

XSGO-PB01 Clinical Protocol
G-Pump™ (glucagon infusion)

Official Protocol Title: A Phase 2 Proof-of-Concept Study of Sensor-Guided, Clinician-Administered Delivery of G-Pump™ (Glucagon Infusion) From an OmniPod® to Prevent Post-Prandial Hypoglycemia in Post-Bariatric Surgery Patients

NCT02733588

Document Date: February 13, 2017

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A PHASE 2 PROOF-OF-CONCEPT STUDY OF SENSOR- GUIDED, CLINICIAN-ADMINISTERED DELIVERY OF G-PUMP™ (GLUCAGON INFUSION) FROM AN OMNIPOD® TO PREVENT POST-PRANDIAL HYPOGLYCEMIA IN POST-BARIATRIC SURGERY PATIENTS



Version 1.2
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A Phase 2 Proof-of-Concept Study of Sensor-Guided, Clinician-Administered Delivery of G-Pump™ (glucagon infusion) from an OmniPod® to Prevent Post-Prandial Hypoglycemia in Post-Bariatric Surgery Patients	
Principal Investigators:	Mary-Elizabeth Patti, MD
IND:	120653
Project phase:	Phase 2a
Compound(s):	G-Pump™ (glucagon infusion)
Objectives:	<p>The primary objective of this study is to test an optimized control system for sensor-guided delivery and test Proof-of-Concept (POC) in a clinical setting in patients with severe hypoglycemia following bariatric surgery. The primary endpoint for this study will be validation of the controller algorithm, defined as ability to detect and direct timing of the glucagon dose as programmed.</p> <p>The secondary objectives include the following:</p> <ul style="list-style-type: none"> • Prevention of severe hypoglycemia (defined as glucose levels below 60 mg/dl) • Prevention of rebound hyperglycemia (defined as glucose levels above 180 mg/dl) • Time in goal range (60-180 mg/dl), reported in minutes.
Study design:	<p>As a first step to developing new glucagon infusion delivery strategies for hypoglycemia, development of computer algorithms to predict timing and severity of hypoglycemia onset has been initiated, in collaboration with computational scientists at Harvard University School of Engineering. We have analyzed data collected from clinically-indicated diagnostic continuous glucose monitoring systems (iPRO CGMS) obtained from patients enrolled in the hypoglycemia clinic at the Joslin Diabetes Center. 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.</p> <p>This will be a Phase 2a, single-center, open-label, proof-of-concept study designed to test the ability of the control algorithm to detect and direct timing of G-Pump™ glucagon infused from an OmniPod® pump to prevent hypoglycemia in patients with post-bariatric hypoglycemia syndrome. While the algorithm will provide an alert as to when glucagon</p>

	should be dosed to prevent hypoglycemia, there will be <i>no automation</i> in this clinical trial and it will ultimately be up to the physician to initiate dosing via the OmniPod® controller.
Study location:	Joslin Diabetes Center, Boston, MA USA.
Study duration:	The total length of the study will be approximately one week per patient, and involve up to two infusions of G-Pump™ glucagon at a single visit. The total time for enrollment and treatment will be approximately 3 months.
Sample size:	For this proof-of-concept study, success will be defined as meeting the primary endpoint in 3 of 5 participants. If this is not achieved, the algorithm will be revised, and an additional 5 participants may be recruited for additional study.
Subjects:	Adult male or female patients with post-bariatric hypoglycemia syndrome
Inclusion Criteria:	<ol style="list-style-type: none"> 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:	<ol style="list-style-type: none"> 1. Documented hypoglycemia occurring in the fasting state (> 12 hours fast); 2. Chronic kidney disease stage 4 or 5; 3. Hepatic disease, including serum ALT or AST greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3.0 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; 6. History of a cerebrovascular accident; 7. Seizure disorder (other than with suspect or documented hypoglycemia); 8. Active treatment with any diabetes medications except for acarbose; 9. Active malignancy, except basal cell or squamous cell skin cancers; 10. Personal or family history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von

	<p>Hippel-Lindau disease);</p> <p>11. Known insulinoma;</p> <p>12. Major surgical operation within 30 days prior to screening;</p> <p>13. Hematocrit $\leq 33\%$;</p> <p>14. Bleeding disorder, treatment with warfarin, or platelet count $< 50,000$;</p> <p>15. Blood donation (1 pint of whole blood) within the past 2 months;</p> <p>16. Active alcohol abuse or substance abuse;</p> <p>17. Current administration of oral or parenteral corticosteroids;</p> <p>18. 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.</p> <p>19. Use of an investigational drug within 30 days prior to screening.</p> <p>20. There will be no involvement of special vulnerable populations such as pregnant women, prisoners, institutionalized or incarcerated individuals, or others who may be considered vulnerable populations.</p>
Brief outline of treatments:	<p>Methods:</p> <p>Visit Day 1 - Screening:</p> <ul style="list-style-type: none"> • Adult male or female patients with PBH will be recruited from the hypoglycemia clinic at Joslin. • 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). • Consent forms will be reviewed in detail with potential participants. <p>Visit Day 2 - CGM Sensor Placement:</p> <ul style="list-style-type: none"> • Two continuous glucose monitor sensors (Dexcom® G4 Platinum) will be placed on the anterior abdominal wall (to ensure sensor availability and calibration for visit day 3). Participants will be provided a glucometer and instructed in both sensor insertion and calibration techniques. • If patient has prior experience with sensor insertion and calibration

then this visit may occur concurrent with visit 1.

Visit Day 3 – Mixed Meal Testing (<= 3 days following Visit 2):

- Subjects will arrive in the morning after an overnight fast.
- An intravenous line will be inserted for blood sampling and to provide intravenous access. Placement of the Dexcom sensor will be verified, and calibration verified using at least 2 venous blood glucose samples obtained 15 minutes apart.
- An OmniPod® containing G-Pump™ glucagon will be inserted.
- Two blood samples will be obtained for measurement of plasma glucose (via YSI analytical device) immediately and for subsequent hormonal assays.
- The subject will then be asked to drink a liquid mixed meal containing 60 g of carbohydrates, e.g. Boost® Nutritional Drink, over 10 minutes.
- Blood samples will be collected for immediate (in room) glucose measurements (YSI) every 10 minutes, and hormonal profiles at 10, 20, 30, 60, 90, 120, 150, and 180 minutes. Once venous glucose levels fall below 90 mg/dl, glucose will be measured at 5 minute intervals (YSI). This blood sampling series will conclude once sensor glucose levels fall to <75 mg/dl. (See below for subsequent sample timing after clock is reset when glucagon is delivered.)
- The open-loop system will be set to recognize sensor glucose values <75 mg/dl, triggering an alert to the physician, who will deliver a bolus of 150 or 300 µg of glucagon via the pump, with the goal of preventing further decline in glucose values. Time will be reset to 0 at the time of glucagon delivery.
- Plasma glucose will be measured (YSI) at 5, 10, 20, 30, 45, 60, 90, and 120 minutes after glucagon administration to ensure successful treatment and glucose stability, and glucagon levels will be analyzed concurrently to determine magnitude of increase above baseline.
- If the open-loop algorithm issues a predictive alert or detects a sensor glucose level under 75 mg/dl within 30-120 minutes after the first dose of glucagon, a second dose of glucagon (either 150 micrograms if a predicted hypoglycemia alert, or 300 micrograms if sensor glucose is under 75 mg/dl) will be administered. If a second dose of glucagon is given, glucose levels will be monitored every 15 minutes for an additional 60 minutes.
- At time of alarm trigger and before each administration of glucagon, the Edinburgh Hypoglycemia Symptoms Score will be

	<p>assessed. This will be repeated at 15, 30 and 60 minutes following glucagon infusion.</p> <ul style="list-style-type: none"> • Thirty minutes after the last glucagon treatment, the OmniPod® pump will be removed, and lunch will be provided. • Venous blood glucose will be monitored every 15 minutes for at least 2 hours to ensure stability prior to discharge from the clinical research unit. Prior to discharge, the pump insertion site will be examined, and sensors will be removed. Patient will be given a snack on discharge. • Sensors will be downloaded for subsequent analysis of appropriateness of alert timing and trigger for glucagon bolus delivery. • Blood samples collected during this visit will be processed and stored at -80 until analysis for insulin and incretin hormone levels (to verify typical patterns in response to meal ingestion), for baseline levels of cortisol, and for glucagon, to assess endogenous responses as well as post-bolus plasma levels. <p>Follow-Up Phone Call (1 to 3 days following Visit 3)</p>
Biostatistical Considerations:	<p>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.</p> <p>Sensor and glucagon delivery request will be collected and evaluated for specificity and response time.</p> <p>Glucagon, insulin, and incretin plasma concentration profiles will be analyzed with commercially available analytical methods and examined using repeated-measures ANOVA.</p> <p>Success will be defined as meeting the primary endpoint in 3 of 5 participants. If this is not achieved, the algorithm will be revised, and an additional 5 participants may be recruited for additional study.</p>