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Joslin Diabetes Center

Committee on Human Studies

Application for Review and Approval of Research and Training Projects Involving Human Research

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Project Title: Closed-Loop Glucagon Pump for Treatment of Post-Bariatric Hypoglycemia

Funding: NIH Fast-track R44 (1R44DK107114)

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1. PURPOSE OF PROTOCOL:

Obesity and related comorbidities, such as type 2 diabetes and cardiovascular disease, are increasingly recognized as major threats to individual and public health. Unfortunately, it is very difficult to achieve sustained weight loss with current medical approaches. Given these critical unmet needs, both clinicians and patients alike have embraced the results of recent controlled clinical trials demonstrating potent effects of bariatric surgical procedures to not only induce sustained weight loss but also to improve or normalize obesity-related comorbidities, including type 2 diabetes . Remarkably, surgery is superior to medical therapy for weight loss and diabetes, improves lifespan, and results in sustained improvement in glycemic control and reduced need for medications [1]. Such data have led to an explosion in the number of bariatric surgeries performed in the US – an estimated 179,000 in 2013 [2]. While benefits of bariatric surgery are achieved with low operative mortality [3], longer-term intestinal and nutritional complications can occur.

One particularly challenging and sometimes severe complication of bariatric surgery is hyperinsulinemic hypoglycemia [4, 5]. While most commonly associated with roux-en-Y gastric bypass, hypoglycemia has also been observed with sleeve gastrectomy [6]. Post-bariatric hypoglycemia (PBH) in this setting is defined as a documented plasma glucose level below 70 mg/dl in conjunction with symptoms and the relief of symptoms with the normalization of glucose levels. Hypoglycemia typically occurs within 1-3 hours after meals, particularly meals rich in simple carbohydrates, and is not present after prolonged fasting. Plasma insulin concentrations are inappropriately high at the time of hypoglycemia, indicating dysregulation of insulin secretion as an important mechanism [7]. Hypoglycemic symptoms may be autonomic (e.g., palpitations, lightheadedness, sweating) or neuroglycopenic (e.g., confusion,

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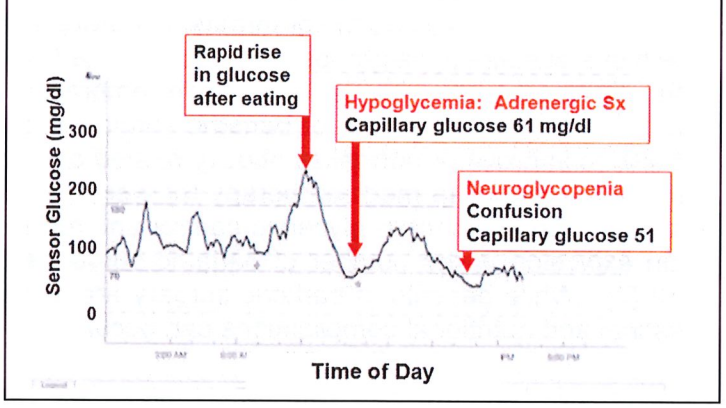
decreased attentiveness, seizure, loss of consciousness) in nature. Early in the post-operative period, hypoglycemia is usually mild, often associated with dumping syndrome, and effectively treated with low glycemic index diets. Mild, often unrecognized, hypoglycemia is increasingly recognized as a potential contributor to increased appetite and weight regain after surgery [8].

Metabolic studies in these patients reveal profound alterations in glycemic and hormonal patterns in the postprandial state occurring with gastric bypass anatomy and profound weight loss (recent review by Co-PI in [9]). A typical pattern in the ambulatory state, as revealed by continuous glucose monitoring (CGM), can be seen in **Figure 1**. Food intake and rapid emptying of the gastric pouch triggers a brisk and excessive rise in glucose (1st red arrow), with subsequent rapid decline in glucose precipitating adrenergic symptoms (2nd red arrow). Despite treatment with glucose tablets, the patient subsequently developed more severe hypoglycemia (51 mg/dl) with neuroglycopenic symptoms (3rd red arrow). While initial reports demonstrated pancreatic islet hypertrophy, pancreatic resection does not cure hypoglycemia [5, 10], and excessive islet number has not been observed in all series [4, 5, 11, 12]. One candidate mediator of increased insulin secretion in PBH is GLP-1, an incretin peptide released from intestinal L-cells in response to meals, in turn stimulating insulin secretion in a glucose-dependent manner. Indeed, postprandial levels of the incretin hormone GLP-1 are increased by >10-fold in post-bypass patients, are even higher in those with hypoglycemia, and correlate inversely with postprandial glucose levels [7, 13]. Furthermore, short-term pharmacologic blockade of the GLP-1 receptor markedly attenuates insulin secretion in post-bypass individuals, but increases GLP-1 levels in some studies [14, 15]. Interestingly, plasma levels of counterregulatory hormones such as cortisol and glucagon do not differ in patients with PBH vs. asymptomatic post-bypass patients [7]. Additional gastrointestinal factors which could modify systemic metabolism include dietary composition, gut microbiota [16], bile acid composition [17], and intestinal adaptive responses [18]; these may influence absorption of glucose and other nutrients, intestinally-derived hormonal responses, and the magnitude of CNS-gut-liver regulatory loops. Finally, genetic variation could also contribute to altered hormonal responses and sensitivity [19]. Thus, **while many interacting pathways contribute to PBH and may ultimately serve as targets for pharmacotherapy, an effective strategy to treat incipient hypoglycemia is urgently needed.**

A subset of post-bariatric patients develops very severe hypoglycemia with neuroglycopenia, with **loss of consciousness, seizures** and **motor vehicle accidents**, typically occurring 1-3 years following bypass. For these patients, a comprehensive multidisciplinary approach is required. Treatment of hypoglycemia, once it develops, requires rapid-acting carbohydrates, such as glucose tablets. Unfortunately, this treatment can contribute to rebound hyperglycemia, triggering further insulin secretion and recurrent hypoglycemia. Thus, initial prevention of hypoglycemia is essential. A cornerstone of therapy is dietary modification, aimed at reducing intake of high glycemic index carbohydrates [20]. Both diet and pre-meal acarbose [21] aim to minimize rapid postprandial surges in glucose which are triggers for glucose-dependent insulin secretion. Continuous glucose monitoring can be helpful to improve patient safety, particularly for those with hypoglycemic unawareness [22]. Additional therapies include octreotide (to reduce incretin and insulin secretion) [23], diazoxide (to reduce insulin secretion) [24], calcium channel blockade (to reduce insulin secretion) [25], gastric restriction or banding (to slow gastric emptying) [26], and providing nutrition solely through a gastrostomy tube placed into the bypassed duodenum [27]. Surprisingly, reversal of gastric bypass is not uniformly successful [5, 10], suggesting the importance of underlying genetics and/or compensatory mechanisms which persist after

Figure 1. CGM tracing in patient with PBH.



surgical reversal. Finally, while pancreatic resection was initially employed for patients with life-threatening hypoglycemia [4, 5], this procedure is not uniformly successful in remitting hypoglycemia and thus is not routinely considered at the present time.

Despite strict adherence to medical nutrition therapy and clinical use of multiple medical options above, usually in combination, patients continue to have frequent hypoglycemia. While hypoglycemia most commonly occurs in the postprandial state, it can also be observed in response to increased activity and emotional stress. Importantly, patient safety is additionally compromised when hypoglycemia unawareness develops with recurrent hypoglycemia. Patients are often disabled by hypoglycemia which occurs multiple times per day, leading to inability to drive or maintain employment, and causing fear of eating and exercise due to potential provocation of hypoglycemic events, cardiac arrhythmias [28], syncope, falls, and seizures. Thus, **there is an urgent need for improved approaches to the treatment of severe hypoglycemia to maintain health, allow optimal nutrition, and improve safety in PBH.**

Glucagon injection therapy is highly effective for treating severe hypoglycemia in patients with PBH. However, this approach is very expensive (average wholesale price of Lilly Glucagon emergency kit was $181 in 2013, Truven Health Analytics RedBook® Online) if used several times daily (as is needed for some patients), and once standard glucagon powder is reconstituted, it needs to be discarded after 24 hours. Furthermore, use of the standard dose of glucagon in emergency kits (0.5-1 mg) or with continuous infusion [29] can provoke rebound hyperglycemia, triggering further meal-dependent insulin secretion and initiating a roller coaster of recurrent hypoglycemia.

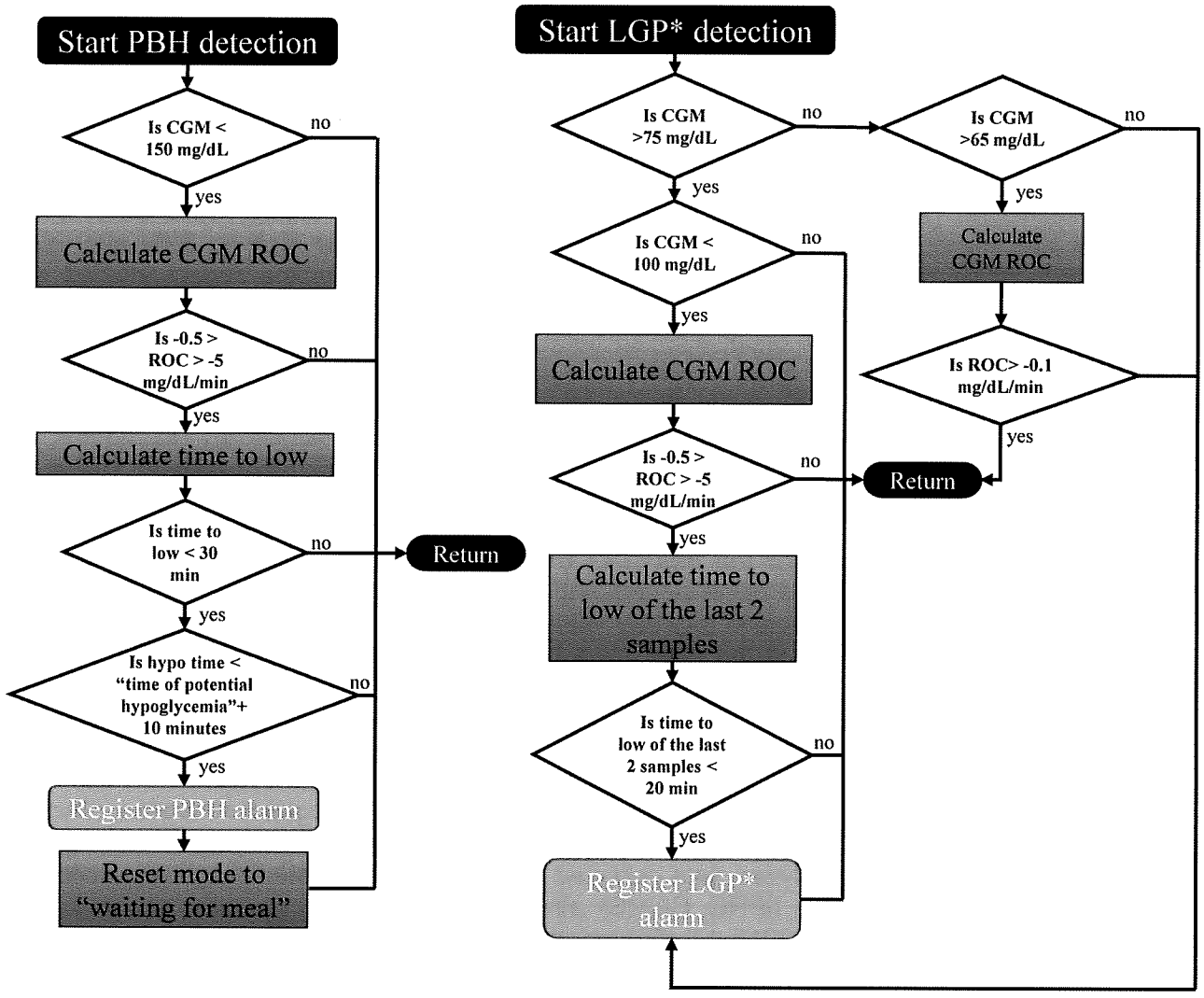
The prevalence of this disorder remains uncertain due to both incomplete analysis and recognition [30]. For example, a retrospective study of nationwide registries in Sweden demonstrated that gastric bypass was associated with a low overall rate (<1%), but a 2-7 fold increased risk of hypoglycemia and related confusion, syncope, and seizures[31]. Similar patterns were observed in other retrospective studies with patient self-report [20, 32]. Studies employing glucose tolerance testing have demonstrated prevalence of hypoglycemia as high as 72% [8] following bypass and as high as 33% after sleeve gastrectomy [6]. While provoked testing may not be physiologic, worrisome recent studies using continuous glucose monitoring demonstrate that unrecognized hypoglycemia is far more frequent. For example, glucose values <70 mg/dl occur 63 $\pm$ 23 minutes per day in post-bypass patients known to have hypoglycemia, and even 34 $\pm$ 22 minutes per day in completely asymptomatic post-bypass individuals [22]. A recent abstract demonstrated even more severe hypoglycemia, with glucose < 50 mg/dl for 21 minutes per 24 hours, with 36% of patients reporting concurrent symptoms [33]. Furthermore, Schauer and colleagues reported recently that 64% of post-bypass patients with a prior history of T2D had hypoglycemic episodes [1].

To meet the critical unmet needs for the treatment of patients with severe hypoglycemia following bariatric surgery, we aim to develop a novel closed-loop glucagon system (CLG) incorporating a novel, stable non-aqueous glucagon formulation together with an infusion pump system guided by real-time continuous glucose monitoring that is triggered by a hypoglycemia alert algorithm. This innovative approach will permit delivery of glucagon via a subcutaneous pump format and algorithm that can be personalized to the individual need and also allow use of more physiologic lower doses of glucagon, preventing "rebound" hyperglycemia and "roller-coaster" hypoglycemia.

In initial studies, we developed and optimized a system to use a stable glucagon formulation, physician-delivered with an infusion pump system, within an open-loop system guided by continuous glucose monitoring. As a first step, we analyzed data collected from clinically-indicated diagnostic continuous glucose monitoring system testing (iPRO CGMS) already obtained from patients enrolled in the Hypoglycemia Clinic at Joslin (CHS 2015-18). Extracted data, including continuous glucose monitoring sensor glucose values, age, gender, and body mass index, and food and activity logs, were used to develop computational algorithms to allow prediction of hypoglycemia. When data analysis and

modeling for development of the treatment algorithm were completed, patients were recruited for the first phase of an open label clinical study (CHS 2015-28). In this study, we tested our hypothesis that CGMS-derived recognition of hypoglycemia and rapid treatment with lower, more physiologic doses of glucagon using an open-loop pump system would be an effective strategy to reduce the frequency and severity of hypoglycemia in patients with PBH. As per protocol, we performed mixed meal tolerance testing in 5 individuals with PBH, monitoring both plasma glucose (YSI) and sensor glucose (Dexcom). In CHS 2015-28, we utilized an algorithm specifically developed by study team engineers (Harvard School of Engineering) after analysis and modeling of the postprandial glycemic time course in patients with PBH. **Figure 2A** illustrates the "post-bariatric hypoglycemia algorithm" which was developed to specifically predict hypoglycemia in the setting of the rapidly-changing glucose levels in the postprandial state in this patient population. This algorithm was used together with the "classic" algorithm" to predict hypoglycemia not associated with rapid prandial excursions (similar to that used for patients with type 1 diabetes)(**Figure 2B**). Sensor data successfully triggered alarms to the study physician, who then delivered a dose of glucagon via the pump (thus open loop).

Figure 2. Algorithms used to detect rapid changes in glucose and trigger alarms to study physician. A. PBH algorithm, combined with B. classic LGP* algorithm.



research unit. Prior to discharge, the plasma glucose (measured by YSI) must be between 80 and 200 mg/dL on the final two measurements, taken at least 30 minutes apart. If the plasma glucose is between 80 and 90 mg/dL then the CGM trend arrow must be either stable or increasing during the last 30 minutes of observation.

When the standard meal is consumed, the Omnipod® pump will be removed and the site will be assessed visually using the Draize scale. Prior to discharge, the sensors will be removed to permit analysis of timing of alerts and the site of the Omnipod insertion will be reassessed using the Draize scale.

Blood samples collected during this visit will be will be processed and stored at -80 for subsequent analysis of insulin, glucagon and incretin hormone levels to assess endogenous responses (vehicle delivery days) as well as post-bolus plasma levels (glucagon delivery days). The patient will be called by a study team member within 24 hours of the study visit to collect data for symptoms, glucose values, and any adverse events following study visit.

Between one to two weeks following visit day 3, patient will be scheduled for visit day 5.

Visit Day 4 (Optional): Two to three days prior to visit day 5, patient will have an ***optional*** visit day 4, during which two Dexcom sensors will be placed on the anterior abdominal wall. If the study team and patient are comfortable with sensor placement, sensor placement can occur at home instead, again 2-3 days before visit day 5. The time of sensor placement will be documented by a phone call by a member of the study team and the study physician will review the medication, food and activity recommendations in preparation for study visit 5.

Study Visit Day 5: Mixed Meal Testing: This visit will be identical to visit 3 with the exception that the patient will receive the other treatment (either vehicle or glucagon) during the mixed meal tolerance test when a hypoglycemic event is predicted by the controller algorithms. As with study visit day 3, the patient will be called by a study team member within 24 hours of the study visit to collect data to survey symptoms, glucose values and for any adverse events following study visit.

Part 2: ***Testing control system for sensor-guided delivery of glucagon via closed-loop system to prevent post-exercise hypoglycemia in patients with post-bariatric hypoglycemia***

During these visits we will test the efficacy of pump therapy containing Xeris glucagon in the prevention and management of post-exercise hypoglycemia in up to 20 patients with PBH. If patients studied in Part 1 are recruited for Part 2, there will be at least a two-month interval between completion of Part 1 and initiation of Part 2.

Visit Day 1: Screening: We will recruit adult male or female patients with PBH from the hypoglycemia clinic at Joslin (directed by Dr. Patti). Patients will undergo a history and physical examination, with particular emphasis on inclusion and exclusion criteria. Blood and urine samples will be obtained for screening laboratory testing including hemoglobin A1c, CBC, comprehensive chemistry, urinalysis, and pregnancy test (if applicable). An electrocardiogram will be obtained and reviewed during the visit by the study physician. Consent forms will be reviewed in detail with potential participants. Patient comfort, skill, and independence with sensor insertion will be determined at this visit and reassessed at subsequent visits.

Visit Day 2 (Optional): CGM Sensor Placement: Two continuous glucose monitor sensors (Dexcom) will be placed on the anterior abdominal wall two days prior to visit 3 (to ensure sensor availability and calibration for subsequent visit day 3) and will be blinded during the intervals between patient visits. Participants will be provided a glucometer and instructed in both sensor insertion and calibration techniques. This visit, with sensor placement, may occur concurrent with visit 1 if visit 3 can be scheduled within 2 days of visit 1/2. Alternatively, this visit can be substituted with a phone call if the patient has prior experience with sensor insertion and calibration and is comfortable with this approach. During the call, a study physician will discuss what medications, activities and food adjustments need to be made in anticipation of visit day 3 and will record timing of the sensor placements.

Visit Day 3: **Exercise Protocol:** The exercise protocol to be employed [35] will consist of cycling on a stationary bicycle ergometer in the clinical research center. Subjects will be counseled to avoid vigorous exercise for 24 hours before testing. Participants will arrive in the morning after an overnight (>12 hour) fast. Two intravenous lines will be inserted for blood sampling and to provide intravenous access. Two plasma glucose values greater than 75 mg/dL used to calibrate the sensors will be required to initiate the exercise study visit. Placement of the Dexcom sensors will be verified, and calibration will be performed using at least 2 venous blood glucose samples (YSI) obtained 15 minutes apart. A Garmin Foot Pod accelerometer will be applied. An EKG will be obtained and reviewed by a licensed provider prior to initiation of exercise. An OmniPod® containing glucagon will be inserted, with settings to deliver a dose of 300 µg of glucagon when an alarm is triggered by the controller algorithms which predict a glucose value <75 mg/dl.

Vital signs, including pulse, blood pressure, heart rate, and oxygen saturation will be assessed at baseline and every 2.5 minutes during exercise. Two baseline blood samples will be obtained for measurement of plasma glucose (YSI) immediately, and for subsequent hormonal assays. At time 0, low intensity cycling will be initiated; at time 5 minutes, intensity will be increased at 1 minute intervals until patient reaches target heart rate and will be continued until patient is exhausted, maximum heart rate is reached (220 – (age X 0.7)), or total duration of exercise of 15 minutes is achieved. After exercise is completed, the subject will be returned to the supine position, post-exercise labs will be drawn and glucose levels will be assessed every 10 minutes for up to 180 minutes. Additional labs including insulin, glucagon, and incretins will be drawn at 10, 30, 60, 90 and 120 minutes after exercise.

Exercise will be halted immediately if the participant develops chest pain or chest pressure, undue shortness of breath, hypotension, feelings of being unwell, signs of poor perfusion (e.g., lightheadedness, confusion, ataxia, pallor, cyanosis, nausea, cold and clammy skin, etc.), heart rate above the prespecified maximum heart rate of the subject (MHR), drop in systolic or diastolic blood pressure by more than 20 mm Hg as compared with baseline, or if the participant chooses to stop. In addition at any point during the study visit, if the participant develops severe nausea, abdominal pain or feels the need to stop, they will be able stop the procedure.

As in part 1, the closed-loop system will be set to use both the post-bariatric hypoglycemia algorithm and classic algorithm to predict hypoglycemia below a threshold of 75 mg/dl. Once a hypoglycemic event is predicted this will trigger a pump-delivered bolus of glucagon or vehicle, with the goal of preventing further decline in glucose values. If the sensor glucose value is ≤ 75 mg/dL then 6 units (equivalent volume to 300 µg of glucagon) of glucagon or vehicle will be delivered; if automated delivery of glucagon by the pump is not yet available at the time of these studies, manual dosing of the test compound will be performed by the study physician, as guided by the algorithm.

If the closed-loop system generates a second hypoglycemia alarm after a lockout period (15 minutes for sensor glucose ≤ 60 mg/dL and 30 minutes for >60 mg/dL), then the closed-loop system will deliver a second dose of study drug as noted in part 1.

Plasma glucose will be measured (YSI) at 5 minute intervals for 30 minutes and then every 15 minutes for two hours after treatment to ensure successful treatment. Glucagon and insulin levels will be analyzed concurrently at time of hypoglycemia prediction alarm as well as 30 minutes and 60 minutes following treatment bolus to determine the magnitude of increase above baseline. Lunch will be provided 120 minutes after glucagon treatment.

As in part 1, if the glucose level falls at or below 55 mg/dl (i.e. as a result of vehicle delivery on vehicle treatment days, inadequate trigger, or inadequate pump-delivered glucagon response), or if the patient develops neuroglycopenia or discomfort with signs and symptoms of hypoglycemia then the closed-loop system will be deactivated and the treatment protocol for clinically significant hypoglycemia will be initiated followed by administration of a standard lunch meal (as described in part 1).

Thirty minutes after glucagon treatment, the Omnipod® pump will be removed and the site will be assessed visually using the Draize scale. Following the standard lunch meal, venous blood glucose will

be monitored every 15 minutes for a minimum of 2 hours and then every 30 minutes until the time of discharge. The time of discharge will be set at 6 hours after the exercise is stopped to ensure stability prior to discharge from the clinical research unit. Prior to discharge, the plasma glucose (measured by YSI) must be between 80 and 200 mg/dL on the final two measurements, taken at least 30 minutes apart. If the plasma glucose is between 80 and 90 mg/dL then the CGM trend arrow must be either stable or increasing during the last 30 minutes of observation.

Prior to discharge, the sensors will be removed to permit analysis of timing of alerts and the site of the Omnipod insertion will be reassessed using the Draize scale. Accelerometry data will be used as an input for future integration and modification of the algorithm. Blood samples collected during this visit will be will be processed and stored at -80 for subsequent analysis of insulin, glucagon and incretin hormone levels in response to exercise and treatment. The patient will be called by a study team member within 24 hours of the study visit to collect data for symptoms, glucose values, and any adverse events following study visit.

Hardware Cleaning:

Equipment that touches intact skin will be cleaned prior to and after each use, using methods suggested by manufacturer, including Clorox Healthcare 35309 Germicidal Wipes.

Dexcom G4 Platinum Professional Transmitter Cleaning Procedure: The transmitter is the non-disposable piece inserted into the sensor which is attached to the subject. In brief, the investigator will sanitize his/her hands, and then put on gloves and goggles. The transmitter will be placed contact side down on an absorbent wipe. All surfaces of the transmitter will be wiped in two directions using a folded germicidal wipe (Clorox Healthcare®35309 Bleach Germicidal Wipes). A clean portion of the wipe will be used for second, third, and fourth wipes in both directions (total of 8 wipes for each area of the transmitter). The surface will be allowed to remain wet with the disinfectant for 3 minutes and dried on a nonporous surface. The transmitter will be placed into a beaker containing Clorox Healthcare Bleach Germicidal Cleaner Spray Solution for 1 minute and then rinsed under tap water for 10 seconds. The transmitter will be wiped with a low lint cloth until fully dry. Used wipes and gloves will be disposed, and hands will be washed. Equipment will be stored in a clean zipped bag.

Dexcom G4 Platinum Professional Receiver: This system requires the use of a receiver shield and its components to protect the receiver from contamination. Manufacturer's instructions will be followed, with the receiver shield removed after each patient use to help reduce the risk of contamination for health care team members or subsequent participants. The gloved investigator will wipe the receiver with the disinfectant wipes, allow it to dry, change gloves, and remove the shield components.

Omnipod Pump Receiver: The pump itself is a single-use equipment so will be discarded after each use. The receiver (PDM) will not be handled by the patient, but only by the investigator team members. The PDM will be thoroughly wiped on the surface by gloved personnel with the germicidal wipes after each use, and used wipes and gloves will be disposed.

The EPA registration number for the Clorox Healthcare 35309 Germicidal Wipes, 6 3/4 x 9, Unscented, 70/Canisteris is EPA 67619-12. This hospital-grade disinfectant is EPA-registered to kill a total of 51 microorganisms, including all ESKAPE pathogens (E. faecium, S. aureus, K. pneumonia, A. baumannii, P. aeruginosa, E. aerogenes) in 30 seconds, HIV in 30 seconds, hepatitis viruses and norovirus in one minute, and TB and C. difficile in three minutes.

3. INCLUSION / EXCLUSION CRITERIA

Screening: We will recruit adult male or female patients with PBH from the hypoglycemia clinic at Joslin (directed Dr. Patti). Patients will undergo a history and physical examination, with particular emphasis on inclusion and exclusion criteria. Blood and urine samples will be obtained for screening laboratory testing including hemoglobin A1c, CBC, comprehensive chemistry, and urinalysis. Consent forms will be reviewed in detail with potential participants.

Inclusion criteria:

1. Males or females diagnosed with ongoing post-bariatric hypoglycemia with prior episodes of neuroglycopenia, unresponsive to dietary intervention (low glycemic index, controlled carbohydrate portions) and trial of acarbose therapy at the maximally tolerated dose.
2. Age 18-65 years of age, inclusive, at screening.
3. Willingness to provide informed consent and follow all study procedures, including attending all scheduled visits.

Exclusion criteria:

1. Documented hypoglycemia occurring in the fasting state (> 12 hours fast);
2. Chronic kidney disease stage 4 or 5 (including end-stage renal disease);
3. Hepatic disease, including serum ALT or AST greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3.0 g/dL; or serum bilirubin > 2.0;
4. Congestive heart failure, NYHA class II, III or IV;
5. History of myocardial infarction, unstable angina or revascularization within the past 6 months or 2 or more risk factors for coronary artery disease including diabetes, uncontrolled hypertension, uncontrolled hyperlipidemia, and active tobacco use;
6. History of cardiac arrhythmia or arrhythmia detected by EKG during the screening visit;
7. History of syncope (unrelated to hypoglycemia) or diagnosed cardiac arrhythmia
8. Concurrent administration of β-blocker therapy;
9. History of a cerebrovascular accident;
10. Seizure disorder (other than with suspect or documented hypoglycemia);
11. Active treatment with any diabetes medications except for acarbose;
12. Active malignancy, except basal cell or squamous cell skin cancers;
13. Personal or family history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease);
14. Known insulinoma or glucagonoma;
15. Major surgical operation within 30 days prior to screening;
16. Hematocrit $\leq$ 33%;
17. Bleeding disorder, treatment with warfarin, or platelet count <50,000;
18. Blood donation (1 pint of whole blood) within the past 2 months;
19. Active alcohol abuse or substance abuse;
20. Current administration of oral or parenteral corticosteroids;
21. Pregnancy and/ or Lactation: For women of childbearing potential: there is a requirement for a negative urine pregnancy test and for agreement to use contraception during the study and for at least 1 month after participating in the study. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence;
22. Use of an investigational drug within 30 days prior to screening;

23. Current use of anticholinergic medications;

24. Allergy to a component of the study drug.

There will be no involvement of special vulnerable populations such as fetuses, neonates, pregnant women, children, prisoners, institutionalized or incarcerated individuals, or others who may be considered vulnerable populations.

4. DATA ANALYSIS / SUBJECT SELECTION

Subject Selection:

Approximately 40 subjects may be screened for this study, assuming approximately 30% will not meet inclusion criteria, and assuming 20% dropout rate. The goal is for 20 subjects to complete Part 1 and Part 2 studies. To allow for potential drop-outs, 28 subjects will be randomized.

Data Analysis:

All subjects who have received at least one dose of glucagon will be included in the data analysis set. Adverse events, vital signs, physical examination, laboratory safety variables (Screening to Final Visit), EKG (Screening to Final Visit), and local tolerability data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Sensor and glucagon or vehicle delivery information will be collected and evaluated for specificity and response time.

Plasma glucagon concentrations will be analyzed by a validated LCMS method in a GLP compliant lab (Celerion, Inc. Lincoln, NE). Insulin and incretin plasma concentration profiles with be analyzed with a commercially available radioimmunoassay method (RIA, Millipore) and analyzed using repeated-measures ANOVA.

The primary endpoint for this study is prevention of meal or exercise-provoked hypoglycemia, defined as glucose levels below <65 mg/dl, compared to vehicle control. Secondary outcome measures will compare outcomes for glucagon versus vehicle infusions for the following metrics including: (1) prevention of severe hypoglycemia (defined as glucose levels below 60 mg/dl); (2) prevention of rebound hyperglycemia (defined as glucose levels above 180 mg/dl); (3) time in goal range (65-180 mg/dl), reported in minutes.

Success will be defined as meeting the primary endpoint in 12 of 20 participants. If this is not achieved, the algorithm will be revised, and an additional 5 participants may be recruited for additional study.

Data will be analyzed after 10 individuals have completed the paired analysis of response to glucagon vs. vehicle. At that time, power will be determined, and sample size will be adjusted if needed.

Local Interim Data Analysis/Data Monitoring Plan

Data will be stored using a secure, web-based application designed to support data capture for research studies (such as RedCap), providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data are stored and are backed up on a scheduled basis with data encryption for any regulated data types (private health data (PHI) which require backup media in an encrypted format.

Data will be maintained in protected files at Joslin Diabetes Center. Only deidentified data will be transferred (via secure electronic file transfer) between collaborators.

Data Safety Monitoring Plan: This plan will be implemented and strictly followed, and a Safety Officer will be appointed to provide oversight and review. The PI will be responsible for ensuring that recruitment and phenotypic analyses are conducted in accordance with the IRB-approved protocol and

will review all adverse events and serious adverse events. The Joslin study nurse coordinator will also perform a periodic review of all data from phenotypic analyses. The members of the study team will conduct regularly scheduled meeting approximately weekly as well as on an as-needed basis to review status of the trial inclusive of enrollment, oversight of informed consent, general conduct of the trial as well as reporting of any complications as needed to the NIH and IRB. If permission is provided by the patient, the study team will provide a follow up letter to his or her primary care provider or endocrinologist, as needed, to alert them of their patients' participation in the trial and of any clinically significant findings regarding their respective patients. Patients will not be required to provide permission for the study team to contact their primary care provider, or endocrinologist as needed, in order to participate in the study. Patients will also have the option to elect to receive a letter containing clinically significant results from the study team after conclusion of the study.

5. POSSIBLE BENEFITS:

The purpose of this study is to evaluate a new approach for the treatment of post-bariatric hypoglycemia. This project is not designed to be of direct benefit to any individual subject, although it is hoped that through the knowledge gained from these studies there will be general benefit to persons with or at risk of development of PBH. Subjects enrolled in this study receive comprehensive medical evaluation. As such, risks are appropriate in relation to the potential significant benefits for the significant number of persons with or at risk for hypoglycemia after bariatric surgery. Thus, the potential benefits to society are likely to outweigh the risks to the individual subject.

6. POSSIBLE RISKS:

Risks regarding participation include risks associated with:

Glucagon: Administered in usual rescue dose of 1 mg intramuscularly, glucagon can cause nausea, vomiting, dizziness, and headache, as well as other less common complaints (listed in table below). The doses to be administered in the present study (300 µg) will be less than ½ the usual rescue dose (1 mg).

Likely (≥10 subjects out of 100)	**Less Likely** (3-9 subjects of	**Rare** (2 or fewer subjects out of 100)	
Dizziness	Asthenia	Abdominal pain	Pain
Headache	Palpitation	Back pain	Pharyngitis
Nausea	Sweating	Confusion	Pruritis/Rash
Vomiting	Thirst	Diarrhea	Syncope
	Vasodilation	Dyspepsia	Taste perversion

Nonaqueous glucagon is a formulation of glucagon which is stable at room temperature. Previous studies have demonstrated that adverse events were generally mild to moderate in nature and similar to known effects of glucagon. A prior study of mini-dose glucagon (Xeris protocol XSMP-201) used doses similar to those in the current study (0.075 mg, 0.15 mg, and 0.3 mg); the most frequent adverse event was burning sensation at the injection site (58-75% of patients). Mild-to-moderate nausea was observed at the highest dose only (33%), while numbness was observed at injection site in up to 17% of patients. In 2015-28, glucagon administration resulted in local stinging at the site, with no nausea or other side effects reported by patients.

Glucagon Infusion System: This system being tested with this protocol will consist of an Omnipod pump filled with nonaqueous glucagon. The pump will be programmed to receive sensor glucose values transmitted from the Dexcom continuous glucose monitor, and to trigger glucagon or vehicle delivery when prespecified thresholds are reached based on the algorithm. Risks associated with this

system include:

(1) sensor failure, leading to lack of detection of rapid drops in glucose or hypoglycemia;

(2) failure of communication between sensor and pump,

(3) failure of pump to deliver correct dose of glucagon,

(4) inadequate response to nonaqueous glucagon, resulting in lack of correction of hypoglycemia,

(5) delivery of excessive glucagon by pump, or excessive response to nonaqueous glucagon, could result in nausea or other side effects of glucagon, including hyperglycemia, potentially triggering subsequent hypoglycemia.

Risks of these complications will be mitigated by the presence of the study physician and nurse in the room, who will monitor patient for signs and symptoms of hypoglycemia, changes in vital signs, and real-time glucose levels, as determined by the in-room YSI glucometer. As noted above, if hypoglycemia develops despite pump delivery of glucagon or vehicle, standard approaches for treatment will be used, including glucose tablets and standard glucagon. In addition, participants will be monitored for 2 hours after glucagon delivery and lunch to ensure stability of glucose before discharge.

Risk of Device Reuse: The Dexcom G4 Platinum Professional continuous glucose monitor is approved for multiple patient use. The sensor (the component of the system that enters the skin) will be single use only. Additional components of the system include the transmitter, which is attached to the sensor but does not enter the skin, and the receiver, a hand-held device. Both the transmitter and receiver will be reused after cleaning using manufacturer-specified disinfection protocols using hospital disinfectant, as described above.

The Omnipod System is labeled for single-patient use. The system is comprised of the Omnipod disposable pump and a handheld Personal Diabetes Manager (not attached to the skin). The participant will not touch or interact with the PDM device. The PDM handheld device will be reused for multiple studies, after adhering to cleaning protocol as described above. All infusion set equipment will be single patient use only.

Glucometers will not be cleaned or reused by subjects. A new meter will be given to each new participant.

IV catheter, sensor, and pump placement may cause bleeding, infection, clot formation (all minimal risk), bruising, or discomfort.

Phlebotomy may cause blood loss and discomfort. For Part I, the total volume of blood sampling is up to a maximum of 450 ml. (These calculations are based on the maximum possible. The volume will be lower if the patient has hypoglycemia prior to 180 minutes after mixed meal, which typically occurs at 90 minutes; the estimated volume in this more typical scenario would be 269 ml.) This should not pose significant stress to any individual. Screening prior to Part 1 will verify that Hct is over 33 at study entry.

Part 1 and 2 will be separated in time by at least 2 months. Volunteers will be urged to be very consistent with multivitamin supplementation between Parts 1 and 2, which is a typical part of the post-bariatric medication needs long-term. Hemoglobin/hematocrit will be assessed during the screening visit for Part 2; as for Part 1, patients will not be eligible if they are anemic (Hct$\leq$33). For Part 2, the estimated maximum blood sample volume is 338 ml.

Volunteers will be requested not to donate blood within 2 months of the study. Any subject who has just donated blood will be asked to postpone entry into the study until 2 months have elapsed. Patients previously studied under CHS 2015-28 will not be studied again until at least 3 months have elapsed.

Meal tolerance testing may cause transient nausea or dumping syndrome in post-bariatric hypoglycemia patients. We have performed over 50 meal tolerance tests in this population without complication. Oral intake may also cause hypoglycemia in these patients. However, patients are

unlikely to experience severe low blood sugar because of frequent measurements and protocols in place to treat accordingly. The study physician will be physically present on site in the clinical research unit during testing in order to closely monitor participants and ensure safety.

Exercise Intervention: There is a remote possibility of adverse events including hypoglycemia, abnormal blood pressure, fainting, dizziness, arrhythmia, and in very rare instances, heart attack or stroke. There also exists the risk of bodily injury including injuries to muscles, ligaments, tendons, and joints. To minimize the risk of an adverse event, all participants will be pre-screened by the study physician prior to participation. Specific attention will be focused on history of known cardiac arrhythmias, cardiovascular, cerebrovascular disease or concurrent β-blocker therapy. Participants will be excluded if these conditions are present.

At least one study physician and one study nurse will be present during the exercise portion with careful monitoring of glucose, vital signs and symptoms. The minimum plasma glucose level prior to initiating the exercise should be greater than 75 mg/dl. Exercise will take place on a stationary bicycle which has a low impact on joints and low risk for falls or trauma. Patients will exercise until a threshold of the sensation of exhaustion, max heart rate of (=208 – (0.7 x age) bpm) or 15 minute duration is achieved. Exercise will be halted immediately if the participant develops chest pain or chest pressure, undue shortness of breath, hypotension, feelings of being unwell, signs of poor perfusion (e.g., lightheadedness, confusion, ataxia, pallor, cyanosis, nausea, cold and clammy skin, etc.), Heart rate above the prespecified maximum heart rate of the subject (MHR), drop in systolic or diastolic blood pressure by more than 20 mm Hg as compared with baseline, or if the participant chooses to stop. The study visit will also be halted if the participant develops unremitting nausea, abdominal pain, or wishes to discontinue the study for any reason. In case of an emergency, an emergency medical team will be available on-site at the Joslin Diabetes Center to stabilize the patient prior to transport to Beth Israel Deaconess Medical Center if needed.

Screening Tests and Procedures: It is possible that as a result of the screening process a subject may learn that they have a health disorder that they were unaware they had. Every effort will be made to help the participant obtain the care that they need.

Breach of Confidentiality: While every effort will be made to protect the confidentiality of participant identifiable information, there is the potential loss of confidentiality by participating in this study.

Inconvenience and Unknown Risks: Participants may be inconvenienced by the time commitment involved in participation in the study. There may be other risks from this study not yet identified.

Participants can choose not to participate in the clinical research project and can withdraw consent at any time.

Adequacy of Protection Against Risks

Recruitment and Informed Consent: Subjects will be recruited from the Joslin Hypoglycemia Clinic. The study will be explained to the potential subject initially in the clinical setting or during a subsequent telephone screening session. The informed consent process will be inclusive of various types of education and counseling opportunities including an in-person or telephone screening, allowing for general overview of the procedures as well as options available for all subjects expressing interest in participation.

Those still interested after in person or telephone screening will be scheduled for screening visit(s) at the clinical research center. The consent process will involve initial discussion of the purpose and scope of the research as well as risks and benefits. Ample opportunity will be provided for participants to read consent, share with family or other health care providers as well as have all questions answered by the Principal Investigator or their designated study staff prior to obtaining written informed consent using IRB approved documents. The consent form will include a description of risks and benefits, alternative possible procedures, the availability of the investigating physicians throughout any study to discuss any concerns, the availability of the IRB to the patient throughout any study to discuss any

concerns, and the fact that the patient can withdraw from the study at any time with no change in his/her standard treatment. There can be no changes in the protocol without the prior agreement of the Committee on Human Subjects.

If the patient consents to enroll in the study, and the consent form is signed, further evaluation in the form of the medical and screening visit will take place to determine eligibility. One copy of the consent form will be retained by the principal investigator and one copy will be provided to the subject.

Protections Against Risk: The procedures for minimizing risks are discussed above. Participants will be queried at each visit for potential side effects of testing. Appropriate intervention following standard medical practices will be used in the event of medical complications. The investigators are accountable to the institution's Committee on Human Subjects and must report annually the total experience as well as report immediately any complications.

Safety monitoring will include frequent blood glucose monitoring during study visits by study staff. A study physician will be physically present in the study room at all times to evaluate clinical status and glycemia. All labs will be reviewed by a designated member of the study team within 24 hours. Abnormal labs are communicated by alerts to the principal investigator directly from the laboratory and will be communicated to the participant and treating physician if clinically actionable. Adverse events will be reported to the IRB, FDA, and NIH, as appropriate, to ensure the safety of subjects.

Storage of private health information is solely in locked offices or on secure access protected computer sites and portable devices that may be used for patient data are encrypted to protect privacy. All study staff are trained in privacy protection and the ethical conduct of clinical research.

The study would be halted if the following serious adverse events occur: cardiac arrest, seizure, loss of consciousness, need for emergency transport, severe musculoskeletal injury, stroke, significant hemodynamic crisis including severe hypotension, hypertensive crisis, or any other serious adverse event.

7. CONSENT PROCEDURES:

Subjects will be recruited from the Joslin Hypoglycemia Clinic. The study will be explained to the potential subject initially in the clinical setting or during a subsequent telephone screening session. The informed consent process will be inclusive of various types of education and counseling opportunities including an in-person or telephone screening, allowing for general overview of the procedures as well as options available for all subjects expressing interest in participation.

Those still interested after in person or telephone screening will be scheduled for screening visit(s) at the clinical research center. The consent process will involve initial discussion of the purpose and scope of the research as well as risks and benefits. Ample opportunity will be provided for participants to read consent, share with family or other health care providers as well as have all questions answered by the Principal Investigator or their designated study staff prior to obtaining written informed consent using IRB approved documents. The consent form will include a description of risks and benefits, alternative possible procedures, the availability of the investigating physicians throughout any study to discuss any concerns, the availability of the IRB to the patient throughout any study to discuss any concerns, and the fact that the patient can withdraw from the study at any time with no change in his/her standard treatment. There can be no changes in the protocol without the prior agreement of the IRB.

If the patient consents to enroll in the study, and the consent form is signed, further evaluation in the form of the medical and screening visit will take place to determine eligibility. One copy of the consent form will be retained by the principal investigator and one copy will be provided to the subject.

8. RECRUITMENT / SOURCE OF SUBJECTS:

Patients with post-bypass hypoglycemia will be recruited for this study from the weekly Hypoglycemia

Clinic at Joslin Diabetes Center, directed by Dr. Patti. Post-bariatric hypoglycemia syndrome is the most common diagnosis within this clinic. More than 200 patients with this syndrome have been evaluated to date at Joslin, and over 50 patients have participated in research studies to date. Recruitment will be performed in the Hypoglycemia Clinic by the research fellow or nurse.

9. RIGHTS AND PRIVACY:

Storage of private health information is solely in locked offices or on secure access protected computer sites and portable devices that may be used for patient data are encrypted to protect privacy. All study staff are trained in privacy protection and the ethical conduct of clinical research. Records will be made available for inspection by the safety officer upon request.

Please answer the following questions:

- Will medical history/clinical information be obtained from the subjects' medical records for the purpose of this study? If yes, please list what information will be recorded.

  ■ **YES** o NO

  - o Age, gender, race
  - o Date of surgery
  - o Type of procedure
  - o Pre-surgical BMI
  - o Concomitant medical problems
  - o Active and historical medications
  - o History of hypoglycemia: first onset, symptoms, prior treatment approaches

- Will information resulting from this study (i.e. results of clinical/research lab tests, etc...) become part of the subjects' medical record or provided to the subject and/or others for clinical purposes? If, no, please list what information will not be given to the subject or recorded in their medical record and why.

  ■ **YES** o NO

- Will subjects' identifiable health information* be shared with others outside of Joslin Diabetes Center? If yes, list whom this information will be shared with (please be specific, include names of collaborators, study sponsor contacts)?

  o YES ■ **NO**

10. OMIT PROCEDURES / LEAVE STUDY:

We will inform patients that they may discontinue the study at any time without consequence. They will be informed that their decision will not affect how they are treated.

11. INCENTIVES / REMUNERATION:

Parking or taxi services will be paid for by voucher on the days of study visits. Other necessary travel expenses will be reimbursed to the participant at the discretion of the principal investigator. In addition

participants will receive a subject stipend of $75 for completion of study visit 3 and $250 for participation and completion of study visit 5.

If this study should result in the development of any marketable product, it is not the policy of the Joslin Diabetes Center to share any profits with participants in the research study.

*** Identifiable Health Information**

Data that includes any of the following identifiers are considered identifiable health information:

- Name
- Social Security number
- Medical Record Number
- Address by Street Location
- Address by Town/City/Zip Code
- Date of Birth
- Admission or Discharge Date
- Date of Death
- Telephone Number
- Fax Number
- Electronic E-Mail Address
- Web URLs
- Internet Protocol (IP) Address
- Health Plan Beneficiary Number
- Account Number
- Certificate/License Number
- Vehicle Identification Number and Serial Number, including License Plate Number
- Medical Device Identifiers and Serial Numbers
- Biometric Identifiers (finger and voice prints)
- Full Face Photographic Image
- Any Other Identifier likely to identify the subject

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Please answer the following questions:

12. Where and how will your project utilize the Joslin Diabetes Center?

- ■ **General Clinical Research Center (GCRC)**
  Primary site
- ❑ Clinical Trials Unit (CTU)
- ■ **Joslin Clinic**
- ❑ Eye Unit
- ❑ Other (please specify) _____

13. Will your project involve research on living human fetuses?

- ❑ Yes
- ▪ **No**

14. Does your project involve the use of any new drug or device?

- ■ **Yes** IND# 120653 (Xeris Pharmaceuticals) ; IDE # G170159
- ❑ No

15. Is review required by risk management foundation?

- ❑ Yes
- ■ **No**

_____ _____

Signature of Principal Investigator ***Date***

I have read and reviewed this application for approval by the Committee on Human Studies

_____ _____

Signature of PI's Section Head ***Date***

Please bring the original and twenty-four (24) copies of this form and the informed consent form for the above research project to Leigh Read in the Office of Sponsored Research by the appropriate CHS meeting deadline.

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JDC CHS

If the closed-loop system generates a second hypoglycemia alarm within the two hour observation period but after a lockout period (15 minutes if sensor glucose is ≤60 mg/dL or 30 minutes if sensor glucose >60 mg/dL), then the closed-loop system will deliver a second dose of study drug. The volume of the second dose of study drug will be either 6 or 3 units, equivalent to either 300 or 150 µg of glucagon) as per system algorithm delineated in **Table 1**, above.

- 6 units of study drug if sensor glucose is < 65 mg/dL
- 6 units of study drug if sensor glucose is ≥65 mg/dL but <75 mg/dL, and rate of change of sensor glucose is negative. If sensor glucose rate of change is positive within this range of glucose, no study drug is given.
- 3 units of study drug if sensor glucose is ≥75 mg/dL and <100 mg/dL.
- 3 units of study drug if sensor glucose is ≥100 mg/dL and ≤150 mg/dL and a meal is detected by the algorithm. If no meal is detected, no bolus will be delivered.

Plasma glucose will be monitored by YSI every 5 minutes for an additional 30 minutes, and insulin and glucagon levels will be analyzed concurrently. Lunch will be provided 120 minutes after the initial study drug treatment or 30 minutes after the second study drug treatment, whichever occurs later.

If at any time during the study visit the glucose level falls to or below 55 mg/dl (i.e. as a result of vehicle delivery on vehicle treatment days, inadequate trigger, or inadequate pump-delivered glucagon response), or if the patient develops neuroglycopenia, or if the participant develops severe discomfort with signs and symptoms of hypoglycemia, then the closed-loop pump will be deactivated and treatment for clinically significant hypoglycemia [34] will be initiated. If the participant's previously established IV line is functional, one ampule of D50 (25 grams in 50 mL, 50% glucose solution) will be administered over 2-5 minutes via the intravenous line. Glucose will be re-measured every 5 minutes and intravenous glucose will be given every 15 minutes until blood glucose is >54 mg/dL and neuroglycopenia is resolved, or more frequently at the discretion of the study physician. If clinically significant hypoglycemia develops and the previously established intravenous lines are non-functional then the study nurse or physician will administer 1.0 mg of commercial glucagon subcutaneously. The study nurse will also attempt to re-establish intravenous access, while glucose will continue to be measured every 5 minutes. Intravenous glucose may be used to resolve persistent neuroglycopenia or for glucose levels ≤ 54 mg/dL. If 2 doses of intravenous glucose are required, an infusion of 10% dextrose will be initiated at a rate of 100 mL/hour, and glucose levels will be monitored every 10 minutes and rate adjustments will be made according to glucose results. Once glucose levels are above 100 mg/dL, intravenous infusion will be tapered with continued monitoring as indicated clinically by the study physician.

If after treatment for clinically significant hypoglycemia the glucose remains <70 mg/dL but >54 mg/dL, neuroglycopenia is resolved, and if the patient is able to swallow, then the team will administer oral glucose 15-30 grams (glucose tablets or gel). If the patient is unable to tolerate oral intake (e.g. due to nausea), the team will administer ½ ampule of D50 (12.5 grams in 25 mL) over 2-5 minutes intravenously. Once hypoglycemia has resolved (glucose >70 mg/dL), neuroglycopenia has resolved, and patient is able to able to swallow, then the team will provide a standard lunch meal containing complex, low-GI carbohydrates, fat and protein to maintain euglycemia.

The study visit will also be halted if the participant develops unremitting nausea, abdominal pain, or wishes to discontinue the study for any reason.

If hypoglycemia does not ensue by 180 minutes (highly unlikely with this protocol), the subject will be provided a standard meal.

Following the standard lunch meal, venous blood glucose will be monitored every 15 minutes for a minimum of 2 hours and then every 30 minutes until the time of discharge. The time of discharge will be set at 6.5 hours after the mixed meal test to ensure stability prior to discharge from the clinical