c. Per ADA guidelines, if a subject's glucose falls to ≤ 70 mg/dL (3.89 mmol/L) during any exercise session, then the exercise session should be stopped, the subject should rest, and glucose tabs should be taken every 15 minutes until the hypoglycemia is corrected and euglycemia (confirmed by BGM) is maintained. Subjects will be provided with a supply of glucose tabs and instructed to use these rather than other sources of carbohydrate to treat hypoglycemia.
12. Following completion of exercise:
    a. Basal rate insulin will be returned to the pre-exercise infusion rate.
    b. PI or delegate will administer Draize Scales for erythema and edema and the Injection Site Discomfort Description and Duration Questionnaire.
13. Before, during and after exercise, venous blood samples (YSI) for glucose measurements will take place at the following time points. Subjects will perform a blood glucose measurement using a BGM as indicated below with a window of ± 2 minutes:
    a. -15 minutes (both YSI and BGM)
    b. Time 0 (immediately before exercise) (both)
    c. 15 minutes (YSI only)
    d. 30 minutes (both)
    e. 45 minutes (both, end of exercise)
    f. 60 minutes (YSI only)
    g. 75 minutes (both, thirty minutes after completion of exercise)

14. AE assessment.

10.4. Visit 5 Through 10 – Outpatient Stage

10.4.1. Visits 5 Through 10 – Treatment Day 4-113

During the outpatient stage, subjects will return for clinic visits every two weeks. Activities to be performed at these visits are outlined in the Schedule of Activities (Table 1bookmark7).

In the outpatient setting, subjects will perform moderate to high intensity aerobic exercise with a target of at least 2-3 qualifying sessions per week. To be eligible for study drug dosing, the planned aerobic exercise will be 30-75 minutes in duration. Additionally, the subject's BGM must range between 100-180 mg/dL (5.56 – 10 mmol/L) before the exercise session. Subjects must record their carbohydrate intake (eg, both dextrose tabs and carbohydrates from food) 15 minutes before exercise, during the exercise session, and up to 5 hours post-exercise session.

During the exercise session, the subject is to only drink carbohydrate free liquids (e.g., Powerade Zero or comparable product) and will be provided with glucose tabs to use as needed. The subject will take 5 BGM measurements with exercise: at -15 minutes and just before exercise to establish baseline value, at 30 minutes into the exercise session, at the end of the exercise session, and at 30 minutes after the exercise session. There is a ±2 minute window on all of these time points.

Per ADA guidelines, if a subject's glucose falls to ≤70 mg/dL (3.89 mmol/L) during any exercise session, then the exercise session should be stopped, and no more exercise should be completed that same day; the subject should rest, and glucose tabs should be taken every 15 minutes until the hypoglycemia is corrected and euglycemia (confirmed by BGM) is maintained. Subjects will be provided with a supply of glucose tabs and instructed to use these rather than other sources of carbohydrate to treat hypoglycemia.

During the outpatient phase the subject will be provided with the following items for recording study data and will be provided with instructions for use and uploading data to the cloud if applicable.

1. Blood Glucose Meter: Bayer® Contour Next One
   a. Used to collect blood glucose values during exercise sessions and to confirm blood glucose if a value ≤ 70 mg/dL (3.89 mmol/L) is indicated by CGM.
2. Dexcom® G5 Continuous Glucose Meter
   a. Used to collect interstitial glucose measurements on a continuous basis.
3. Fitbit® Ionic
   a. Use to collect exercise session metrics (heart rate) and daily activity metrics
   b. Subjects will maintain a food log in the Fitbit application
4. Paper Diary
   a. Description of exercise type, start/stop time of exercise
   b. Glucose tab usage and emergency kit usage
   c. Time and volume of administration of Study Medication

10.4.2. Visit 11 – Follow-Up Visit (14-21 Days After Last Exercise Session)/Early Termination

Subjects will be asked to return the clinic 14 - 21 days from the last exercise session for the following evaluations. The subject will be asked to return to the clinic for this same list of evaluations upon early termination from the study.

1. Concomitant medication changes.
2. Focused PE, including measurement of height and weight (no shoes, lightly clothed), but excluding genital/pelvic exams.
3. 12-lead ECG after subject has completed a minimum of 5-minute supine rest.
4. Vital signs measurements, including measurements of temperature, respiration rate, heart rate, and BP, after a 5-minute seated rest.
5. Urine pregnancy test for women of childbearing potential.
6. Collection of venous blood for complete blood count (without differential) and serum chemistry.

   A fasting blood sample (minimum 8 hours) will be taken for measurement of HbA1c.
7. AE assessment.
8. Questionnaires/Forms will be filled out: Barriers to Physical Activity Diabetes (Type 1) (BAPAD-1), Hypoglycemia Fear Survey (HFS) and Hypoglycemia Confidence Scale (HCS).

11. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

11.1. Discontinuation of Study Intervention

The Sponsor has the right to terminate the study at any time. In case of an early termination of the study for safety reasons, or temporary halt by the Sponsor, the REB should be notified by the Investigator within 15 calendar days and should be provided with a detailed written explanation for the termination/halt.

An end-of-study declaration will be submitted to the regulatory authorities and REB after study termination (once all subjects have completed their last follow-up visit). To allow close-out procedures, this notification should be submitted within 90 days after the end of the study.

11.2. Participant Discontinuation/Withdrawal from the Study

Subjects have the right to withdraw from the study at any time for any reason, including personal reasons. A subject can withdraw without giving a reason. The Principal Investigator should however try to find out why a subject withdraws from the study and document the reason for withdrawal in the source documents and on the electronic Case Report Form (eCRF).

Subjects **may** be withdrawn from the study in the event of:

- A severe AE or serious AE (SAE);
- Failure of the subject to comply with the protocol requirements or to cooperate with the Principal Investigator.

Subjects **must** be withdrawn from the study in the event of:

- Withdrawal of consent;
- Difficulties in obtaining blood or other samples;
- For safety reasons, in the Investigator's opinion, it is in the best interest of the subject that he/she be withdrawn;
- A positive pregnancy test (or if the subject is non-compliant with the contraception requirements;
- Development of a medical condition that requires concomitant treatment with a prohibited therapy.

The monitor and Sponsor should be informed: in case of subject withdrawal due to an SAE (for details on AE reporting), and the Sponsor should be notified within 24 hours. In case of withdrawal for other reasons; the Sponsor should be notified within 2 days from the event.

Subjects who are withdrawn from the study prior to completion of the scheduled study procedures for any reason (AE, withdrawal of consent, etc.) should be invited to complete the assessments as indicated in the Schedule of Activities, Early Termination Visit (Table 1). In case of an AE, the appropriate follow-up will be conducted.

12. STATISTICAL CONSIDERATIONS

12.1. General Approach

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and other selected key efficacy endpoints. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, SD, minimum, and maximum for continuous data and frequencies and percentages for categorical data. Subject disposition will be presented for all subjects for each stage (CRC and Outpatient). The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation also will be presented.

Analyses will be performed for data collected during the CRC visits separately from the data collected during the parallel designed outpatient part of the study. A stand-alone Statistical Analysis Plan (SAP) will be developed to include complete details for all planned analyses.

12.2. Sample Size Determination

The primary endpoint of the study is the incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session, which occurred within the 12 weeks outpatient follow-up, as measured by BGM. The null hypothesis is that there is no difference between the treatment groups in the mean incidence of exercise associated hypoglycemia, and the alternative is there is a difference between the treatment groups in terms of the mean incidence of exercise associated hypoglycemia. With an effect size estimate of 0.262 (variance of means 59, common standard deviation 15), 80% power and an alpha of 0.05,using a one way analysis of variance, 14 subjects per treatment group in the Outpatient Stage is required.

Accounting for 15% attrition, a total of 48 subjects will be randomized.

12.3. Populations for Analyses

The following analysis populations have been defined for the parallel group study analysis:

- Intention to Treat (ITT): All randomized participants regardless of whether they received Study Drug.
- Per Protocol (PP): ITT participants who completed a qualified exercise session, and who was dosed in the study window and did not meet any of the key exclusion criteria at screening. The definition of qualified exercise and key exclusion criteria will be specified in the Statistical Analysis Plan (SAP).
- Safety: All randomized participants who received any amount of Study Drug.

12.4. Statistical Analyses

12.4.1. Efficacy Hypothesis

The primary efficacy hypothesis test for the study is as follows:

Null Hypothesis: There is no difference between the treatment groups in the mean incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session occurring within the 12 weeks of out-patient treatment as measured by BGM.

Alternative Hypothesis: There is a difference between treatment groups in the mean incidence of hypoglycemia (glucose ≤ 70 mg/dL (3.89 mmol/L)) associated with an exercise session occurring within the 12 weeks of out-patient treatment as measured by BGM.

Incidence rate per subject is calculated by summing the number of exercise sessions completed within 12 weeks and dividing this denominator by the number of hypoglycemic events that occurred during those exercise sessions.

12.4.2. Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy analysis will be analyzed by ANOVA comparing the mean incidence rate among the 3 treatment groups. All statistical significance testing will be 2-sided with a p-value <0.05. Efficacy endpoints will be analyzed using the ITT and PP analysis populations. After performing the F-test and if an overall $p<0.05$ is achieved, post-hoc analysis of group means will be conducted to statistically determine which group means differ.

12.4.3. Analysis of the Key Secondary Endpoint(s)

Glucose levels will be measured and analyzed as the mean decremental area over the curve (AUC(0-5hrs) in minutes*mg/dL) during exercise. Analysis will be conducted for glucose levels below range (interstitial glucose ≤70 mg/dL (3.89 mmol/L), interstitial glucose between 54-70 mg/dL (3 – 3.89 mmol/L), <54 mg/dL (3 mmol/L)) and proportional time (percentage within serious hypoglycemia <54 mg/dL (3 mmol/L)). Differences between treatment groups in daily glucose requirements with exercise and adherence to IP with exercise will be made using t- tests (not corrected for multiple comparisons). Change from baseline to end of study in BAPAD- 1, HFS-II and HCS will be conducted. Changes from baseline in PROs may be correlated with clinical measurements during the study.

Secondary endpoints will be analyzed using the ITT and PP populations. Glucose levels will be measured and analyzed as the mean decremental area over the curve (AUC(0-5hrs) in minutes*mg/dL) during exercise. Analysis will be conducted for glucose levels below range (interstitial glucose ≤70 mg/dL (3.89 mmol/L), interstitial glucose between 54-70 mg/dL (3 - 3.89 mmol/L), <54 mg/dL (3 mmol/L)) and proportional time (percentage within serious hypoglycemia <54 mg/dL (3 mmol/L)). Differences between treatment groups in daily glucose requirements with exercise and adherence to IP with exercise to determine if subjects use fewer glucose tabs will be made using t-tests (not corrected for multiple comparisons). Change from baseline to end of study in BAPAD-1, HFS-II and HCS will be conducted. Changes from baseline in PROs may be correlated with clinical measurements during the study.

12.4.4. Safety Analyses

All analyses will be conducted in the safety population. Adverse events will be recorded from the time of consent until completion of study. The number and percentage of participants with AEs will be displayed by body system and preferred term using Medical Dictionary for Regulatory

Activities (MedDRA) version 20.0 or higher, by study treatment. Summaries in terms of severity and relationship to Study Drug will also be provided. All SAEs will be summarized in a similar manner. Participant listings of all AEs causing discontinuation of study medication and SAEs will be produced.

All AEs will be listed for individual participants showing both verbatim and preferred terms. Separate summaries of treatment-emergent SAEs and TEAEs related to Study Drug will be generated.

AEs will be summarized separately during the CRC treatment visits. Any AE that occurs after administration of study drug at Visit 3 and prior to administration of the alternate study drug at Visit 4 will be treatment emergent with respect to the study drug received at Visit 3. Any AE that occurs after administration of study drug at Visit 4 and prior to the first administration of study drug in the out-patient phase will be treatment emergent for the study drug received at Visit 4. Any event reported on the eCRF that occurs at the time of or after the initiation of Study Drug in the out-patient phase is defined as treatment-emergent for that study drug. Additionally, an AE that was reported to have started on Day 1 without an associated onset time is assumed to have occurred after the initiation of Study Drug. Hence, AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

SAEs associated with a protocol specified procedure and occurring after the time of consent but before administration of first dose of Study Drug are defined as Non-Treatment Emergent AEs (NTEAE).

12.4.5. Baseline Descriptive Statistics

All subjects will be summarized at baseline using descriptive statistics overall and by treatment group, including demographics and laboratory measurements. Analyses will be presented by CRC setting and by Outpatient setting separately. Summary statistics (e.g., number of participants, mean, median, standard and range) will be generated for continuous variables (e.g., age and weight) and the number and percentage of participants within each category will be presented for categorical variables (e.g., gender, ethnicity, and race).

A detailed description of participant disposition will be provided. It will include:

- A summary of overall participant enrollment status (screened, screen failures, randomized)
- A summary of participants who discontinued the study (CRC, Outpatient)
- An account of identified protocol deviations

All participants who are consented for the study will be accounted for in the summation. The number of participants who do not qualify for certain analysis populations will be summarized.

12.4.6. Planned Interim Analyses

There are no planned interim analyses for this study.

12.4.7. Sub-Group Analyses

There are no planned and powered study sub-group analyses for the study. However, subgroups of interest may be defined in the Statistical Analysis Plan for exploratory purposes.

12.4.8. Tabulation of Individual participant Data

Disposition, demographic, efficacy, and safety data will be listed as specified in the SAP. All eCRFs will have a corresponding listing of raw data reported.

12.4.9. Exploratory Analyses

Exploratory analyses will be described in the SAP.

12.4.10. Missing Data

Every effort will be made to limit the number of missing data elements for the study. All study endpoints for the primary and secondary analyses will be reviewed for missing data and appropriate methodology applied if applicable, as described in the SAP. Sensitivity analyses may be performed.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Regulatory, Ethical, and Study Oversight Considerations

13.1.1. Informed Consent Process

13.1.1.1. Consent/Assent and Other Informational Documents Provided to Participants

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and the reviewing IRB. The informed consent is in accordance with the principles that originated in the Belmont Principles, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

13.1.1.2. Consent Procedures and Documentation

Before enrollment in the study, the Investigator or an authorized member of the clinical staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may refuse to participate or withdraw consent to participate at any time, without penalty or loss of benefits to which the subject was entitled. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her Principal Investigator to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language about the study used in the oral and written information, including the ICF, will be non-technical and practical and should be understandable to the subject (or the subject's legally acceptable representative). The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained consent, a copy of the ICF must be given to the subject.

If a subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to the subjects, is read and explained to the subject (or legally acceptable representative), and after the subject (or legally acceptable representative) has orally consented to the subject's participation in the study and, if capable of doing so, has personally dated and signed the ICF, the witness should personally date and sign the consent form. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject (or

legally acceptable representative), and that informed consent was freely given by the subject (or legally acceptable representative).

13.1.2. Confidentiality and Privacy

Refer to Informed Consent Form.

13.1.3. Safety Oversight

Provided by Xeris Pharmaceuticals Medical Monitor.

13.1.4. Clinical Monitoring

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

The Xeris designated representative (the monitor or auditor) will contact the Investigator and conduct regular visits to the clinical site. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/IEC review, with the stipulation that subject confidentiality will be maintained in accordance with regional, local, and federal regulations (including Health Insurance Portability and Accountability Act of 1996 [HIPAA] requirements). The monitor will also be responsible for confirming adherence to the study protocol, inspecting eCRFs and source documents, and ensuring the integrity of the data. Electronic CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

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

13.1.5. Quality Assurance and Quality Control

13.1.6. Data Handling and Record Keeping

13.1.6.1. Data Collection and Management Responsibilities

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

As defined in the ICH Guidelines for GCP (E6(R2)), Section 1.52, source documents may include: original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing

records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

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

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

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

In most cases, the source documents are the hospital's or physician's subject chart. In these cases, data collected on the eCRFs must match the data in those charts. In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at Xeris and clearly identify those data that will be recorded in the eCRF, and for which the eCRF will stand as the source document. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses to eCRF queries.

13.1.7. Protocol Deviations

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

14. REFERENCES

1. Chu L, Hamilton J, Riddell MC (2011) Clinical management of the physically active patient with type 1 diabetes. Physiol Sports Med 39: 64–77.

2. West DJ, Morton RD, Bain SC, Stephens JW, Bracken RM (2010) Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. J Sports Sci 28: 781–788.

3. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008 Nov;31(11):2108-9.

4. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL (2001) Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care 24: 625–630.

5. Campbell MD, Walker M, Trenell MI, Jakovljevic DG, Stevenson EJ, et al. (2013) Large Pre-and Postexercise Rapid-Acting Insulin Reductions Preserves Glycemia and Prevents Early-but Not Late-Onset Hypoglycemia in Patients With Type 1 Diabetes. Diabetes Care 36: 2217–2224.

6. Severe Hypoglycemia Predicts Mortality in Diabetes Philip E. Cryer Diabetes Care Sep 2012, 35 (9) 1814-1816; DOI: 10.2337/dc12-0749

7. Stenerson M, Cameron F, Payne SR, Payne SL, Ly TT, Wilson DM, Buckingham BA. The Impact of Accelerometer Use in Exercise-Associated Hypoglycemia Prevention in Type 1 Diabetes. J Diabetes Sci Technol. 2014 Sep 17. pii: 1932296814551045.[Epub ahead of print] PubMed PMID: 25231116.

8. Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzimer SA, Buckingham BA, Kollman C, Xing D, Ruedy KJ; Diabetes Research In Children Network Direcnet Study Group. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. J Pediatr. 2005 Oct;147(4):528-34.

9. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in- bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract. 2010 Mar-Apr;16(2):244-8.

10. Campbell MD, Walker M, Trenell MI, Luzio S, Dunseath G, Tuner D, Bracken RM, Bain SC, Russell M, Stevenson EJ, West DJ. Metabolic implications when employing heavy pre- and post-exercise rapid-acting insulin reductions to prevent hypoglycaemia in type 1 diabetes patients: a randomised clinical trial. PLoS One. 2014 May 23;9(5):e97143.

11. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. J Pediatr.2010 Nov;157(5):784-8 .e1. doi: 10.1016/j.jpeds.2010.06.004.

12. Riddell MC, Bar-Or O, Ayub BV, Calvert RE, Heigenhauser GJ. Glucose ingestion matched with total carbohydrate utilization attenuates hypoglycemia during exercise in adolescents with IDDM. Int J Sport Nutr. 1999 Mar;9(1):24-34.

13. Robertson K, Riddell MC, Guinhouya BC, Adolfsson P, Hanas R. Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2014 Sep;15 Suppl 20:203-23. doi: 10.1111/pedi.12176.

14. Camacho RC, Galassetti P, Davis SN, Wasserman DH. Glucoregulation during and after exercise in health and insulin-dependent diabetes. Exerc Sport Sci Rev. 2005 Jan;33(1):17-23.

15. Oskarsson PR, Lins PE, Wallberg Henriksson H, Adamson UC. Metabolic and hormonal responses to exercise in type 1 diabetic patients during continuous subcutaneous, as compared to continuous intraperitoneal, insulin infusion. Diabetes Metab. 1999 Dec;25(6):491-7.

16. Busselo JTM, Domingo AJ, Marra EM. Mini-dose of glucagon: Great efficacy avoiding admission of insulin-dependent-diabetic children with decreasing normoglycemia or hypoglycemie due to vomiting or gastroenteritis. Pediatr Res. 2010; 68:363-4.

17. Glycemic Targets: Standards of Medical Care in Diabetes—2018 American Diabetes Association Diabetes Care Jan 2018, 41 (Supplement 1) S55-S64; DOI: 10.2337/dc18- S006.

18. 2007 Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. UK Hypoglycaemia Study Group. Diabetologia 50:1140–1147

19. Ratzki-Leewing A, Harris SB, Mequanint S, *et al*. Real-world crude incidence of hypoglycemia in adults with diabetes: Results of the InHypo-DM Study, Canada. BMJ Open Diab Res Care 2018;6:e000503. doi:10.1136/bmjdrc-2017-000503.

20. CDC, National Diabetes Statistics Report, 2017

21. Dubé MC, Balois P, Prudhomme D, Weisnagel SJ, Lavoie C. Physical activity barriers in diabetes: Development and validation of a new scale. Diabetes Res and Clin Prac. 2006; 72 (1):20-7.

APPENDIX 1. EXERCISE

CRC EXERCISE

Subjects may proceed with exercise if BG is 100-180 mg/dL (5.56 – 10 mmol/L).

Exercise will consist of 45-minute session of moderate intensity aerobic activity (eg, treadmill jogging/brisk walking/cycling, elliptical). Breaks in exercise may be taken to perform study procedures. Each break will be 5 minutes or less with an aggregate break time of no more than 10 minutes.

The same type of aerobic activity will be performed for each exercise session and for the entire duration of each exercise session. The target is for exercise sessions to be initiated at approximately the same clock time during each CRC visit, with a window of ±1 hour.

The goal is to achieve a target of 80% of maximum calculated heart rate during the session as shown in the following equation:

Recommended exercise goal:

$$\text{Heart Rate} = 0.80 \times (220 - \text{Age in Years})$$

Stopping rule: As long as glucose remains >70 mg/dL, exercise may continue. If the subject's glucose falls to ≤ 70 mg/dL (3.89 mmol/L), the exercise session will be stopped, the subject should rest, and 16g (4 tabs, 4g/tab) of glucose tabs, or per standard of care, should be taken every 15 minutes until hypoglycemia is corrected and euglycemia is maintained.

OUTPATIENT EXERCISE

During the out-patient phase, subjects will be instructed to self-administer Study Medication when the following three conditions are met:

1. The subject plans to perform an aerobic to exercise session lasting at least 30 minutes and not more than 75 minutes in duration,
2. The subject plans to exercise continuously at moderate-to-high intensity to achieve a target heart rate of 80% of maximum calculated heart rate, during the session.
3. The subject has a confirmed blood glucose (BGM) of 100-180 mg/dL (5.56–10 mmol/L).

Subjects may perform exercise at any point in the day, but dose themselves for a maximum of one exercise session per day. The requested exercise frequency is an average of 2-3 sessions weekly. An instruction manual for self-administration of study drug will be provided to subjects.

Examples of aerobic exercise qualifying for dosing include powerwalking, hiking, running/jogging, cycling, swimming, cross country skiing, and aerobic fitness classes.

High intensity interval training (HIIT) such as sprinting, volleyball, basketball, hockey, CrossFit, weight lifting, etc. is not eligible for investigational product dosing.

APPENDIX 2. BAPAD 1 QUESTIONNAIRE

Indicate the likelihood that each of these items would keep you from practicing regular physical activity during the next 6 months?	**Score (1=extremely unlikely, to 7=extremely likely).**
1. The loss of control over your diabetes	1 2 3 4 5 6 7
2. The risk of hypoglycemia	1 2 3 4 5 6 7
3. The fear of being tired	1 2 3 4 5 6 7
4. The fear of hurting yourself	1 2 3 4 5 6 7
5. The fear of suffering a heart attack	1 2 3 4 5 6 7
6. A low fitness level	1 2 3 4 5 6 7
7. The fact that you have diabetes	1 2 3 4 5 6 7
8. The risk of hyperglycemia	1 2 3 4 5 6 7
9. Your actual physical health status excluding your diabetes	1 2 3 4 5 6 7
10. Weather conditions	1 2 3 4 5 6 7
11. The location of a gym	1 2 3 4 5 6 7
12. Your work schedule	1 2 3 4 5 6 7

Source: Dubé MC, Balois P, Prudhomme D, Weisnagel SJ, Lavoie C. Physical activity barriers in diabetes: Development and validation of a new scale. Diabetes Res and Clin Prac. 2006; 72 (1):20-7.

APPENDIX 3. HFS-II (ADULTS) QUESTIONNAIRE

I. Behavior: Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar and its consequences. Circle one of the numbers to the right that best describes what you have done during the last 6 months in your daily routine to AVOID low blood sugar and its consequences. (**Please do not skip any!**).

	Never	Rarely	Sometimes	Often	Almost Always
To avoid low blood sugar and how it affects me, I …					
1. Ate large snacks.	0	1	2	3	4
2. Tried to keep my blood sugar above 150.	0	1	2	3	4
3. Reduced my insulin when my blood sugar was low.	0	1	2	3	4
4. Measured my blood sugar six or more times a day.	0	1	2	3	4
5. Made sure I had someone with me when I go out.	0	1	2	3	4
6. Limited my out of town travel.	0	1	2	3	4
7. Limited my driving (car, truck or bicycle).	0	1	2	3	4
8. Avoided visiting friends.	0	1	2	3	4
9. Stayed at home more than I liked.	0	1	2	3	4
10. Limited my exercise/physical activity.	0	1	2	3	4
11. Made sure there were other people around.	0	1	2	3	4
12. Avoided sex.	0	1	2	3	4
13. Kept my blood sugar higher than usual in social situations.	0	1	2	3	4
14. Kept my blood sugar higher than usual when doing important tasks.	0	1	2	3	4
15. Had people check on me several times during the day or night.	0	1	2	3	4

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

	Never	Rarely	Sometimes	Often	Almost Always
Because my blood sugar could go low, I worried about …					
16. Not recognizing / realizing I was having low blood sugar.	0	1	2	3	4
17. Not having food, fruit, or juice available.	0	1	2	3	4
18. Passing out in public.	0	1	2	3	4
19. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
20. Having a hypoglycemic episode while alone.	0	1	2	3	4
21. Appearing stupid or drunk.	0	1	2	3	4
22. Losing control.	0	1	2	3	4
23. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
24. Having a hypoglycemic episode while driving.	0	1	2	3	4
25. Making a mistake or having an accident.	0	1	2	3	4
26. Getting a bad evaluation or being criticized.	0	1	2	3	4
27. Difficulty thinking clearly when responsible for others.	0	1	2	3	4
28. Feeling lightheaded or dizzy.	0	1	2	3	4

29. Accidently injuring myself or others.	0	1	2	3	4
30. Permanent injury or damage to my health or body.	0	1	2	3	4
31. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
32. Becoming hypoglycemic during sleep.	0	1	2	3	4
33. Getting emotionally upset and difficult to deal with.	0	1	2	3	4

APPENDIX 4. DRAIZE SCALE

- *Study Personnel Instructions:* The modified Draize Scale as shown in the table below will be used for physical examination/rating of abnormalities at the injection site.
- The injection site should be examined for formation of both erythema and edema and results recorded in the Case Report Form. Evaluations of the injection site should be performed at 10 ± 5 and 60 ± 5 minutes after the completion of the exercise session

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

Source: Guidance for Industry, Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 1999. Appendix A.

Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *Journal of Pharmacology and Experimental Therapeutics.* November 1944;82(3):377-390.

APPENDIX 5. HYPOGLYCEMIC CONFIDENCE SCALE

How confident are you that you can stay safe from serious problems with hypoglycemia:	Not Confident At All	A Little Confident	Moderately Confident	Very Confident
1. When you are exercising?				
2. When you are asleep?				
3. When you are driving?				
4. When you are in social situations?				
5. When you are alone?				

In general, how confident are you that you can:	Not Confident At All	A Little Confident	Moderately Confident	Very Confident
6. Avoid serious problems due to hypoglycemia?				
7. Catch and respond to hypoglycemia before your blood sugars get too low?				
8. Continue to do things you really want to do in your life, despite the risks of hypoglycemia?				

9. <u>If you have a spouse or partner</u>: What is your best guess about how confident your spouse or partner feels about your ability to avoid serious problems due to hypoglycemia?				

APPENDIX 6. INJECTION SITE DISCOMFORT DESCRIPTION AND DURATION QUESTIONNAIRE

Study Personnel Instructions: Question 1a should be completed by the subject after injection of study drug and when the exercise is completed. Any subject reporting discomfort other than "none," should complete Question 1b at the same time. All subjects should also answer Question 1c at the end of the visit (90 ±5 mins post-injection). The goal is for the subject to report the qualitative nature and duration of discomfort, if any, associated with injection of study drug, ignoring any transient pain associated with needle insertion.

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

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

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

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

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

_____Itching

_____Tingling, twitching or numbness

_____Irritation (e.g., burning, stinging)

Other or additional comments: _____

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

_____Less than 1 minute

_____1-2 minutes

_____3-5 minutes

_____6-9 minutes

_____at least 10 minutes

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

_____ Minute

Source: Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis*. 1978;37:378–381.

Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care & Research. November 2011;63(S11):S240-S252.

Document Approvals

Approved Date: 6/20/2019

Approval Task Verdict: Approve	Khaled Junaidi, (kjunaidi@xerispharma.com) Medical Affairs Approval 17-Jun-2019 16:43:49 GMT+0000

Approval Task Verdict: Approve	Marty Cummins, (mcummins@xerispharma.com) SME Approval 17-Jun-2019 21:07:43 GMT+0000

Approval Task Verdict: Approve	Nicole Close, (nclose@xerispharma.com) SME Approval 18-Jun-2019 13:40:07 GMT+0000

Approval Task Verdict: Approve	Aziz Alam, (aalam@xerispharma.com) Regulatory Approval 20-Jun-2019 04:46:42 GMT+0000

QA Approval Task Verdict: Approve	Ed Drower, (edrower@xerispharma.com) Quality Assurance Approval 20-Jun-2019 15:18:16 GMT+0000