T1D Exchange®

The Use of Mini-dose Glucagon to Prevent Exercise-induced Hypoglycemia in Type 1 Diabetes

PROTOCOL

Version 3.0
April 14, 2016

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

The study is being conducted by the T1D Exchange Clinic Network and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida.

1.1 Study Background and Rationale

Exercise is at the cornerstone of type 1 diabetes (T1D) management (1). However, blood glucose stability during exercise, and for up to 12-24 hours in recovery, remains a major challenge (2). A 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 sports and competition, games and training (1). 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% (1), 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 unadjusted (6).

Post-exercise nocturnal 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 (7). If insulin administration occurs to correct post-exercise meal-related hyperglycemia (often called rebound hyperglycemia), severe post-exercise hypoglycemia can occur which may even result in death (8). Patients can reduce the dose of rapid-acting insulin administered with the dinner meal after late day exercise to reduce nocturnal hypoglycemia risk (9) or lower basal insulin delivery for 6 hours at bedtime (10) to help mitigate risk, but these strategies often result in hyperglycemia (9, 10). Although extra carbohydrate ingestion not covered by insulin administration can help prevent hypoglycemia during and after exercise (11), excessive intake defeats the ability of the patient to have a negative caloric balance, thereby limiting the capacity for patients to maintain or lose 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 (12). This is a somewhat cumbersome and unpredictable task that is usually not performed correctly, even by the most educated and motivated patients. Since glucose production by the liver during moderate intensity exercise is primarily facilitated by a rise in the glucagon to insulin ratio (13) and patients with T1D have a reduction in this ratio during exercise because of a relative peripheral hyperinsulinemia (13) and impaired glucagon secretion (14), it may be better to attempt to change this ratio by the administration of glucagon at the onset of exercise. The recent development of a more stable form of soluble glucagon (e.g. G-Pen Mini™ glucagon 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. However, to date, studies have not been done that examine the efficacy of mini-dose glucagon administration for exercise.

1.2 Synopsis of Study Protocol

This project focuses on the development of a new strategy for the prevention of exercise-associated hypoglycemia using mini-dose glucagon.

1.2.1 Objectives

The primary objective of the protocol is to determine if the administration of mini-dose glucagon administered subcutaneously just before exercise produces better glucose stability than no adjustments for moderate intensity exercise in patients with T1D. It will also be assessed whether mini-dose glucagon before exercise produces better glucose stability than basal insulin reductions or extra carbohydrate consumption. In addition, the impact of mini-dose glucagon administration before exercise on nocturnal glycemia after exercise will be evaluated.

1.2.2 Study Design

This is a randomized, 4-way crossover trial.

1.2.3 Major eligibility criteria

- Clinical diagnosis of presumed autoimmune type 1 diabetes, receiving daily insulin
- Age 18-<65 years
- Duration of type 1 diabetes ≥2 years
- Random C-peptide < 0.6 ng/ml
- Using CSII (e.g., insulin pump) for at least 6 months
- Exercises regularly: i.e. ≥30 minutes moderate or more vigorous aerobic activity ≥3 times/week

See section 2.2 for a complete listing of inclusion and exclusion criteria.

1.2.4 Visit Schedule

1. Screening/Baseline Visit
    - Sign informed consent form and assessment of eligibility
    - Assessment of VO_2max for fitness evaluation and for the determination of exercise intensity for the experimental trials.

2. Randomized Crossover Trial

    Each participant will undergo four aerobic exercise sessions (in random order) in the CRC, with different strategies for glucose regulation:

    - Control Trial: Fasted exercise, no basal insulin reduction
    - Strategy 1: Fasted exercise, basal insulin reduction only (50% reduction in basal rate five minutes before exercise, for the duration of the exercise)
    - Strategy 2: Fasted exercise, no basal adjustment + pre-exercise glucose tabs (buccal route-40 grams in total)
    - Strategy 3: Fasted exercise, no basal adjustment + pre-exercise mini-dose glucagon (sc)

    In all 4 sessions, aerobic exercise will be performed in the fasted state (before a standardized meal) for 45 minutes at ~50-55% of the participant's pre-determined aerobic

capacity (see flow chart in section 1.4). The strategies for select sessions will be blinded as described in section 3.2.2.

1.2.5 Primary Outcome

The primary outcome for this study will be the glycemic response during exercise and early recovery.

1.2.6 Main Safety Outcomes

- Hypoglycemic events
- Hyperglycemic events
- Dizziness, pallor and other symptoms of poor perfusion and/or exercise intolerance

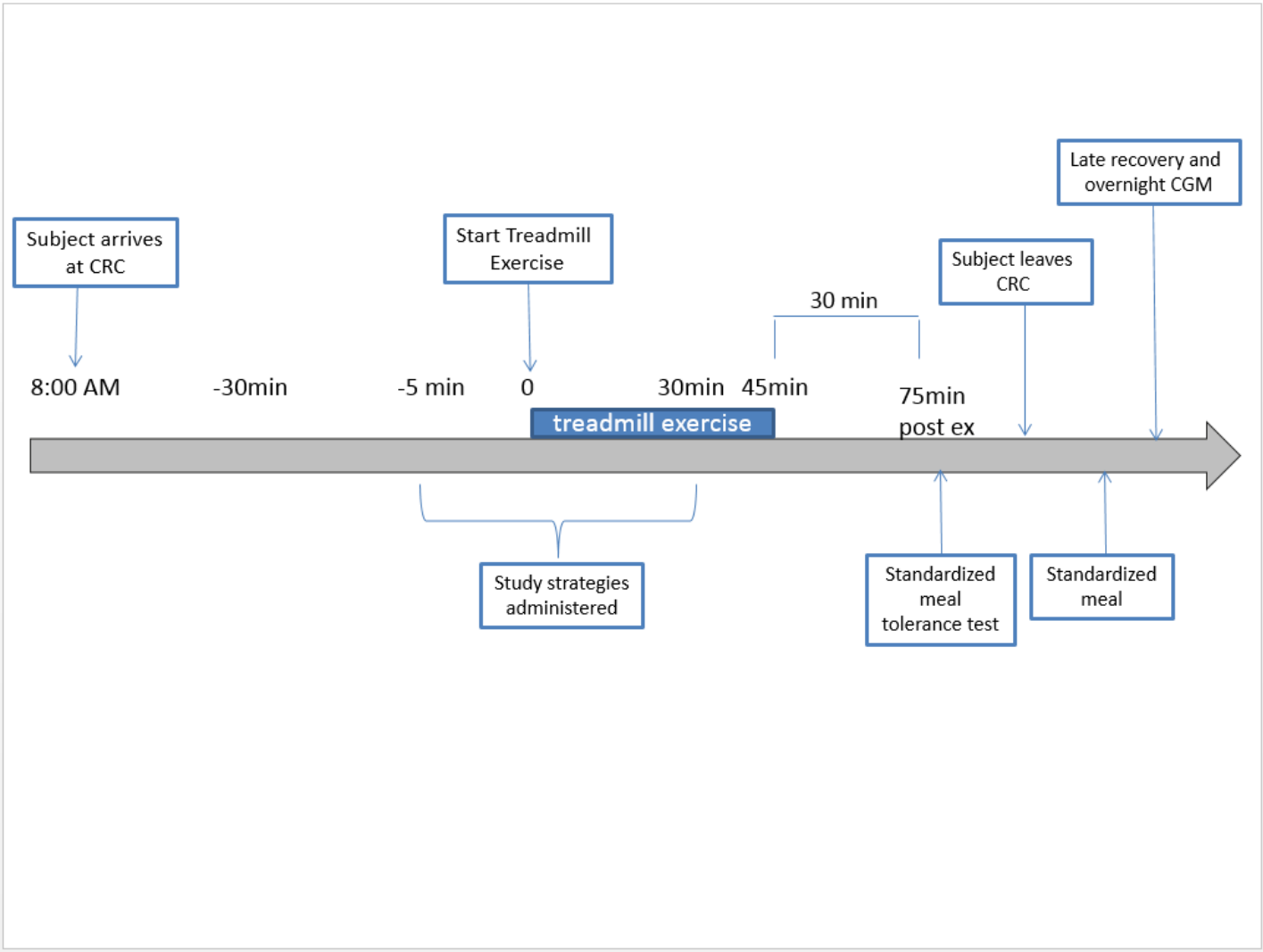
1.3 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

The mini-dose glucagon preparation (G-Pen Mini™) is not FDA approved. Therefore, an IND (#119733) has been received from the FDA by Xeris in order to conduct the study. The Daily Dose™ syringes used to inject the mini-dose glucagon are also not FDA approved in the U.S. While use of the syringes will be considered investigational, the study investigators believe they do not meet significant risk device criteria per 21 CFR 812.3(m) and thus an IDE from the FDA is not needed.

1.4 Flow Chart of Exercise Sessions



CHAPTER 2: PARTICIPANT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

The crossover trial will include 16 participants who complete the study. Participants may be replaced if a participant does not complete the entire protocol. Each site is expected to have 8 participants completing the crossover trial, but this could be increased at a given site if necessary to meet the recruitment goal.

2.2 Eligibility

To be eligible for the study, a participant must meet the following inclusion criteria and none of the exclusion criteria:

2.2.1 Inclusion Criteria

1) Clinical diagnosis of presumed autoimmune type 1 diabetes, receiving daily insulin
2) Age 18-<65 years
3) Duration of T1D ≥ 2 years
4) Random C-peptide < 0.6 ng/ml
5) Using CSII (e.g., insulin pump) for at least 6 months, with no plans to discontinue pump use during the study
6) Exercises regularly, i.e. ≥30 minutes moderate or more vigorous aerobic activity X ≥3 times/week
7) Body mass index (BMI) <30 kg/m^2
8) Females must meet one of the following criteria:
    a. Of childbearing potential and not currently pregnant or lactating, and agrees to use an accepted contraceptive regimen as described in the study procedure manual throughout the entire duration of the study; or
    b. Of non-childbearing potential, defined as a female who has had a hysterectomy or tubal ligation, is clinically considered infertile or is in a menopausal state (at least 1 year without menses)
9) In good general health with no conditions that could influence the outcome of the trial, and in the judgment of the investigator is a good candidate for the study based on review of available medical history, physical examination and clinical laboratory evaluations
10) Willing to adhere to the protocol requirements for the duration of the study
11) Must be enrolled in the T1D Exchange clinic registry or willing to join the registry

2.2.2 Exclusion Criteria

1) One or more severe hypoglycemic episodes in the past 12 months (as defined by an episode that required third party assistance for treatment)
2) Active diabetic retinopathy (PDR or VH in past 6 months) that could potentially be worsened by exercise protocol
3) Peripheral neuropathy with insensate feet
4) Cardiovascular autonomic neuropathy with inappropriate heart rate response to exercise (could be diagnosed with screening EKG: rule out tachycardia with fixed RR interval)
5) Use of non-insulin anti-diabetic medications
6) Use of beta-blockers

7) Use of agents that affect hepatic glucose production such as beta adrenergic agonists, xanthine derivatives
8) Use of Pramlintide
9) Currently following a very low calorie or other weight-loss diet
10) Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before screening for the current study or planning to participate in another such study during participation in the current study

2.3 Screening Visit and Patient Enrollment

Potential participants will have a screening visit to assess eligibility through the elicitation of a medical history and performance of a physical examination by a study investigator. Screening labs will be collected as outlined in section 2.3.1. A urine pregnancy test will be done for females with child-bearing potential. Clinical sites will keep a record of the reason why screened participants are not enrolled.

2.3.1 Laboratory Testing

The following laboratory testing results, typically obtained as part of routine care, will be assessed by the investigator as part of the general assessment for eligibility. Time periods prior to enrollment for which each test should have been performed are given in parenthesis.

- Basic Metabolic Panel (within 3 months)
- Complete Blood Count (within 3 months)
- Liver Function Panel (within 6 months)
- Random C-peptide (since diagnosis, subjects must be < 0.6 ng/ml)
- Lipids (within 6 months)
- Thyroid-Stimulating Hormone (within 12 months)
- HbA1c will be measured using point-of-care device or local lab if not available within the 3 months prior to enrollment.
- Urine pregnancy test if indicated (see inclusion criteria)

2.3.2 Historical Information and Physical Exam

A history will be elicited from the participant and extracted from available medical records with regard to the participant's diabetes history, current diabetes management, other past and current medical problems, past and current medications, drug allergies, and family history. A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or his or her designee (an endocrinologist, endocrine fellow, endocrine nurse practitioner or a physician assistant).

2.3.3 Informed Consent

The study will be discussed with potential participants. A copy of the consent form will be provided to the participant and another copy will be added to the participant's clinic chart.

Written informed consent will be obtained prior to performing any study-specific procedures that are not part of the participant's routine care.

2.3.3.1 Authorization Procedures

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

2.3.4 T1D Exchange Clinic Registry

If a participant is not already enrolled in the T1D Exchange clinic registry, he/she will become part of the registry when joining this study. Registry participants' information from their medical record may be entered into the registry database at least once a year and they will have an opportunity to provide their email address to be contacted in the future about other studies for which they may be eligible. Participants also may be asked to complete a questionnaire(s) either on a computer, paper, or via telephone. Participants may be given the option to have questionnaires emailed to them and may decide whether or not to complete a questionnaire each time they are asked.

CHAPTER 3: STUDY PROTOCOL

3.1 Procedures Prior to First Exercise Session

- Assessment of VO_2max following the Bruce protocol
- Optimization of basal insulin dose as per investigator's usual routine

3.2 Exercise Sessions

Each participant will be assigned to a sequence of control trial, strategy 1, strategy 2, and strategy 3 through a randomization process as outlined in section 3.2.2. Each exercise session will be separated by at least 3 days and participants will be expected to complete all sessions within 12 weeks from the time of the baseline/screening visit. Participants will be advised to avoid any vigorous exercise within 24 hours before or after the laboratory-based exercise tests. Subjects will be asked about activity to monitor adherence to these recommendations.

3.2.1 Prior to Exercise Sessions

The day before each exercise session participants will:

- Insert new insulin infusion set into abdomen or upper buttock (ensure not in exercising limb).
- For CGM users, insert a new CGM sensor
- For non-CGM users, come into clinic to have a CGM sensor inserted to use with a blinded receiver

The participant will be contacted by the research staff on the evening before and the morning of each exercise session to review glucose levels and help mitigate pre-exercise hyperglycemia or hypoglycemia.

- If at the time of the morning call, the glucose concentration is below target (<100 mg/dL), then supplemental fast-acting carbohydrate will be taken. If above target (>140 mg/dL), then a conservative correction bolus will be recommended (based on insulin sensitivity factor).

The participant will arrive at the CRC in a fasted state (minimum of 8 hour fast) by 9 a.m., but exercise sessions can begin as early as 8 a.m.

- Blood glucose concentration will be checked upon arrival to the clinic. Oral glucose or IV glucose may be given to bring participant into range before exercise.
- Females will have a urine pregnancy test performed prior to each exercise session (if applicable).

Before an exercise session can begin:

1. Participant glucose must be: 100- 140 mg/dL (venous, plasma)
2. Last insulin bolus (mealtime or correction) should be ≥3 hours previously

3.2.2 During Exercise Sessions

At each visit, participants will complete one of the following four exercise sessions (sequence of sessions determined by randomization):

Control Trial: No basal insulin adjustment, no carbohydrate intake until glucose drops <70 mg/dL. Then 20 grams of dextrose will be given orally.

Strategy 1: Basal insulin reduction to 50% five minutes before the start of exercise. Basal insulin rate will be returned to usual rate 45 minutes after the start of exercise.

Strategy 2: Dextrose tabs taken orally (20 grams) five minutes before the start of exercise and at 30 minutes of exercise (total 40 grams).

Strategy 3*: Glucagon (150 µg) five minutes before the start of exercise (SQ-abdomen).

*The dose for strategy 3 will likely be 150 µg, but may be modified to be lower or higher, with a possible range of 75-300 µg. One or more pilot phases of up to 6 participants will be conducted prior to study initiation to determine the most appropriate dose.

The participant's pump will be blinded during the control trial, strategy 1, and strategy 3 and an injection of saline will be given during the control trial and strategy 1 so that participant is blinded to strategy.

Exercise will consist of moderate intensity aerobic activity (treadmill jogging/brisk walking) performed at 50-55% of predetermined VO_2max for 45 minutes. Continuous heart rate measurements will be conducted along with intermittent ratings of perceived exertion (Borg 6-20 scale).

Exercise will be terminated if:

- Glucose is <70 mg/dL; participants will be treated for hypoglycemia (initially 20 grams of oral dextrose tabs or IV dextrose or IM glucagon depending on the severity of the hypoglycemia).
- Participants experience dizziness, pallor and other symptoms of poor perfusion and or exercise intolerance

Any treatment given will be recorded.

Participants who are not able to complete an exercise session due to termination will still complete remaining study procedures as outlined in sections 3.2.3 and 3.2.4.

3.2.3 Following Exercise Sessions

Following each exercise session, the participant will rest for 30 minutes and then consume a standardized meal containing 44-50 grams of carbohydrate that constitute ~55% of calories, together with ~20% calories from protein and ~25% calories from fat. The amount of bolus insulin given will be based on the carbohydrate content of the meal and the patient's own individualized insulin to carbohydrate ratio. Insulin will be administered five minutes before the standardized meal. In the first phase of the experiments, insulin "corrections" will not be given unless subjects have post exercise/ pre meal hyperglycemia ≥270 mg/dl. If hypoglycemia occurs prior to the meal, subjects will be treated with 20 grams of fast acting carbohydrate prior to meal consumption.

The participant will be monitored for at least 2 hours after the meal prior to discharge.

Participants will be given a meal log and another standardized meal to take with them at discharge. Participants will be instructed to eat the standardized meal for their next meal and log the time it was eaten. They will also be asked to log any meals they consume through noon the following day.

For participants using the blinded CGM, the sensor will be removed at 12PM the next day at home (~ 24 hours after the end of exercise). The participant will bring the device to the next visit or mail it back to the clinic.

Participants will receive a phone call the day after each exercise session to elicit any adverse events.

For CGM users, the CGM data will be downloaded at each visit and arrangements made to transmit the data following the last exercise session.

The participant's insulin pump will be downloaded at each visit and arrangements made to transmit the data following the last exercise session.

3.2.4 Sample collection

Blood samples collected through a venous catheter with plasma glucose measured by an YSI analyzer. Blood samples will be collected at:

- Baseline (at -30, -15, -5, 0 min)
- During exercise (at 5, 10, 15, 25, 35, 45 min)
- In recovery post exercise (at 50, 55, 60, 75 min)
- Regularly following a standardized mixed meal for 90 minutes (at 90, 105, 120, 135, and 165 min)

Plasma from the collected blood samples will be used to measure the following hormones, proinflammatory markers and metabolites at baseline, during exercise, in recovery post exercise, and regularly following the standardized mixed meal:

- Insulin
- Glucagon
- Cortisol
- Growth hormone
- Catecholamines (epinephrine and norepinephrine)
- Interleukin-6, tumor necrosis factor-α
- Nonesterified fatty acids
- β-hydroxybutyrate
- Lactate

CHAPTER 4: ADVERSE EVENT REPORTING AND SAFETY MONITORING

4.1 Adverse Event Reporting and Monitoring

4.1.1 Definition

A reportable adverse event is any untoward medical occurrence in a study participant, irrespective of whether or not the event is considered treatment-related, that occurs 12 hours prior, during, or the day after each exercise session, except for hypoglycemia, hyperglycemia, injection-related, and exercise-induced events which are only reported as adverse events when the criteria described below are met.

Hypoglycemic events are recorded as Adverse Events if the event required IV dextrose or IM glucagon to treat.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a health care provider or if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or in the absence of DKA if evaluation or treatment was obtained from a health care provider or an acute event involving hyperglycemia or ketosis.

Hyperglycemic events are classified as DKA if all of the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Serum ketones >1.5 mmol/L or large/moderate urine ketones
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15
- Treatment provided in a health care facility

Injection-related events are recorded as Adverse Events if sufficiently severe that treatment was given.

Exercise-induced events are recorded as Adverse Events if the subject falls during the exercise protocol or develops signs or symptoms of a myocardial infarction, poor perfusion (pallor, cyanosis), angina, pathologic arrhythmia, or another medical condition not expected to occur during or following the exercise.

4.1.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings.

All adverse events whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on a web-based case report form specifically for adverse event reporting.

The study investigator will assess the relationship of each adverse event to be related or unrelated to study drug by determining if there is a reasonable possibility that the adverse event may have been caused by the treatment. Reasonable possibility is not the same as "any possibility." The following should be considered when evaluating the relationship:

- Timing of event
- Patient's history

- Prevalence of finding in population at risk
- Other possible causes - diseases, exposures, therapies, etc
- Known pharmacology of study drug (and control) or side effect of drug

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

Each reported adverse event is reviewed by the Medical Monitor to verify the coding and the reporting that is required. Adverse events will be coded using the MedDRA dictionary.

4.1.3 Reporting Serious or Unexpected Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect
- Could have resulted in death, be life-threatening, or require hospitalization without medical or surgical intervention to prevent any of these events

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Medical Monitor responsible for reviewing serious or unexpected adverse events is:

Roy W. Beck, M.D., Ph.D.
Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Phone: (813) 975-8690
Fax: (888) 795-2859
Email: rbeck@jaeb.org

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related to the study drug or procedures, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event. The Coordinating Center also will notify Xeris of any such events, who will be responsible for fulfilling reporting requirements to the Food and Drug Administration (FDA).

Each principal investigator is responsible for informing his/her IRB of serious, related, and unexpected adverse events and abiding by any other reporting requirements specific to his/her IRB.

4.2 Risks

4.2.1 Potential Risks and Side Effects

Glucagon has a long history of medical use in the U.S., and is currently marketed by Eli Lilly & Co. as Glucagon for Injection [rDNA origin], and Novo Nordisk as GlucaGen® HypoKit®, both reference listed drugs for treatment of severe hypoglycemia. Glucagon has a rapid onset of action and an extremely short half-life, and its safety, efficacy and clinical pharmacology have been well established.

In a Phase 2 study, Protocol No. XSGP-201, healthy, fasted adult volunteers were administered rescue doses of Xeris G-Pen™ (glucagon injection) (0.5 mg and 1.0 mg) and Lilly Glucagon for Injection [rDNA origin] (1.0 mg) in a randomized, crossover fashion. Overall, all Xeris and Lilly treatments were well tolerated. There were no SAEs during the study, and all AEs observed were transient and generally expected with rescue injections of glucagon. The most commonly reported AE was injection site pain, and the incidence of this AE was significantly higher in the Xeris 0.5 mg and Xeris 1 mg groups compared with the Lilly 1 mg group; however, edema and erythema at the injection site occurred infrequently and did not vary significantly with treatment. Within the Lilly 1 mg group, the most commonly reported AE was nausea, the incidence of which was significantly higher compared with the Xeris 0.5 mg and 1 mg groups. The incidences of all remaining AEs were low and not notably different across treatment groups.

However, as reported by Haymond (15), when subcutaneous glucagon in dosages of 20–150 μg was given to children to manage impending hypoglycemia due to gastroenteritis or poor oral intake of carbohydrates, it did not result in a perceived worsening of the patient's nausea, nor did it result in emesis immediately after glucagon administration, as is commonly observed with the recommended single large 500–1,000 μg rescue dose.

In Xeris' completed Phase 2a safety/PK/PD study, Protocol No. XSMP-201, which tested 75–300 μg G-Pen Mini™ doses in adult T1D patients, neither nausea nor vomiting were observed with doses of 75-150 μg. Nausea, but not vomiting was reported by 4/12 subjects given the 300 μg dose (3 mild, 1 moderate). Since doses of subcutaneous G-Pen Mini™ (glucagon injection) given to adults per this protocol will range from 75–300 μg, some nausea is possible, but the incidence is expected to be relatively low and severe nausea is not expected.

Although available data from prior studies indicate that mini-dose glucagon is likely to successfully treat mild to moderate hypoglycemia, this is not definitively proven. Therefore, there is a risk that mini-dose glucagon will not work as well as glucose tablets or other oral carbohydrates and if this is the case, severe hypoglycemia could result.

Endurance exercise, as will be performed in this study, may be associated with generalized fatigue and mild to moderate hypoglycemia. In rare situations, exercise can promote myocardial infarction, sudden cardiac death or arrhythmias. In persons who have proliferative retinopathy, exercise that increases blood pressure significantly (>180 mmHg) can promote retinal bleeding (PMID: 21800941). Since all participants will be screened prior to the exercise test for diabetes-related complications and glucose monitoring will be performed throughout the experiments, the risk of a serious exercise-associated adverse event will be extremely remote.

The blood draws and IV placement could result in discomfort or bruising, or rarely, an infection or a blood clot. Fainting may also occur. The exact blood volumes collected may vary according to local IRB regulations. The maximum blood volume collected from adults >18 years will not exceed 250 ml at each visit.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Benefits

Participants may benefit by gaining a better understanding of how to prevent exercise-associated hypoglycemia.

5.2 Participant Compensation

5.2.1 Participant Reimbursement

The participant will receive $100 for the screening visit/VO_2 max testing and $225 for each exercise session. Participants will receive compensation for transportation to and from each exercise session. Participants who participate in the pilot phase will receive $100 for the screening visit/ VO_2 max testing and $100 for each exercise session that is part of the pilot. Participant compensation will be paid by check, merchandise gift card or money card.

Additional travel expenses may be paid in select cases for participants with higher expenses.

5.2.2 Study Costs

All study costs will be covered by the study. The participant will use his/her own pump, blood glucose meter, and CGM (if used). The participant will be asked to insert a new infusion set on the day prior to each exercise session and if CGM is used, a new CGM sensor. The participant will also be asked to perform additional blood glucose meter checks. Participants will be permitted to request reimbursement through their site for any CGM sensors, infusion sets, or blood glucose meter strips required specifically for the purpose of the study.

5.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The investigator may withdraw a participant who is not complying with the protocol. For participants who withdraw or are withdrawn, their data will be used up until the time of withdrawal.

Participants will not be withdrawn from the study if the study drug is discontinued due to adverse events.

5.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the Coordinating Center, the Jaeb Center for Health Research in Tampa, FL. Information also may be provided to Xeris, Inc which is providing the glucagon for the study, and Unitio, Inc., which is a T1D Exchange collaborating organization.

Some of the study data will be entered on the Coordinating Center's secure website through an SSL encrypted connection. The Coordinating Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with strong encryption. The study website is password-protected and restricted to users who have been authorized by the Coordinating Center to gain access. No identifiable health information of an enrolled participant will be released by the Coordinating Center.

5.5 Discontinuation of Study

Participation of a participant can be discontinued at any time at discretion of the investigator, particularly if the investigator believes that there is a safety concern with continued participation.

The study can be stopped by the Steering Committee if events occur that warrant discontinuation of the study.

CHAPTER 6: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

6.1 Sample Size

A target of 16 subjects, with replacement of any participants who do not complete the study, was selected as a reasonable sample size for this feasibility study. Considering the primary outcome of glucose, power was approximated using a t-test. The table below provides power estimates based on a paired t-test comparing glucose during the mini-dose glucagon treatment and glucose during the control treatment.

Power Estimates*

Mean difference (mg/dL)	Correlation						
	0.2	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**
20	32%	35%	40%	47%	55%	68%	84%
25	46%	51%	57%	65%	74%	85%	96%
30	60%	66%	73%	80%	88%	95%	99%
35	74%	79%	85%	91%	96%	99%	>99%

*Power was calculated for a sample size of 16 participants with a two-sided alpha of 0.05 and assuming a standard deviation of 40 mg/dL for each treatment. (A previous DirectNet exercise study was considered when estimating standard deviation [16].)

6.2 Analysis Plan

6.2.1 Primary Outcome

The primary outcome for this study will be glucose, as measured by YSI analysis, during exercise and early recovery.

6.2.2 Primary Analysis

The primary analysis for this study will be a descriptive comparison of glycemic response during exercise and early recovery between the mini-dose glucagon group (strategy 3) and the control group. Summary statistics will be calculated. In the event that exercise is terminated early due to glucose <70 mg/dL and the participant is treated for hypoglycemia, the nadir glucose value will be carried forward through early recovery.

To obtain a test of significance, a treatment comparison of glucose during exercise and early recovery will be completed using a linear mixed model with repeated measures that accounts for the correlation due to the cross-over design and the correlation due to multiple measures, adjusting for baseline glucose level and period. Regression diagnostics will be performed and if the distribution of residuals is skewed, non-parametric methods and transformations will be considered.

6.2.3 Secondary Outcomes

The following outcome measures will also be analyzed.

- Occurrence of hypoglycemia (<70 mg/dL) as measured by YSI analysis during exercise or early recovery

- Occurrence of hyperglycemia (≥270 mg/dL) as measured by YSI analysis in the following time periods: during exercise, after exercise in early recovery/prior to meal ingestion and for 90 minutes after the meal (2 hours after the end of exercise)
- Glucose levels during exercise and early recovery (venous plasma)
- Glucose levels after a standardized meal (glucose area under the curve analysis, venous plasma)
- Glucose levels in late recovery (afternoon and overnight following the exercise protocols- CGM analysis)
    - Mean
    - Nadir
    - Area above and below curve threshold (i.e. area above or below 70-180 mg/dL)
    - % of time in range (70-180 mg/dL)
    - % of time below 70 mg/dL
    - Occurrence of hypoglycemia (<70 mg/dL) overnight
- Carbohydrate intake (before, during and for 30 min post exercise)
- HR and ratings of perceived exertion
- Insulin and glucose counterregulatory hormones (glucagon, GH, catecholamines, cortisol)
- Inflammatory cytokines (TNFα, IL-6)
- Metabolites (nonesterified fatty acids, β-hydroxybuterate, lactate)

6.2.4 Secondary Analyses

The primary and secondary outcomes will largely be examined in a descriptive manner. Summary statistics will be calculated by treatment strategy. For binary variables, percentage of participants developing the outcome, with 95% confidence interval, will be calculated by strategy. Each of the three strategies will be compared to the control in secondary analyses.

Tests of significance will also be obtained using a 2-sided alpha of 0.05. For binary variables, a generalized linear mixed model with a logistic link function for a binary outcome will be fit to assess differences between strategy 3 and each of the other strategies. The model will be adjusted for baseline glucose and period. For continuous variables, repeated measures linear regression models will be fit adjusting for period and where applicable the baseline value. Regression diagnostics will be performed and if the distribution of residuals is skewed, non-parametric methods and transformations will be considered. No formal correction will be made for multiple comparisons.

6.3 Safety Analyses

Adverse events will be tabulated by strategy:

- Proportion reporting at least one adverse event
- Proportion with an adverse event thought by investigator to be related to strategy
- Proportion who stopped study treatment in response to an adverse event
- Total number of adverse events reported
- Number of serious adverse events reported
- Number of non-serious adverse events reported

Adverse events will be tabulated by MedDRA categories with frequencies compared between strategies. Similar models and diagnostics will be performed as described for the efficacy outcomes above.

CHAPTER 7: DATA COLLECTION AND MONITORING

7.1 Data Collection

Data will be collected directly on electronic case report forms and will be considered source documents when data are directly entered. Other data will be collected from participant logs, downloads of devices and from laboratories processing the samples.

7.2 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study. The RBM plan will focus mainly on data related to eligibility, adverse events and the primary efficacy analysis. As much as possible, remote monitoring will be performed in real-time, with on-site monitoring performed to evaluate the verity and completeness of the key site data.

Xeris, the Jaeb Center for Health Research, or their representatives may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

CHAPTER 8: 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) 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.

7) 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.

8) 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.

9) 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.

10) 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.

11) 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.

12) 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.

13) 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.

14) 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.

15) Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. Diabetes Care. 2001;24:643-5.

16) Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, et al; Diabetes Research In Children Network Direcnet Study Group. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care. 2006; 29:2200-4.