

Title: **Bihormonal Bionic Pancreas for the Treatment of Diabetes Post-Pancreatectomy in Individuals with Congenital Hyperinsulinism – A Pilot Study**

Short Title Bionic Pancreas in HI - Pilot

Device Name: Bionic-Pancreas Glycemic-Control System

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ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|-------|---|
| AE | Adverse event |
| BG | Blood glucose |
| BP | Bihormonal bionic pancreas |
| CBC | Complete blood count |
| CGMS | Continuous glucose monitoring system |
| CHI | Congenital hyperinsulinism |
| CHOP | Children's Hospital of Philadelphia |
| CMP | Comprehensive metabolic panel |
| CRF | Case report form |
| DKA | Diabetic ketoacidosis |
| FDA | (United States) Food and Drug Administration |
| GUI | Graphical user interface |
| HbA1c | Glycosylated hemoglobin |
| HI | Hyperinsulinism |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| ICF | Informed consent form |
| IM | Intramuscular |
| IRB | Institutional review board |
| LAR | Legally-authorized representative |
| MGH | Massachusetts General Hospital |
| PG | Plasma glucose |
| PI | Principle investigator |
| SC | Subcutaneous |
| T1D | Type 1 diabetes |

ABSTRACT

Congenital hyperinsulinism (HI) is a disorder of β -cell dysregulation in the pancreas that results in severe hypoglycemia. Frequently, pancreatectomy is necessary to control hypoglycemia. After near-total pancreatectomy, diabetes is common with 91% of the individuals requiring insulin before puberty. Current treatment involving insulin administration offers inadequate blood glucose (BG) control in these individuals. We propose a novel approach to better treat these individuals through use of a bihormonal “bionic pancreas” to replace both hormones, insulin and glucagon, through an automated glycemic management system.

In collaboration with the Bionic Pancreas Project, we propose a pilot study to evaluate the efficacy and safety of the bionic pancreas in individuals with HI and post-pancreatectomy diabetes. Potential subjects will be recruited from The CHOP Congenital Hyperinsulinism Center. Eligibility entails six to 30 years in age, an HI diagnosis, and post-pancreatectomy diabetes managed by subcutaneous insulin pump. Subjects will be studied during two research inpatient admissions at the CHOP HI Center. During one admission - standard care - subjects will continue their home insulin regimen via their insulin pump; during the other admission – bihormonal bionic pancreas admission - subjects will receive insulin and glucagon via the bihormonal bionic pancreas. Glycemic control will be evaluated through a continuous glucose monitoring system. Mean glucose and episodes of hypoglycemia will be compared during the two admissions. Data generated from this pilot study will be used to plan a larger study.

PROTOCOL SYNOPSIS

| | |
|------------------------------------|---|
| Study Title | Bihormonal Bionic Pancreas for the Treatment of Diabetes Post-Pancreatectomy in Individuals with Congenital Hyperinsulinism – A Pilot Study |
| Funder | Zealand Pharma A/S |
| Sponsor (IDE holder)/Funder | Edward Damiano, PhD (Dept of Biomedical Engineering, Boston University) |
| Clinical Phase | Pilot Study |
| Study Rationale | <p>The management of diabetes following pancreatectomy for HI generally consists of the same approaches that are used for individuals with type 1 diabetes (T1D). However, there are significant differences in individuals with HI and post-pancreatectomy diabetes that increases the risk of hypoglycemia in these individuals and prevent achieving tight glycemic control. Individuals with HI have glucagon deficiency and unlike T1D, individuals with HI and post-pancreatectomy diabetes have residual dysregulated insulin secretion that results in marked hypo- and hyper-glycemia. Furthermore, pancreatic insufficiency can result in disturbances in nutrient absorption and fluctuations in glucose concentrations.</p> <p>Current treatment approaches with intermittent subcutaneous insulin administration or insulin pump therapy offer inadequate glycemic control in these individuals. We propose a novel approach to the management of these individuals with the bihormonal bionic pancreas to replace both hormones, insulin and glucagon, through an automated glycemic management system.</p> |
| Study Objective(s) | <p>Primary</p> <ul style="list-style-type: none"> To determine if the bihormonal bionic pancreas improves glycemic control in individuals with HI who develop diabetes post-pancreatectomy. <p>Secondary</p> <ul style="list-style-type: none"> To evaluate the safety of the bihormonal bionic pancreas in individuals with HI who develop diabetes post-pancreatectomy. |
| Test Article(s) | The Bionic-Pancreas Glycemic-Control System has been shown to improve glycemic control and to reduce the frequency of hypoglycemia in children and adults with T1D. Insulin and glucagon are administered by a fully automated, bihormonal, bionic pancreas with the use of control algorithms that adapt to changes in insulin/glucagon requirements. The device consists of an iPhone®, which runs the control algorithm, and a Dexcom® continuous glucose monitor system (CGMS) connected by a custom software |

| | |
|---------------------------|---|
| | interface. Insulin and glucagon are administered subcutaneously by a Tandem® t:slim™ infusion pump, which are controlled wirelessly by the iPhone®. In adults and children with T1D, the combination of insulin and glucagon has been shown to improve glycemic control and reduce the occurrence of hypoglycemia. |
| Study Design | This will be an open-label, pilot clinical trial to assess efficacy and safety of the bihormonal bionic pancreas in children and adults with HI who have developed post-pancreatectomy diabetes. Subjects will be studied during two research inpatient admissions at the CHOP HI Center. The order of the interventions will be randomized. |
| Subject Population | <p>Abbreviated Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Individuals 6 years to 30 years of age. 2. Diagnosis of hyperinsulinism. 3. Previous pancreatectomy. 4. Diagnosis of diabetes. 5. Treatment with subcutaneous insulin by pump at the time of recruitment. <p>Abbreviated Exclusion Criteria</p> <ol style="list-style-type: none"> 1. Evidence of a medical condition that might alter results or compromise the interpretation of results, including active infection, kidney failure, severe liver dysfunction, severe respiratory or cardiac failure. 2. Evidence of severe hematologic abnormality including severe anemia and/or thrombocytopenia. |
| Number of Subjects | 12 subjects enrolled to produce 10 evaluable subjects |
| Study Duration | Each subject's participation will last approximately 8 days (screening visit and two, 4-day inpatient admissions). The entire study is expected to last one year. |
| Study Phases | <ul style="list-style-type: none"> • Screening: medical records will be reviewed to determine eligibility. Medical history, physical examination, CBC, CMP, and HbA1c will be obtained during this visit after informed consent. • The order of admissions will be determined using a randomized, cross-over design and will occur at least 1 week apart. • Standard Care Admission: A 4-day inpatient admission in which subjects will continue their home insulin regimen. The first day will be a run-in period. The last 3 days involve collection of plasma glucose data for analysis (CGMS and fingerstick). • Bihormonal Bionic Pancreas Admission: A 4-day inpatient admission in which subjects will wear the bihormonal pancreas. |

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| | <p>The bihormonal pancreas will be placed upon admission and there will be 1 day of run-in followed by 3 days of data collection for comparison with the data obtained from the standard of care during the control admission. Following this, the patient will transition back to their home regimen and discharged home.</p> |
| Efficacy Evaluations | <p>The co-primary efficacy evaluations are (1) mean glucose concentration as measured by the CGMS during the last 3 days of the Standard Care Admission and the last three days of the Bihormonal Bionic Pancreas Admission, and (2) the mean proportion of time that the CGMS-measured glucose concentration was less than 60 mg/dL during the same periods.</p> <p>Secondary efficacy evaluations include the proportion of time that CGMS-measured glucose concentrations are in clinically relevant ranges (< 70 mg/dL, 70-180 mg/dL, >180 mg/dL), the mean glucose concentration measured by fingerstick, the proportion of glucose concentrations measured by scheduled fingersticks that were below 60 mg/dL, and the number of interventions required for hypoglycemia per day.</p> |
| Safety Evaluations | <p>Safety variables will be assessed by comparison of frequency of serious adverse events (SAEs) during the two study periods.</p> |
| Statistical and Analytic Plan | <p>This is a pilot study to generate data to assess feasibility of study design/procedures and for formal sample size estimation for a larger study of the efficacy of the bihormonal bionic pancreas in children and adults with hyperinsulinism and post-pancreatectomy diabetes. The sample size for this pilot study may be too small to detect statistical significance, however, we offer the following plan for analysis of the outcomes for this study.</p> <p>Descriptive statistics will be used to characterize demographic, baseline, and outcome measures in subjects. Mean CGMS-measured glucose concentration (calculated as the mean of all CGMS-measured concentrations [measured every 5 min] over the study period) and the mean proportion of time when the CGMS-measured glucose concentration was < 60 mg/dL during the last 3 days on the bionic pancreas will be compared to the same outcomes during the standard care period by paired-sample Student's t-test (or Wilcoxon signed rank test if data is not normally distributed) to determine if the intervention conferred an improvement in glycemic control. Secondary outcomes will be analyzed with univariate analysis.</p> |
| Data and Safety Monitoring Plan | <p>The Principle Investigator (PI) will be ultimately responsible for data quality management and ongoing assessment of safety. Safety variables will be assessed by comparison of frequency of serious adverse events (SAEs) during the two study periods.</p> |

Table 1: Schedule of Study Procedures

| Study Phase ^A | Screening | Standard Care Admission | | | | Bihormonal Bionic Pancreas Admission | | | |
|---|-----------|-------------------------|----------------|----------------|-----|--------------------------------------|----------------|----------------|-----|
| | | S.1 | C.0 | C.1 | C.2 | C.3 | E.0 | E.1 | E.2 |
| Visit ID | X | | | | | | | | |
| Informed consent/assent | X | | | | | | | | |
| Review inclusion/exclusion criteria | X | | | | | | | | |
| Demographic/medical history | X | | | | | | | | |
| Physical examination | X | | | | X | | | | X |
| Vital Signs: Ht, Wt, Temp, BP, HR, RR | X | X | X ^D | X ^D | X | X | X ^D | X ^D | X |
| Pregnancy test ^B | X | | | | | | | | |
| Safety laboratory tests | X | | | | | | | | |
| Insulin administered per home regimen | | X | | | | | | | |
| Insulin/Glucagon administration via bionic pancreas | | | | | | | X | | |
| Standardized diabetic meals | | | | | | X | | | |
| BG check by fingerstick ^C | | | | | | X | | | |
| BG monitoring by CGMS | | | | | | X | | | |
| BG telemetric monitoring | | | | | | X | | | |
| Prior/Concomitant Medications | | | | | | X | | | |
| Adverse Event Assessment | | | | | | X | | | |

^A Order of admissions will be determined using a randomized, crossover design.

^B Pregnancy test will be completed for females 11 years of age or older.

^C BG will be checked by fingerstick before each meal, at bedtime, and at least once overnight; episodes of hypoglycaemia will be treated as per standard clinical practice with 15 grams of simple carbohydrates and/or glucagon, if necessary.

^D Vital signs will be measured twice daily on these days. Height will only be measured on Study ID Days S.1, C.0, and E.0. Weight will be measured on Study ID days S.1, C.0, E.0, and at discharge from each admission.

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Congenital hyperinsulinism is a rare genetic disorder of pancreatic β -cell function characterized by dysregulated insulin secretion resulting in severe hypoglycemia that can cause brain damage or death if inadequately controlled. The estimated incidence of HI in the United States is 1 per 50,000 live births¹. While HI can be managed with medication or a focal resection of affected pancreatic tissue in some patients, the most severe cases require a near-total pancreatectomy to control hypoglycemia.

After near-total pancreatectomy, the frequency of diabetes increases over time with 91% of children diagnosed with diabetes before puberty². There are significant differences between individuals with typical T1D and individuals with HI and post-pancreatectomy diabetes that require special emphasis. The slow evolution of diabetes post-pancreatectomy is characterized by marked hypo- and hyper-glycemia, resulting from dysregulated insulin secretion from the remaining pancreatic tissue and from glucagon deficiency. Furthermore, exocrine pancreatic dysfunction can affect absorption and result in unpredictable fluctuations in blood glucose concentrations. Current treatment approaches with intermittent subcutaneous insulin administration or insulin pump therapy offer inadequate glycemic control in these individuals.

1.2 Name and Description of Investigational Product or Intervention

Bihormonal Bionic Pancreas (BP) System: Our collaborators from Boston University and Massachusetts General Hospital have developed an autonomous, self-learning BP that requires only the subject's weight for initialization, and then autonomously adapts, modestly or dramatically, as needed, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with diabetes. The BP removes the need for the patient to know, or even appreciate, their insulin requirements, and does not require patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

The Bionic-Pancreas Glycemic-Control System, referred to as the bihormonal bionic pancreas, has been shown to improve glycemic control and to reduce the frequency of hypoglycemia in children and adults with T1D³⁻⁶. Insulin and glucagon are administered by a fully automated, bihormonal, bionic pancreas with the use of control algorithms that adapt to changes in insulin/glucagon requirements. The device consists of an iPhone®, which runs the control algorithm, and a Dexcom® continuous glucose monitor system (CGMS) connected by a custom software interface. Insulin and glucagon are administered subcutaneously by a Tandem® t:slim™ infusion pump, which are controlled wirelessly by the iPhone®.

The core technology is the insulin controller, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics. Our collaborators were the first to incorporate insulin pharmacokinetics (PK) into the algorithm, by augmenting it with a mathematical formulation for estimating the concentration of insulin in the blood and predicting its future concentration. It is essential to compensate for the slow absorption rate

of SC insulin analogs (peak time in blood of 30-90 min, clearance in 4-8 hr), and to enable the algorithm to refrain from stacking and overdosing insulin. Furthermore, the model predictive control algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with the model predictive control algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements.

Unlike current insulin pumps, and all insulin-only control algorithms of which we are aware, the adaptive basal insulin algorithm does not require the user to set, or even know, his or her “basal-rate profile.” Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g. circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g. hormonal changes that occur during puberty or menopause).

Additionally, the adaptive meal dose controller does not require the user to set, or even know, his or her “carbohydrate-to-insulin ratios,” as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day. The BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It could occur preemptively even if glucose is above range and it includes a feedback term to account for the pending effects of recent glucagon doses.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge the developers of the BP have met is enabling the technology to remain completely autonomous in managing insulin and glucagon delivery even when the Dexcom® CGMS is offline. Specifically, when the Dexcom® CGMS is offline, the BP invokes the high-resolution “basal rate profile” that it had recently learned and stored when the Dexcom® CGMS was online. Based on what the system learned and stored about meal announcements when the Dexcom® CGMS was online, it can respond to meal announcements in the same manner when the Dexcom® CGMS is offline.

Finally, it automatically responds to user-entered BG values when the Dexcom® CGMS is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the Dexcom® CGMS was online. Thus, the BP never relies on, or burdens the user with, the determination of subjective dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with diabetes that comprehensively manages glycemia across a broad range of individual needs and across a large spectrum of circumstances and challenges to glycemic control.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

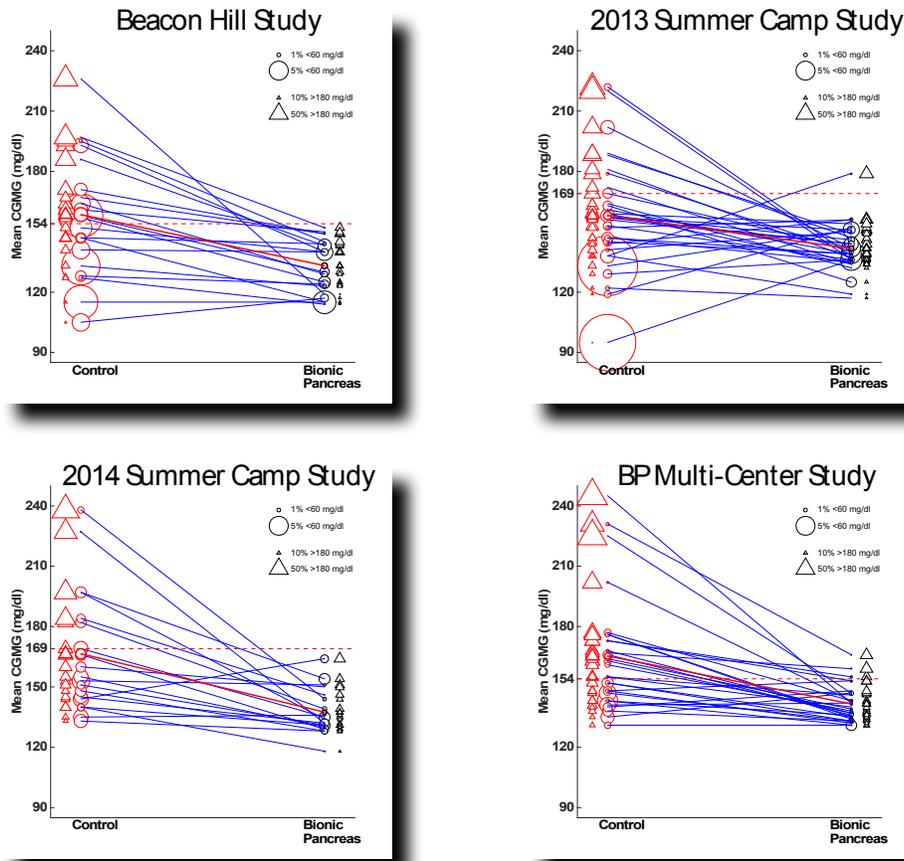
Our collaborators from Boston University and Massachusetts General Hospital (MGH) have developed the bihormonal artificial pancreas which was first tested in a swine model of T1D⁷. Results from these preclinical studies supported further development efforts of the bihormonal pancreas to allow for better glycemic control. Our collaborators developed the device's algorithm for insulin and glucagon infusion based on control studies that showed that the device was able to achieve near-normal mean BG, therefore demonstrating the feasibility of an *in vitro* bihormonal artificial endocrine pancreas⁸.

1.3.2 Clinical Studies

1.3.2.1 Development and Summary of Clinical Studies

The BP hardware platform has evolved over the years from a laptop-driven system, which was used in all the inpatient studies (between 2008--2012), to the first truly mobile wearable iPhone®-driven platform, which was used in all outpatient studies thus far (between 2013—2015). Using the iPhone®-driven BP system, our collaborators have conducted >110 outpatient experiments of 5-11 days in duration in each subject (> 800 patient days or > 2 patient years of data), and across subjects ranging in age between 6 and 76 years old and in body mass between 21 and 128 kg. The robust adaptation capabilities of the BP is evident in the fact that the average total daily dose of insulin among these subjects varied by over 13-fold (from 11 to 145 units/day).

The preclinical studies at Boston University testing the BP in a diabetic swine model of T1D^{8,9} and all of the inpatient clinical trials in the Clinical Research Center at MGH testing the BP in adults and adolescents with T1D^{4,5,10} set the stage for the outpatient studies that followed. In November 2012, our collaborators obtained FDA approval to conduct the first outpatient study testing the BP in adults 21 years or older with T1D. This study, which we referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1D participated in 5 days on our iPhone®-based BP and 5 days of usual care in which they wore a Dexcom® CGMS with blinded display and muted alarms. In the BP arm, subjects kept to a three-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to two gyms. Analysis was pre-specified to focus on Days 2-5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1¹¹. Results are summarized in the plots and table of Figure 1 (unpublished data).



| Study | Age (years) | Bionic Pancreas (BP) | | | Control | | | p-value (BP versus Control) for: | | |
|--|-------------|---------------------------------|---------------------------------------|------------------|---------------------------------|---------------------------------------|------------------|----------------------------------|-----------------------------------|--------------|
| | | Mean CGMG glucose level (mg/dl) | % of CGM glucose levels <60 mg/dl (%) | 70-180 mg/dl (%) | Mean CGMG glucose level (mg/dl) | % of CGM glucose values <60 mg/dl (%) | 70-180 mg/dl (%) | Mean CGMG glucose level | % of CGM glucose values <60 mg/dl | 70-180 mg/dl |
| Beacon Hill (n=20, 5-day experiments) | ≥21 | 133 | 1.5 | 80 | 159 | 3.7 | 59 | <0.001 | 0.020 | <0.001 |
| 2013 Summer Camp (n=32, 5-day experiments) | 12-20 | 142 | 1.3 | 76 | 158 | 2.2 | 65 | 0.004 | 0.192 | <0.001 |
| 2014 Summer Camp (n=19, 5-day experiments) | 6-11 | 137 | 1.2 | 81 | 168 | 2.8 | 58 | 0.004 | 0.001 | <0.001 |
| BP Multi-Center (n=29, 11-day experiments) | ≥21 | 142 | 0.6 | 78 | 165 | 1.6 | 61 | <0.001 | <0.001 | <0.001 |

Figure 1. Outpatient results summarizing the distribution of mean CGMS glucose levels and hypoglycemia in the BP and control arms. Mean CGMS glucose levels for each subject under usual care (shown as a red circle on the left) is connected with the subject's mean CGMS glucose level on the BP (shown as a black circle on the right). For each subject, the circle diameter is proportional to the percentage of CGMS glucose values < 60 mg/dL, and the size of the triangle is proportional to the percentage of CGMS glucose values > 180 mg/dL. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal for each age group tested, which corresponds to 154 mg/dL (HbA1c <7%) for adults and 169 mg/dL (HbA1c <7.5%) for children. Results are summarized in the table below, where the co-primary outcomes (mean CGMS glucose level and percentage of CGMS glucose values < 60 mg/dL) for the BP are highlighted in red for each of the four studies^{6,11,12}.

In April 2013, our collaborators obtained FDA approval to conduct the first outpatient study testing the BP in adolescents 12--20 years old with T1D. This study, which we referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1D participated in 5 days on the BP and 5 days of supervised camp care in which they wore a Dexcom® CGMS with blinded display and muted alarms. Subjects were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone®-based BP that was used in the Beacon Hill Study. The mean HbA1c of the entire all 32 subjects at baseline (pre-study) was 8.2%, which corresponds to a mean BG of 189 mg/dL. Results are summarized in the plots and table of Figure 1¹¹.

In April 2014, FDA approval was obtained to conduct the first outpatient study testing the BP in pre-adolescents 6--11 years old with T1D. This study, which we referred to as the 2014 Summer Camp Study, was similar in design to the 2013 Summer Camp Study. Results are summarized in the plots and table of Figure 1. In April 2014, FDA approval was obtained to conduct the first multi-center study, which was also the first home study, to test the BP in adults 18 years or older with T1D. This study, which we referred to as the Bionic Pancreas Multi-Center study, followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included four medical centers (10 subjects per center), which included MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill.

Preliminary results from an interim analysis of a subset of the data from the Bionic Pancreas Multi-Center study are summarized in the plots and table of Figure 1.

1.3.2.2 Clinical Studies in Adolescents and Adults

Twenty adults and 32 adolescents with T1D participated in a cross-over study comparing standard care (insulin pump) with a bihormonal bionic pancreas. Mean glucose was approximately 20 mg/dL lower in both adolescents and adults when using the bihormonal artificial pancreas. There was also a reduction in the percentage of time spent with hypoglycemia and the number of interventions required for hypoglycemia⁴ (Figure 1).

1.3.2.3 Clinical Studies in Children

The safety and efficacy of the bihormonal bionic pancreas was also demonstrated in children age 6-11 years old with T1D. This study was conducted in a summer camp setting and the design was similar to the adolescent and adult studies. The use of the bionic pancreas was associated with a lower mean CGMS-measured glucose compared to standard pump therapy (137 ± 11 mg/dL vs. 167 ± 31 mg/dL $p=0.00037$) and a lower proportion of time with a CGMS-measured glucose concentration below 60 mg/dL ($1.2\pm 1.1\%$ vs. $2.8\pm 1.2\%$ $p<0.0001$)⁶ (Figure 1).

1.4 Relevant Literature and Data

Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in children, which can result in permanent brain damage¹¹. For some infants with severe HI, medical treatment is not effective in controlling hypoglycemia, and pancreatectomy is

necessary¹³. After near-total pancreatectomy diabetes is common with up to 91% of children requiring insulin before puberty^{2,11}. Diabetes following pancreatectomy has unique features that make this condition difficult to manage. Unlike T1D, individuals with HI and post-pancreatectomy diabetes have residual endogenous insulin secretion that is dysregulated in addition to glucagon deficiency¹⁴. Thus, the evolution of diabetes post-pancreatectomy is characterized by marked hypo- and hyper-glycemia. Furthermore, exocrine pancreatic insufficiency can affect absorption and result in unpredictable fluctuations in plasma glucose concentrations.

Current treatment approaches with intermittent subcutaneous insulin administration or insulin pump therapy offer inadequate glycemic control in these individuals. We propose a novel approach to the management of post-pancreatectomy diabetes with the “bionic pancreas” to replace insulin and glucagon through an automated glycemic management system. The bi-hormonal artificial pancreas has been shown to reduce hypoglycemia and improve glycemic control in T1D^{3,4,6}. This consists of a continuous glucose monitoring system (CGMS) paired with a pump that can administer glucagon and insulin in response to blood glucose concentrations¹¹. In collaboration with the Bionic Pancreas project team, we propose to evaluate the efficacy and safety of the bi-hormonal bionic pancreas in individuals with HI and post-pancreatectomy diabetes. *Our hypothesis is that the bi-hormonal bionic pancreas will result in improved glycemic control in these individuals.*

1.5 Compliance Statement

This study will be conducted in full accordance all applicable Children’s Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46; 21 CFR Parts 50, 54, 56, 312, 314 and 812; and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with ICH guidelines and this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children’s Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

This is a pilot study to determine the efficacy and safety of a bi-hormonal bionic pancreas for the treatment of post-pancreatectomy diabetes in individuals with congenital hyperinsulinism.

2.1 Study Rationale

As discussed above, all experiments with the bi-hormonal bionic pancreas to date in human subjects with T1D have demonstrated the practicality of a wearable automated, bionic pancreas control system for robust glucose regulation using continuous glucose monitoring devices as input to the controller. These studies have shown that a bi-hormonal bionic endocrine pancreas is capable of achieving good glycemic control automatically with

minimal hypoglycemia during the study in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals). Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent blood glucose monitoring, estimating the effects of specific meals and exercise activity on blood glucose levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance. The degree of glycemic control achieved is predicted to dramatically reduce the deleterious and debilitating complications of diabetes. Moreover, a consistent finding in all of the bionic pancreas (BP) studies has been a reduction in hypoglycemia despite lower mean plasma glucose concentrations, relative to usual care. The potential of reducing episodes of hypoglycemia while achieving good glycemic control, during exercise and independent of meals is particularly important for individuals with hyperinsulinism and post-pancreatectomy diabetes.

The current study is designed to determine the efficacy of the bihormonal bionic pancreas on achieving glycemic control and reducing hypoglycemia in individuals with hyperinsulinism and post-pancreatectomy diabetes.

2.2 Primary Objective (or Aim)

To determine if the bihormonal bionic pancreas improves glycemic control in individuals with HI and post-pancreatectomy diabetes. We hypothesize that, when compared with current standard diabetes care, the bihormonal bionic pancreas will reduce: (1) the mean glucose concentration, and (2) the fraction of time with glucose concentrations < 60 mg/dL.

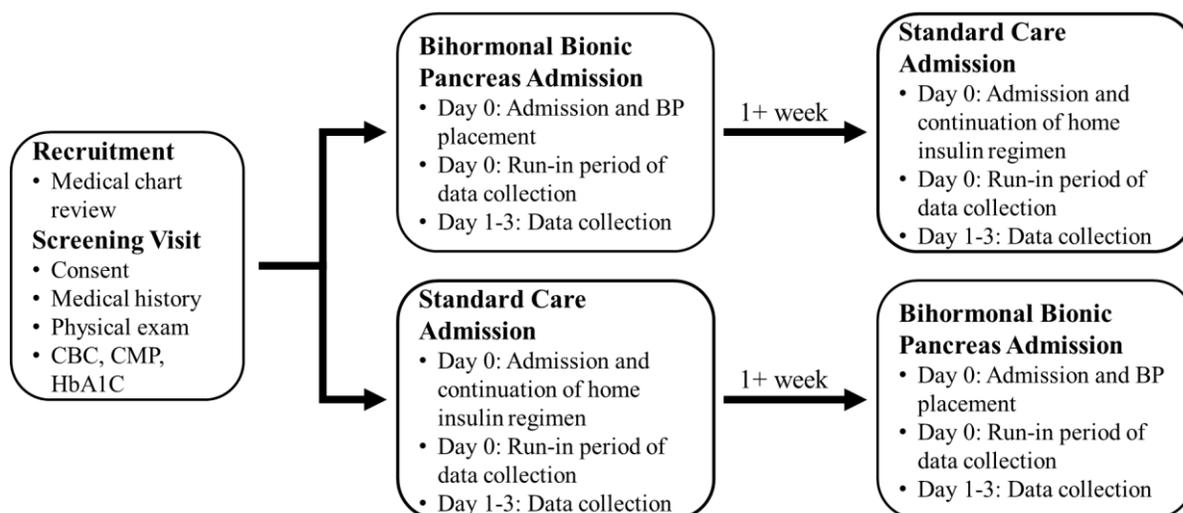
2.3 Secondary Objectives (or Aim)

The secondary objective is to evaluate the safety of the bihormonal bionic pancreas in individuals with HI and post-pancreatectomy diabetes. We hypothesize that the bionic pancreas will be sufficiently well tolerated to permit continued clinical investigation in individuals with HI and post-pancreatectomy diabetes based on an assessment of clinical adverse events.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This will be an open-label, pilot clinical trial to assess efficacy and safety of the bihormonal bionic pancreas in individuals with HI and post-pancreatectomy diabetes. Subjects will be studied during two research inpatient admissions at the CHOP Congenital HI Center.

Figure 2: General Schema of Study Design

3.1.1 Screening Phase

Potential subjects will be screened using the protocol inclusion and exclusion criteria. Individuals with HI and post-pancreatectomy diabetes will be recruited from the CHOP Congenital Hyperinsulinism Center.

Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed.

Medical records will be reviewed to determine eligibility. Medical history, physical examination, CBC, CMP, and hemoglobin A1c will be obtained during this visit after informed consent. Blood samples will be drawn to confirm eligibility based on clinical laboratory parameters. Females ≥ 11 years of age will have a urine pregnancy test.

The order of admissions will be determined based upon a randomized, crossover design with at least one week between admissions.

3.1.2 Standard Care Admission

Standard Care Admission: A 4-day inpatient admission in which subjects will continue their home insulin regimen. The first day will constitute a run-in period where no changes will be made to the participant's home regimen. Plasma glucose data from scheduled fingersticks and from CGMS will be collected throughout the admission. Data for analysis will be limited to data collected during the last 3 days.

3.1.3 Bihormonal Bionic Pancreas Admission

Bihormonal Bionic Pancreas Admission: The BP will be placed on the subject upon admission and there will be 1-day run-in period to allow for transition to the bionic pancreas system. Plasma glucose data from scheduled fingersticks and from CGMS will be collected throughout the admission. Data for analysis will be limited to data collected during the last 3 days. Following this, the patient will transition back to their home regimen and will be discharged home.

3.2 Allocation to Treatment Groups and Blinding

Because this is an open-label, pilot clinical trial, all subjects will receive study intervention (application of the bihormonal bionic pancreas). No blinding will be pursued in this study.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

We anticipate most participants will complete the study in 8 days plus 1 hour for Screening. This consists of three phases: (1) 1 hour for Screening; (2) 4 days for Standard Care Admission; and (3) 4 days for Bihormonal Bionic Pancreas Admission. The Bihormonal Bionic Pancreas Admission may be slightly longer for subjects who require additional time to transition back to their home regimen but, as stated, we do not anticipate this to be the case in most subjects.

3.3.2 Total Number of Subjects Projected

It is expected that approximately 12 subjects will be enrolled to produce 10 evaluable subjects.

3.3.3 Total Number of Sites

The entirety of this research study will be conducted at one site, The Children's Hospital of Philadelphia.

3.4 Study Population

Our study population will adhere to the following inclusion and exclusion criteria.

3.4.1 Inclusion Criteria

- 1) Males or females age 6 to 30 years.
 - 2) Diagnosis of hyperinsulinism.
 - 3) Previous pancreatectomy.
 - 4) Diabetes confirmed by one or more of the following:
 - a) Glycosylated A1c > 6.4%.
 - b) Fasting glucose > 125 mg/dL.
 - c) 2-hour post-prandial glucose > 200 mg/dL.
 - d) Random glucose > 200 mg/dL with symptomatic hyperglycemia.
 - 5) On insulin therapy with a regimen of at least 11 units/day.
 - 6) Treatment with subcutaneous insulin by pump at the time of recruitment.
 - 7) Prescription medication regimen stable for > 1 month (except for medications that will not affect the safety of the study and are not expected to affect any outcome of the study,
-

in the judgment of the site PI).

- 8) Females \geq 11 years of age must have a negative urine/serum pregnancy test and must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive, for the duration of the study.
- 9) Parental/guardian permission (informed consent) and if appropriate, child assent.

No subjects will be excluded based on gender or race. The requirement that subjects manage their diabetes using subcutaneous insulin infusion pump therapy is imposed because multiple daily injection therapy involves the use of medium-acting or long-acting basal insulin that would require an extended washout period.

3.4.2 Exclusion Criteria

- 1) Unable to provide informed consent (e.g. impaired cognition or judgment).
 - 2) Evidence of a medical condition that might alter results or compromise the interpretation of results, including active infection, kidney failure, severe liver dysfunction, severe respiratory or cardiac failure.
 - 3) Evidence of severe hematologic abnormality including severe anemia and/or thrombocytopenia.
 - 4) Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to radio frequency interference.
 - 5) Unable to completely avoid acetaminophen for duration of study.
 - 6) History of adverse reaction to glucagon (including allergy) besides nausea and vomiting.
 - 7) Established history of allergy or severe reaction to adhesive or tape that must be used in the study.
 - 8) Use oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) anti-diabetic medications.
 - 9) Any investigational drug use within 30 days prior to enrollment.
 - 10) Pregnant or lactating females.
 - 11) History of more than one episode of DKA and/or severe hypoglycemia within the six months prior to study enrollment.
 - 12) Current history of sub-optimally treated nausea and/or vomiting.
 - 13) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.
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- 14) Current and sustained use of insulin formulation (delivered via pump) not approved/advised to be used in the Tandem t:slim pump.

Subjects that do not meet all the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

Table 1: Schedule of Study Procedures (page *x*) provides a tabular view of the following information.

4.1 Recruitment Procedures

A study staff member will review the potential subject's medical health record to determine eligibility for the study based upon inclusion/exclusion criteria. When identified, the prospective participants and designated contacts will be briefed by a study staff member by phone, email, or during clinic visits regarding the study procedure and the inclusion and exclusion criteria. Subjects may also be informed about the study by internal and external recruitment methods (i.e., CHOP Congenital Hyperinsulinism Center newsletter, Congenital Hyperinsulinism International newsletter, Pediatric Endocrine Society newsletter). Potential subjects and contacts will be sent an informed consent document by mail, fax, or email, or will be given the consent form during their clinic visit.

4.2 Consent Procedures

Once potential subjects and/or parents/guardians have had time to review the consent document, they will speak with a study physician who can further explain the study and answer any questions the subject and/or parent/guardian may have. The subject will then complete the informed consent process with a study physician, should the subject desire to participate in the study. Study staff will answer any questions that the subjects may have during their participation. They will share any new information in a timely manner that may be relevant to the subject's willingness to continue participating in the trial. The subjects and/or parents/guardians may choose to discontinue their participation at any time without prejudice.

4.3 Experimental Procedures and Data Collection

4.3.1 Screening Visit

- After informed consent is obtained, all subjects will have a screening visit to confirm eligibility.
 - The subject will be interviewed and the case report form will be completed by study staff to establish whether the subject is eligible to continue with the screening according to inclusion/exclusion criteria, in the event the medical record review provided outdated data.
 - Demographic/medical history data to be recorded:
 - Age
 - Sex
 - Race and ethnicity
-

- Date of HI diagnosis
- Date of pancreatectomy and percentage removed
- Date of diabetes diagnosis/insulin initiation
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription)
- Duration of insulin pump use
- Type of insulin used in pump
- Average total daily dose of insulin in the last 30 days (from pump history, as available – for comparison with insulin dosing during the standard care and bionic pancreas arms of the study)
- Usage of CGMS, if any (type of CGMS, days per month worn, usage of data, whether insulin is dosed based on CGMS alone, alarm settings)
- Physical examination
- Vital Signs: height, weight, temperature, blood pressure, heart rate, respiratory rate
- Pregnancy test (for female subjects 11 years and older)
- Safety laboratory tests: CBC, CMP, hemoglobin A1c
- Once all the laboratory results have been returned, a study physician will review the case report form to determine subject eligibility to continue in the study. If subjects are not eligible to continue in the study, the results of abnormal tests will be reported to the subjects.
- Subjects who have been screened and are eligible can participate without having to be rescreened for a period of one year. The study staff should obtain verbal confirmation that there have been no health events that would make them ineligible if the interval between screening and participation is longer than 3 months.
- Upon confirmation of eligibility and participant’s willingness to continue, subjects will be assigned to an order of admissions based upon a randomized, crossover design. There will be a minimum of 1 week time between admissions.
- Pediatric subjects will be required to have a parent or guardian accompanying them during the inpatient admissions.

4.4 Standard Care Admission

A 4-day inpatient admission in which subjects will continue their home insulin regimen. Blood glucose data will be collected from finger-stick and from CGMS during the study.

4.4.1 Run-in period (Day 0)

- Medical history
 - Prior/concomitant medications
 - Vital signs: height, weight, temperature, blood pressure, heart rate, respiratory rate
 - Standardized diabetic diet
 - Insulin administered via insulin pump per home regimen
 - Placement of Dexcom® CGMS for BG monitoring
-

- Blood glucose check by finger-stick before breakfast, before lunch, before dinner, at bedtime, and at 03:00am. PRN blood glucose checks may occur at the discretion of the study physician(s)
- Initiation of telemetric monitoring of CGMS connectivity
- Adverse event monitoring

4.4.2 Days 1-3

- Vital signs: temperature, blood pressure, heart rate, respiratory rate every 12 hours (appx.)
- Standardized diabetic diet
- Insulin administered via insulin pump per home regimen. Subjects will be asked to change their insulin infusion set and reservoir at least every two days, just as they will during the bionic pancreas arm
- Study staff confirms CGMS is running
- Dexcom® calibration twice daily (before breakfast and dinner). Calibration will be delayed if there is a steep rise or fall in the blood glucose or if there has been carbohydrate intake in the last 30 minutes. If a calibration is delayed for any of these reasons, it will be performed at the next opportunity.
- Blood glucose check by finger-stick before breakfast, before lunch, before dinner, at bedtime, and at 03:00am. PRN blood glucose checks may occur at the discretion of the study physician(s)
- Telemetric monitoring of CGMS connectivity
- Adverse event monitoring

4.4.3 Discharge

Subjects will be discharged on the fourth day of the admission.

4.5 Bihormonal Bionic Pancreas Admission

Study staff at CHOP will undergo thorough in-person training on all functions of the Bionic Pancreas System by the device's developers from Massachusetts General Hospital. Briefly, this training will constitute application and removal of the BP to a human subject, operating and overseeing the BP system daily functioning, filling and priming the pumps, understanding the information and settings on the BP's display screen, using the meal bolus feature, and troubleshooting of expected and unexpected issues. Our colleagues at Massachusetts General Hospital will be available throughout the study to respond to questions, concerns, and comments.

The bihormonal pancreas will be placed upon admission and there will be 1 day run-in period. This will be followed by 3 days of data collection for comparison with the data obtained from the standard of care during the Control Admission. Following this, the patient will transition back to their home regimen and will be discharged home.

4.5.1 Run-in Period (Day 0):

- Medical history
 - Prior/concomitant medications
 - Vital signs: height, weight, temperature, blood pressure, heart rate, respiratory rate
-

- Standardized diabetic diet
- Insulin administered via insulin pump per home regimen until transition to the BP
- Placement of Dexcom® CGMS for BG monitoring
- Blood glucose check by finger-stick before breakfast, before lunch, before dinner, at bedtime, and at 03:00am. PRN blood glucose checks may occur at the discretion of the study physician(s).
- Initiation of telemetric monitoring of CGMS connectivity
- The study staff will place the two infusion sets, fill and prime one Tandem® t:slim™ pump with insulin and one Tandem® t:slim™ pump with glucagon and label all pieces appropriately
- The control algorithm will be initialized only with the subject weight
- Diagnostics will be performed to ensure that the CGMS device is appropriately calibrated and that all of the components of the bionic pancreas (Dexcom® G5® Platinum AP, iPhone® running the control algorithm, Tandem® t:slim™ infusion pumps) are in good communication with each other
- The subject's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed
- The staff will start the bionic pancreas as close as possible to a minute divisible by 5 minutes (i.e. on a 5-minute mark) and before 4:00 PM.
- We will initiate bionic pancreas control with a glucose target of 110 mg/dL to 130 mg/dL, according to the Investigator's discretion. Study physician(s) reserve the right to adjust the subjects' glucose targets to a value between 110 mg/dL and 140 mg/dL (inclusive), according to Investigator's discretion.

4.5.2 Days 1-3

- Vital signs: temperature, blood pressure, heart rate, respiratory rate twice daily
 - Standardized diabetic diet
 - Study staff confirms CGMS is running
 - Blood glucose check by finger-stick before breakfast, before lunch, before dinner, at bedtime, and at 03:00am. PRN blood glucose checks may occur at the discretion of the study physician(s).
 - CGMS calibration twice daily (before breakfast and dinner). Calibration will be delayed if there is a steep rise or fall in the blood glucose (>2 mg/dL/min), there has been carbohydrate intake in the last 30 minutes, or there has been a glucagon dose in the last 15 minutes. In the immediate aftermath of carbohydrate intake or glucagon dosing it is possible for BG to be rising without a change in interstitial fluid glucose. If a calibration is delayed for any of these reasons, it will be performed at the next opportunity. Additional calibrations may be performed if the CGMS is inaccurate relative to a BG measurement as long as it is not calibrated within 30 minutes of food intake or 15 minutes of glucagon dosing. Extra calibrating will not be performed if the CGMS is within 15 mg/dL when the BG is ≤ 75 mg/dL and within 20% if the BG is >75 mg/dL at times when the rate of change is low.
-

- Telemetric monitoring of CGMS connectivity. Alarms will sound if the CGMS glucose is less than 50 mg/dL. The first step for all glucose-related alarms will be to perform a fingerstick BG measurement. If the BG measurement is not consistent with the fact that a threshold alarm has occurred:
 - The staff will assess the possibility of a compression artifact. If a compression artifact is suspected, steps to relieve the pressure on the transmitter will be taken. If no compression is suspected, the CGMS will be calibrated as long as there has been no carbohydrate intake in the last 30 minutes, no glucagon dosing in the last 15 minutes, and there is no steep rise or fall in glucose (>2 mg/dL/min). If a calibration is delayed for this reason, it will be performed at the next opportunity.
 - If the BG measurement is consistent with a low threshold alarm, the hypoglycemia will be treated with carbohydrate ingestion according to the usual practice. The staff will investigate the glucagon infusion set and consider replacing it.
 - The first step in responding to hyperglycemia according to the CGMS will be to perform a fingerstick BG measurement. If the BG measurement is not consistent with the CGMS, the CGMS will be calibrated as long as there has been no carbohydrate intake in the last 30 minutes and there is no steep rise or fall in glucose (>2 mg/dL/min). If a calibration is delayed for this reason, it will be performed at the next opportunity. If the BG measurement is consistent with the CGMS, the insulin infusion site will be investigated and replacement will be considered.
 - If there is a complete failure of bionic pancreas operation and it is anticipated that restarting it will take more than an hour, subjects may take over their own BG control using their own insulin pump or with insulin injections until the bionic pancreas can be brought back online with the help of study staff. During the day, this should be rare. If the failure occurs at night, every effort should be made to correct the problem as soon as possible, which should almost always be possible within 12 hours.
 - If a CGMS sensor fails during the course of an experiment, the system will provide basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated as CGMS data and may result in administration of insulin and/or glucagon. The CGMS sensor will be replaced as soon as possible and normal bionic pancreas control will resume when the new sensors is calibrated.
 - Subjects will be asked to announce the three major meals of the day, but not snacks, to the bionic pancreas. The meal announcement will consist of choosing the type of meal (breakfast, lunch, dinner) and the size of the meal relative to typical meals for that subject (snack, smaller than typical, typical, larger than typical).
 - The insulin infusion set and reservoir will be changed at least every two days.
-

- The glucagon reservoir will be replaced every day. Each reservoir will be filled with two vials of freshly reconstituted Lilly glucagon. The glucagon infusion set will be changed daily with the reservoir change.
- On days when both the insulin and glucagon reservoirs will be changed, they will be changed at different times in the day, separated by at least one hour. The infusion sets and tubing will be labeled to avoid confusion or cross connection.
- All episodes of hypoglycemia, carbohydrate interventions, any nausea and/or vomiting, any other adverse events, time spent exercising, and any unscheduled infusion set changes, alcohol use, etc. will be recorded.
- Adverse event monitoring.
- At the end of the 4-day period, subjects will return the bionic pancreas.

4.5.3 Discharge

- Bionic pancreas will be disconnected and the subject will be asked to connect and initiate home insulin pump.
- Meters and the bionic pancreas will be downloaded.
- The body weight of the subject will be documented.
- Physical exam prior to hospital discharge.
- Subjects will be discharged on the fourth day or afterward if the subject requires additional time to transition back to his/her home regimen. Prior to discharge, subjects must have a recent history and glucose trajectory that is sufficiently stable for safe discharge in the judgment of a study provider.

4.6 Standardized Meals

Standardized meals will be provided on all inpatient admission study days. A bio-nutritionist will speak with each participant to develop a meal plan during the inpatient admissions. All efforts will be made to have daily meals identical across admissions; in that, the same 4-day meal plan will be used for both admissions. All subjects will receive standard diabetic diets with meals containing the range of carbohydrates that constitute the subjects typical amount of carbohydrates for each meal type and size (e.g., 50-60 g of carbohydrates for breakfast, etc.). Subjects will be asked to consume their meal as much as possible.

4.7 Physical Activity

This study will take place in the inpatient setting; therefore subjects will not be engaging in any significant physical activity (aerobic or anaerobic) but will be allowed to ambulate within the hospital boundaries.

4.8 Prior and Concomitant Medication

All prior and concomitant medications used within 1 week prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.9 Rescue Medication Administration

4.9.1 Response to Hypoglycemia

- BG will be checked for any symptoms of hypoglycemia.
- Hypoglycemia will be treated according to standard of practice according to the “rule of 15s”: take 15 grams of rapid acting carbohydrate and recheck in 15 minutes, then repeat as needed. For severe episodes of hypoglycemia that are not responsive to carbohydrate ingestion or if the subject cannot drink/eat, 1 mg of glucagon subcutaneously or intramuscularly will be administered as necessary.
- During the bionic pancreas admission the glucagon infusion site and the bionic pancreas will be checked for normal operation any time hypoglycemia occurs. If there is any suspicion of glucagon infusion set malfunction, the site will be replaced.
- If a subject experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the study will be discontinued.

4.9.2 Response to Hyperglycemia

- Beta hydroxybutyrate will be collected and recorded when BG is > 240 mg/dL.
- The insulin infusion site and the pump or bionic pancreas will be checked for normal operation any time BG is greater than 300 mg/dL. If there is any suspicion of insulin infusion set malfunction, the site will be replaced.
- If no correctable fault is found, but there is doubt regarding the correct function of the bionic pancreas system, an entirely new backup bionic pancreas system will be used.
- If a subject experiences diabetic ketoacidosis, his or her participation in the study will be discontinued.

4.9.3 Response to Nausea/Vomiting

If significant nausea or vomiting occurs during the bionic pancreas study the study staff will troubleshoot, such as checking the calibration of the CGMS (excessive glucagon dosing may occur if the CGMS is reading lower than the true blood glucose). If a subject experiences persistent nausea and vomiting thought to be related to glucagon dosing, his or her participation in the study will be discontinued.

4.10 Monitoring of Bionic Pancreas Performance

The Bionic Pancreas team will be readily available by phone for consultation at all times during the course of each experiment. They will have the capability of viewing diagnostic information regarding the connection of the CGMS with the bionic pancreas, the functioning of the bionic pancreas, and the connection of the bionic pancreas with the insulin and glucagon pumps remotely during the experiment, in order to monitor and assist in any needed troubleshooting. The connection will be secure and password protected, and will be set up so that only viewing of the screen is possible - no input or changes to the controller can be made remotely.

4.11 Supervision by Study Staff

A study physician (MD or NP) will be on call at all times during the course of each experiment. All trained staff will have the capability of remotely viewing diagnostic information on an iPhone® or iPad® to facilitate phone troubleshooting and decide about whether additional assistance is needed.

4.12 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or SAEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF. When a subject discontinues/withdraws prior to study completion, the study staff reserves the right to analyze data from studies completed prior to withdrawal.

5 STUDY EVALUATIONS AND MEASUREMENTS

Adverse events and concomitant medication use will be monitored continuously throughout subject confinement. Procedures should be performed as close to the scheduled time as possible, and in all cases the actual time of the procedure will be accurately recorded.

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Medical history will be recorded at Screening and will include full HI and diabetes history and history of all other significant conditions for the previous 10 years. Data that will be collected includes:

- Date of birth
 - Sex
 - Race and ethnicity
 - Date of last menstrual period for female volunteers
 - Date of HI diagnosis
 - Date of pancreatectomy
 - Date of diabetes diagnosis/insulin initiation
 - Medical, surgical, and social history, allergies, and review of systems relevant to confirmation of inclusion and exclusion criteria (i.e., date of pancreatectomy)
 - Medications (prescription and non-prescription) and date of last change in medication regimen
 - Duration of insulin pump use
 - Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
 - Average total daily dose of insulin in the last 30, 60, and 90 days as available (from pump history)
-

- Usage of CGMS, if any (type of CGMS, days per month worn, usage of data, whether insulin is dosed based on CGMS alone, alarm settings)
- History of insulin types used (beef insulin, pork insulin, regular human insulin, NPH insulin, ultralente insulin, insulin aspart, insulin lispro, insulin glulisine, insulin detemir, insulin glargine)
- Average number of BG tests daily in the last 30, 60, and 90 days as available (from meter download – if more than on meter is used all will be downloaded)
- Dietary patterns (estimation of daily carbohydrate and calorie intake)
- Results from any previous imaging studies of relevance
- Results from previous HI tests
- Previous hemoglobin A1c results

5.1.2 Physical Examination

All physical examinations include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician or nurse practitioner (or equivalent) will examine each subject.

Physical examination may be performed at various unscheduled time points if deemed necessary by the Investigator.

5.1.3 Vital Signs

Body height will be measured in centimeters (cm) via stadiometer. Body weight will be measured in kilograms (kg) with a step-on scale. Vital signs include body temperature (measured in °C with an automated device), respiratory rate (measured manually while subject is seated and relaxed), blood pressure (measured with an automated device on the subject's upper arm while subject is seated and relaxed), and heart rate (measured manually by qualified personnel or by an automated machine).

Vital signs may be measured at unscheduled time points, if deemed necessary by the Investigator.

5.1.4 Laboratory Evaluations

Blood sampling will be performed for the following laboratory evaluations

- Hematology
- Chemistry profile
- Hemoglobin A1c

5.1.4.1 Table: Clinical Laboratory Tests

| Category | Tests |
|----------------------|--|
| Hematology | RBC, hemoglobin, hematocrit, platelet count, WBC |
| Liver function tests | SGOT/AST, SGPT/ALT, total Bilirubin |

| | |
|----------------------|-----------------|
| Renal function tests | BUN, creatinine |
| Other | Hemoglobin A1c |

5.1.4.2 Pregnancy Testing

A urine pregnancy test will be performed for female subjects ≥ 11 years of age and girls <11 years who are physically capable of becoming pregnant.

5.2 Efficacy Evaluations

See section 6.5.2 *Efficacy Analysis*.

5.3 Safety Evaluation

Subject safety will be monitored by adverse events, vital signs, physical examinations, and laboratory data. Additionally, see sections 4.8 *Prior and Concomitant Medications* through 4.12 *Subject Completion/Withdrawal*.

6 STATISTICAL CONSIDERATIONS

All analytical data will be collected and stored on a 21 CFR Part 11 compliant LIMS system. The analyses of the data obtained from this study will be conducted by the investigators.

6.1 Primary Endpoint

The co-primary outcomes are (1) mean glucose concentration as measured by the CGMS during the final 3 days of each admission, and (2) the mean proportion of time that the CGMS-measured glucose concentration was less than 60 mg/dL during the same periods. Both metrics will be generated from the Dexcom® CGMS data during the Standard Care Admission and the Bihormonal Bionic Pancreas Admission.

6.2 Secondary Endpoints

All following metrics will be generated from the Dexcom® CGMS data during the Control and Experimental Admissions. Each of these measures will be calculated for the entire period and separately for the daytime and nighttime (based on self-reported sleep time and wake times self-reported on daily questionnaire).

- Mean CGMS
 - Fraction of time spent within each of the following glucose ranges:
 - < 50 mg/dL
 - < 60 mg/dL
 - < 70 mg/dL
 - 70-120 mg/dL
 - 70-180 mg/dL
 - >180 mg/dL
 - >250 mg/dL
 - Percentage of subjects with mean CGMS < 154 mg/dL (estimated average glucose corresponding to an A1c of 7%).
 - Percentage of schedule fingerstick checks < 70 mg/dL, < 60 mg/dL, <50 mg/dL.
-

6.3 Safety Endpoints

All of following metrics will be generated during both phases of the study. Each of these measures will be calculated for the entire period and, as appropriate, separately for the daytime and nighttime.

- Number of episodes of symptomatic hypoglycemia.
- Number of carbohydrate interventions for hypoglycemia.
- Total grams of carbohydrate taken for hypoglycemia.
- Insulin total daily dose (TDD).
- Glucagon total daily dose during the bionic pancreas use (TDD).
- Fraction of time bionic pancreas off-line or not functioning properly (e.g. due to system crash, communication problem between CGMS and bionic pancreas, communication problem between bionic pancreas and pumps, pump malfunction).
- Mean daily nausea score (0-10 cm VAS).

6.4 Exploratory Outcomes

6.4.1 CGMS

- Reliability index, calculated as percent of possible values actually recorded by CGMS.
- CGMS mean absolute relative difference versus time-stamped BG values from meter downloads (any other BG values will not be considered).

6.4.2 BG

- Mean number of daily BG measurements downloaded from the subject's meter.

6.4.3 Non-glycemic

All following metrics will be generated during the bionic pancreas and standard care admissions. Each of these measures will be calculated for the entire period and, as appropriate, separately for the daytime and nighttime (based on self-reported sleep time and wake times self-reported on daily questionnaire).

- Number of glucagon doses.
- Mean daily basal insulin dose.
- Mean daily bolus insulin dose.
- Number of unscheduled infusion set replacements.
- Number of unscheduled CGMS sensor changes.
- List of technical faults associated with the bionic pancreas including cause and resolution.

6.5 Statistical Methods

Only data from subjects that complete both study periods will be included in the analysis. In patients that complete the study, the primary analysis of the designated endpoints will be calculated on an intention-to-treat basis, including data from periods when the bionic pancreas was not in use, if available (CGMS data may not be available in some failure

modes). We may also perform secondary, exploratory analyses excluding bionic pancreas down-time, since this may better represent the performance possible with a fully integrated system. We will calculate percentages, means, standard deviations, and ranges in descriptive analyses. We will use paired t-test for comparison of means. In a secondary analysis, we will look for any period effect and any interaction between treatment and period, although no such interaction is predicted and there is probably insufficient power to identify a small interaction. We may, in exploratory analyses, also stratify subjects for secondary analyses of the pre-specified endpoints by the following characteristics: sex, age, usual care insulin total daily dose, body mass index, A1c, and use of CGMS in usual care.

The following populations are defined for the analysis and reporting of data.

- All Subjects as Treated (AST): All subjects who had the bihormonal artificial pancreas placed for any period of time. This population will be used for assessment of safety and tolerability.
- Per-Protocol (PP): The set of data generated by subjects who received protocol procedures sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model.

6.5.1 Baseline Data

Descriptive statistics will be used to characterize baseline measures in subjects.

6.5.2 Efficacy Analysis

As a general strategy, continuous endpoints will be summarized using the five-number summary (mean, standard deviation, median, minimum, and maximum). Categorical endpoints will be summarized using frequency distributions.

Subgroup analyses may also be performed to further delineate study data. These analyses may include t-tests, Wilcoxon rank-sum tests, and Pearson correlation/Spearman correlation for continuous measures; for categorical variables, chi-square and Fisher's exact tests may also be performed, as appropriate.

This is a pilot study to generate data to assess feasibility of study design/procedures and for formal sample size estimation for a larger study of the efficacy of the bihormonal bionic pancreas in children and adults with hyperinsulinism and post-pancreatectomy diabetes. The sample size for this pilot study may be too small to detect statistical significance, however, we offer the following plan for analysis of the outcomes for this study.

Mean CGMS-measured glucose concentration (calculated as the mean of all CGMS-measured concentrations [measured every 5 min] over the study period) and the mean proportion of time when the CGMS-measured glucose concentration was < 60 mg/dL during the last 3 days on the bionic pancreas will be compared to the same outcomes during the control period by paired-sample Student's t-test (or Wilcoxon signed rank test if data is not normally distributed) to determine if the intervention conferred an improvement in glycemic control. Secondary outcomes will be analyzed with univariate analysis.

6.5.3 Safety Analysis

Safety will be assessed through an examination of the incidence, severity, and type of treatment-emergent adverse events and changes in vital signs, physical examination results, glucose monitoring, and use of concomitant medications and concomitant treatment from baseline to specified time points throughout the trial. All subjects entered study at either admission will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study device will be summarized. SAEs (if any) will be described in detail. Safety variables will be assessed by comparison of frequency of adverse events (AEs) and serious adverse events (SAEs) during the two study periods.

6.6 Sample Size and Power

The proposed sample size of 10 subjects for this pilot study is a sample of convenience based on the number of subjects that we can feasibly study during one year and with the funds available. The study may not be powered to achieve statistically significant differences between the bihormonal bionic pancreas study period and the standard care period, but the data from this pilot study will be used for formal sample size estimation for a larger study. However, we offer the following sample size considerations based on previous studies in children and adolescents with type 1 DM.

The two co-primary outcomes are (1) mean glucose concentration as measured by the CGMS during the final 3 days of each admission, and (2) the mean proportion of time that the CGMS-measured glucose concentration was less than 60 mg/dL during the same periods. In children and adolescents with type 1 DM, the use of the bionic pancreas was associated with a lower mean CGMS-measured glucose compared to standard pump therapy (137 ± 11 mg/dL vs. 167 ± 31 mg/dL, $p=0.00037$) and a lower proportion of time with a CGMS-measured glucose concentration below 60 mg/dL ($1.2 \pm 1.1\%$ vs. $2.8 \pm 1.2\%$, $p<0.0001$)⁶. The standard deviation of the difference will depend on the within-subject correlation r in this crossover study design. If we assume that the standard deviation of both groups would be the same as above the following table shows the sample size needed to detect a similar difference (an effect size of 1.2 and 2, respectively) with an alpha of 0.05 and a power of 0.8 for different values of r .

6.6.1 Mean CGMS-measured glucose

| r | Sample size ($1-\beta=0.8$) |
|-------|----------------------------------|
| 0.001 | 12 |
| 0.01 | 12 |
| 0.05 | 12 |
| 0.1 | 11 |
| 0.2 | 11 |
| 0.3 | 10 |
| 0.4 | 10 |
| 0.5 | 9 |

6.6.2 Proportion of time with a CGMS-measured glucose concentration below 60 mg/dL

| r | Sample size (1- β =0.8) |
|-------|----------------------------------|
| 0.001 | 11 |
| 0.01 | 11 |
| 0.05 | 10 |
| 0.1 | 10 |
| 0.2 | 9 |
| 0.3 | 8 |
| 0.4 | 8 |
| 0.5 | 7 |

6.7 Interim Analysis

This is an open label study. Safety data will be examined on an ongoing basis to ensure safety of the study subjects.

7 DRUGS/DEVICES

7.1 Drugs

The study involves subcutaneous administration of insulin lispro (Humalog®, Lilly) or insulin aspart (Novolog®, Novo Nordisk); and rDNA-origin glucagon for injection (Glucagon™, Lilly). All are commercially available by prescription and are indicated for patients with diabetes, but not for use in a bionic pancreas. Subjects will use their usual rapid-acting insulin analog during the usual care arm of the study and during the bionic pancreas arm. The study also involves subcutaneous administration of glucagon for injection, which is indicated for the treatment of severe hypoglycemia, but not for use in a bionic pancreas.

The control system can administer bolus doses of each drug up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 μ l] and a single meal-priming dose, which is triggered by the user, will not exceed 12 units [120 μ l]. A single bolus of glucagon will not exceed 80 μ g [80 μ l]. The insulin pumps can administer as little as 0.5 μ l (0.05 units of U-100 insulin or 0.5 μ g of 1 mg/ml glucagon) in single programmable bolus doses.

It is expected that the total daily dose of glucagon will be < 1.5 mg daily as in previous studies. The mean daily glucagon dose in the previous outpatient study was 0.72 mg/day (range 0.22-1.34 mg/day). The recommended dose of glucagon for patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in the previous inpatient studies have been above the normal fasting range for glucagon only 1% of the time. Therefore, the glucagon exposure of subjects is expected to be modest.

7.2 Devices

7.2.1 Personal Insulin Pumps

Subjects will retain and wear their personal insulin pumps for the Control Admission. There will be no intervention to the subjects' insulin pumps as part of this study, except for them being removed during the Bihormonal Bionic Pancreas Admission of this study.

7.2.2 Bionic Pancreas System

Infusion sets: Subjects will wear two FDA approved commercially available infusion sets, one for insulin infusion and one for glucagon infusion, when applicable. Infusion sets that are compatible with the Tandem® t:slim™ insulin pump (leur lock connection) will be used during the bionic pancreas phase that are similar to the infusion sets they use during the control phase. If an infusion set falls off or is clinically suspected of failing, it will be replaced with a new one. The insulin infusion set will be changed at least every 48 hours; the glucagon infusion set will be changed every 24 hours.

Bionic Pancreas Control Unit: The Beta Bionics mobile application that runs the control algorithm and the Dexcom® G5® app are both installed on a stock iPhone® 6s running iOS 10. The Betabionics app receives the CGM glucose values that are captured by the Dexcom® G5® app.

The control algorithm app has a graphical user interface (GUI) that displays the current Dexcom® CGM glucose, a graphical history of the Dexcom® CGM glucose, and doses of insulin and glucagon delivered by the control algorithm. The GUI can also be used to input meal announcements, designating the size of the meal as larger than typical, typical in size, smaller than typical, or just a bite, and the type of meal as breakfast, lunch, or dinner. This will trigger a partial meal-priming bolus the size of which will adapt during the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level in the bionic pancreas will be programmed by the study staff prior to the start of each admission. This will be locked and the subject will be unable to accidentally change or tamper with this setting. Subjects will be aware of what their glucose target is.

The GUI can also be used to manage meal boluses as usual, and will administer correction boluses in response to entered BG values, during periods when the Dexcom® CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the administration of insulin basal rates either based on the subject's weight early in the experiment, or on the average of adaptively determined basal rates for that time of day once sufficient experience has been accumulated (i.e. 24 hours or more) by the control algorithm. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were Dexcom® CGM values.

The GUI also displays local audio and visual alarms if communication is dropped between the Dexcom® CGM transmitter and the bionic pancreas control unit or between the control unit and the two insulin pumps. The Dexcom® CGM also has its own hard-coded alarm

distinct from the bionic pancreas when the CGM glucose crosses below 55 mg/dl. These alarms may be configured so that they require the entry of a code to dismiss.

The iPhone® communicates wirelessly via the Bluetooth Low Energy (BTLE) protocol with up to two Tandem® t:slim™ insulin pumps to deliver insulin and glucagon.

In all configurations, if communication failures between the Dexcom® CGM and the bionic pancreas or the bionic pancreas and the cloud are not resolved within 15 minutes they trigger alerts to study staff who will then contact the wearer according to study protocol. If communication failure between the bionic pancreas and pumps is not resolved within 15 minutes this triggers and alert to study staff who will contact the wearer. Also in both configurations, if the Dexcom® CGM glucose drops below 50 mg/dl and the user does not enter a BG into the bionic pancreas GUI within 15 minutes, this will trigger an alert to study staff, who will then contact the wearer according to the study protocol. Monitoring will be the same in all study arms.

Tandem® t:slim™ Pumps: These pumps are FDA approved insulin pumps with reservoirs capable of holding 300 units (3 ml) of insulin or 3 ml of a glucagon solution. The pumps have a mechanical dosing resolution of 1/120 (0.00833) unit and can deliver liquids at a maximal rate of ~ 33 µl per minute (2 ml per hour). They are slave to the bionic pancreas control unit and are controlled wirelessly via the Bluetooth Low Energy protocol by the iPhone® 6S.

7.2.3 Continuous Glucose Monitoring System

During each admission, a Dexcom® G5® continuous glucose monitor system (CGMS) will be placed to measure glucose concentration continuously. The CGMS will be calibrated twice daily before breakfast and dinner and as requested by the CGMS. During Control Admission, the CGMS will be connected to an iPhone® to allow remote monitoring. During Experimental Admission, the CGMS will be part of the bionic pancreas system and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the CGMS receiver. If the CGMS sensor fails for any reason during the experiment it will be replaced promptly.

Prior to any reuse of the CGM transmitter between patient admissions, study staff will thoroughly clean and disinfect the transmitter according to the manufacturer's best practices (detailed instructions included in the Dexcom® User Guide).

7.2.4 Bedside Glucometer

Capillary glucose will be monitored before each meal, at bedtime, at least once overnight and PRN (Nova StatStrip® point-of-care glucose monitor, Nova Biomedical Corporation, Waltham, MA).

7.2.5 Drug Accountability

For this study, patients will be administered rDNA-origin glucagon for injection (Glucagon™, Lilly) via the Bionic Pancreas. Dosage is 1 mg/mL; route of administration is subcutaneous. The glucagon drug supply for this study will be purchased from

Investigational Drug Service at The Children's Hospital of Philadelphia. Drug will be dispensed by Investigational Drug Service following prescription by the Investigator or her medically-licensed designee and may not be used for any purpose other than that described in this protocol. At study completion, all drug supplies, including partially used and empty containers, will be disposed of according to manufacturer recommendations.

Adequate records of study drug purchase and dispensation will be maintained by the CHOP Investigational Drug Service. Records of investigational drug orders, dispensing records, and disposition forms may be examined during the course of the study.

8 SAFETY MANAGEMENT

8.1 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.2 General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

8.3 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.4 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.5 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.5.1 Reporting Hypoglycemia and Hyperglycemia Adverse Events

To maintain consistency across protocols under the Bionic Pancreas IDE, we have consulted with the team who holds the IND at Boston University and our clinical trial collaborators at Massachusetts General Hospital to determine appropriate and consistent methods for reporting the expected adverse events of hypoglycemia and hyperglycemia. Study team will report hypoglycemia and hyperglycemia if they meet the threshold of a severe adverse event. Hypoglycemia and hyperglycemia will be reported in line with CHOP and FDA requirements (and GCP guidelines) requirements for reporting serious adverse events.

Specifically, hypoglycemia will be reported if a patient experiences hypoglycemia that results in a compromised neurologic status to the extent that the patient requires assistance to treat, including seizure or loss of consciousness. Hyperglycemia will be reported as an AE if it is prolonged and associated with replacing the infusion set, or removing the BP and giving correction insulin. Additionally, hyperglycemia will be recorded as an AE if the subject mounts ketones > 0.6 mmol/L. Hyperglycemia will be recorded as a serious adverse event if the subject becomes diabetic-ketoacidotic.

8.6 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.6.1 Relationship of SAE to Study Intervention

The relationship of each SAE to the study intervention will be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely, or unrelated.

8.7 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

| Type of Unanticipated Problem | Initial Notification (Phone, Email, Fax) | Written Report |
|--|---|---|
| Internal (on-site) SAEs Death or Life Threatening | 24 hours | Within 2 calendar days |
| Internal (on-site) SAEs All other SAEs | 7 days | Within 7 business days |
| Unanticipated Problems Related to Research | 7 days | Within 7 business days |
| All other AEs | N/A | Brief summary of important AEs may be reported at time of continuing review |

8.7.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.8 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with regulatory requirements.

8.9 Medical Emergencies

As this study involves inpatient hospital admissions, any medical emergencies will be handled per standard operating procedure.

9 STUDY ADMINISTRATION

As this is an open-label, pilot clinical trial, there will be no control or experimental cohort assignments and no blinding.

9.1 Data Collection and Management

9.1.1 Confidentiality of Data

All information that is collected for this research protocol will be kept confidential. All subjects will be assigned a unique study identification number (study ID). This study ID will be used on all case report forms (CRFs). The investigators will maintain a master list

separate from data forms that have only a study number. Only password-protected files will be used to store the data.

9.1.2 Security

A copy of the password-protected file will be kept in the investigator's office computer, with the original in one of the Hospital's secure servers.

9.1.3 Anonymization, de-identification or destruction

All data will be maintained the longer of either (A) 6 years after completion of the study or (B) 2 years after the last marketing approval or if no application is filed or approved, 2 years after the FDA is notified of discontinued application. The investigator maintains a file drawer specifically for such archives, each folder labeled "Destroy by....," with the earliest dates at the front. The CHOP PI will monitor and review the study progress and the accuracy and security of the emerging data.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigators and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards are described under Data Collection and Management.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.3 Regulatory and Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. Investigators will follow ICH guidelines as they pertain to this study.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form will be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

9.3.1 Data and Safety Monitoring Plan

The principal investigator will monitor study progress, ensure subject safety, and the accuracy and security of the data at CHOP, and will report any adverse events in accordance with the FDA regulations and IRB policies.

Prior to trial initiation, pre-trial visit will be completed by the Office of Research Compliance (ORC) to confirm trial readiness. After the first subject enrolls and completes the first investigational admission, the PI will contact ORC to arrange a monitoring visit. Thereafter, ORC will monitor the study annually. Monitoring activities will be guided by ICH E6 section 5.18. Interim monitoring activities will include a review of regulatory files as well as a percentage of enrolled subject records, source documents, applicable informed consent forms, and case report forms. The percentage of subject data review may be amended throughout the course of the study based on an ongoing risk assessment. A tapered approach to monitoring may be employed if conduct and documentation of the study reaches a level of reliability that would permit valid conclusions based upon a sampling of data.

During the experiment, CGMS data will be collected in various ways. CGMS data, calibration data, insulin dosing data, and glucagon dosing data will be automatically stored in the bionic pancreas device (from which it will be downloaded) and wirelessly streamed to the cloud where it will be stored to provide redundancy in data storage and mitigate the risk of data loss. During the control phase, CGMS data will be downloaded at intervals. All data will be combined in a single database that will be compared against the primary data files for integrity. The computer database will be backed up at least monthly and the backup media stored in a secure location.

The PI and the Bionic Pancreas team will be involved in education of the staff prior to the start of the protocol and will communicate with staff as required during the performance of the trial. Study staff will be encouraged to raise any concerns they may have or problems they have identified at any time. The PI will decide a course of corrective action, and resolution or progress will be assessed no later than the next meeting.

A numeric code will be substituted for the subjects personal identifying information in the study database, which will be password protected. The key linking the medical record number of the subject with the numeric code, along with case report forms, and all information that is personally identifiable, will be kept in a locked filing cabinet in an investigator's locked office. All electronic records will be kept in a password protected computer database. All printed computer data will be disposed of confidentially when no longer needed. Only the study staff will have access to the study database. Subjects may not withdraw from the de-identified database, but they may elect to have the key linking their medical record to the de-identified database destroyed.

Data/CRFs will be stored in OnCore Clinical Trials Management System, a CHOP Research IS secured electronic data capture system. OnCore Clinical Trials Management System is a secure electronic data capture system with access controls and a data backup plan. The system is password protected. Only study team members will have access to subject data and case report forms stored in OnCore. Access to the system is monitored and logged for review if needed.

The study data will be shared with collaborators from the Bionic Pancreas team, but only in a form in which all personally identifiable information has been removed (e.g. combined database including blood glucose values, record of insulin and glucagon delivered by the device, and blood insulin and glucagon levels). Shared data will be in the form of a database in which only a number identifies subjects.

Subjects may not withdraw their data, as it will be stored in non-personally identifiable form.

9.3.2 Safety Monitoring

An Independent Safety Officer with expertise in Diabetes and Clinical Trials will oversee the conduct of the study and review its results after 3 subjects have completed the study and again when all subjects complete the study. Additionally, the Safety Officer will be informed in the event of any severe or unexpected adverse events. The Safety Officer will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. Safety and efficacy data will also be reported to the FDA in compliance with applicable regulations.

The study will stop and discussion with the Safety Officer will be required to restart it if more than one subject experiences the same adverse event due to malfunction of the bionic pancreas system:

- Diabetic ketoacidosis requiring hospitalization
- Seizure or unconsciousness associated with hypoglycemia
- Persistent nausea and vomiting thought to be related to glucagon dosing.

If more than 3 subjects must be withdrawn from the study for these reasons, the study will stop and discussion with the Safety Officer will be required to restart it. All serious and unexpected events will be reported to the Safety Officer within 72 hours.

Note that subjects may discontinue participation at any time and subjects may be removed from the trial for other reasons, for instance failure to comply with study procedures or inter-current illness that is unrelated to the bionic pancreas but that precludes safe participation. Discontinuation of participation for these reasons will not contribute to a decision to discontinue the trial.

9.3.3 Risk Assessment

This study involves greater than minimal risk and limited prospect of direct benefit to the subject, but likely to yield generalizable knowledge about the condition. The interventions and procedures included in the study are commensurate with those experienced by individuals with this condition.

Subjects may experience mild discomfort associated with the insertion of the infusion sets and sensor into the subcutaneous tissues. In the bionic pancreas phase, the risk discomfort due to insertion of infusion sets and sensors is expected to be greater than in their lives

outside the trial because more infusion sets and sensors will be inserted. In the control phase, these risks are expected to be of the same nature and magnitude as during the subjects' lives outside of the trial.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Due to remote monitoring of severe biochemical hypoglycemia, the risk is expected to be reduced relative to during the subjects' lives outside the trial. In the bionic pancreas phase, this risk is expected to be further reduced relative to the risk during the subjects' lives outside of the trial based on data from earlier trials.

This study will take place in the inpatient setting; therefore subjects will not be engaging in any significant physical activity (aerobic or anaerobic) but will be allowed to ambulate within the hospital boundaries. Thus, the risk of exercise-induced hypoglycemia is minimal.

There is a risk of headache, nausea, or vomiting in subjects due to the administration of exogenous glucagon. There is a possible risk of skin rash due to administration of exogenous glucagon. The magnitude of other possible risks due to daily administration of small amounts of glucagon are unknown, but are not expected to be high because mean glucagon levels have been in the normal fasted range in previous trials and there have been no other adverse events in previous bionic pancreas trials lasting up to five days. Of note, the risk of nausea or vomiting has been extremely low in prior studies.

9.3.4 Potential Benefits of Trial Participation

Based on evidence from previous trials of the bionic pancreas and the design of this trial, subjects enrolled in the study may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a better mean glucose during the bionic pancreas admission. They may also benefit from a reduction in risk of severe hypoglycemia during the standard care admission due to monitoring for severe events. However, because of the short duration of this study, these potential benefits are minimal.

The data derived from this study will allow us to evaluate the robustness and effectiveness of the bionic pancreas control system. The data obtained may be used to further improve the bionic pancreas.

This study is a necessary step in the process of making the bionic pancreas available to people with hyperinsulinism and post-pancreatectomy diabetes. Wide availability of the bionic pancreas could improve the care of children and adults with hyperinsulinism and post-pancreatectomy diabetes.

9.3.5 Risk-Benefit Assessment

Overall, this study involves greater than minimal risk and limited prospect of direct benefit to the subject, but it is likely to yield generalizable knowledge that would benefit individuals with hyperinsulinism and post-pancreatectomy diabetes. This study is a necessary step in the process of making the bionic pancreas available to people with hyperinsulinism and post-pancreatectomy diabetes. Because of the difficulties in the management of diabetes in individuals with hyperinsulinism and post-pancreatectomy diabetes, the prospect of having access to a treatment paradigm that will improve glycemic control and reduce the risk of hypoglycemia, makes the risk-benefit favorable and justifies this trial.

9.4 Recruitment Strategy

Subjects will be recruited from the Congenital Hyperinsulinism Center at The Children's Hospital of Philadelphia, the largest center in this country caring for children with disorders of insulin regulation. Every year our center treats approximately 30 children with medically unresponsive hyperinsulinism that require pancreatectomy. Currently we have approximately 1200 in-patient days a year. Additionally, we follow many of our patients in the outpatient setting which entails managing the patients' post-pancreatectomy diabetes. This put us in a unique position to conduct research directed to develop new therapies for this disorder.

9.5 Informed Consent/Assent and HIPAA Authorization

A written Institutional Review Board (IRB)-approved informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization must be obtained from each subject, and legally authorized representative (LAR) if applicable, before any study related activities are conducted. The Investigator must retain all original signed and dated ICFs (together with any subsequent IRB-approved amended versions) in the subject's file. A copy of the signed and dated ICF (and any amendments) must be given to the subject and LAR.

The ICF documents the study-specific information the Investigator provides to the subject and subjects LAR and the subject's and subjects LAR's agreement to participate. Among other things, the Investigator or his/her designee will fully explain in layman's terms the nature of the study, along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. Potential participants will be allowed time to review the study procedures prior to consenting. Any questions the potential participants and/or LARs have regarding the study will be answered by the Investigator or a designated study staff member.

Subjects and LAR will be informed of findings from earlier or concurrent bihormonal bionic pancreas clinical studies (including AEs and SAEs), if it is considered that such information could potentially affect subject's willingness to participate or continue in the study. Depending on the nature, severity, and seriousness of these AEs and/or SAEs, the ICF may be amended as deemed appropriate. The original and any amended signed and dated ICF(s) and subject information sheet(s) must be retained in the subject's file at the study site; and a copy must be given to the subject and subject's LAR.

If applicable, separate pediatric assent documents required by the IRB will be implemented per the same process detailed above.

The informed consent form and subject information sheet will be appropriately signed and dated before the subject enters the study.

9.6 Payment to Subjects/Families

9.6.1 Reimbursement for travel, parking and meals

Many of the subjects that will be recruited for this study live outside the tri-state area. Therefore, these subjects will be offered reimbursement for travel expenses depending on

distance up to a maximum of \$2,000 for the whole study. Whenever possible the air/train travel for participants will be booked and pre-paid by study staff. If a subject books his/her own travel, they will receive reimbursement for travel at the end of their participation. If for some reason, the subject cannot complete the study at the time of study visit, they will still receive the travel reimbursement. This reimbursement will be in the form of a check. If a subject is under the age of 18, the compensation will be paid to the parent or legal guardian of the subject.

9.6.2 Payments to subject and parent for time and inconvenience (i.e. compensation)

This study requires that subjects and their family must take time out of their schedules in order to participate. For Subjects under 18 years of age, a time and inconvenience compensation of \$25/scheduled day of admission (maximum \$200) will be given to the subject and a compensation of \$50/scheduled day of admission (maximum \$400) will be given to the parent or legal guardian. If subjects under 18 years and their parents remain admitted to the hospital after the study procedures are complete as a means for the PI to monitor the subject on his/her home regime, subjects and their parent will receive \$25 and \$75, respectively, for each additional day up to 3 days (maximum \$300 total).

Subjects 18 years of age or older will receive a time and inconvenience compensation of \$75/scheduled day of admission (maximum \$600). If these adult subjects remain admitted to the hospital after the study procedures are complete as a means for the PI to monitor the subject on his/her home regime, subjects will receive \$100 for each additional day up to 3 days (maximum \$300 total).

Subjects/parents or legal guardians will receive this compensation only once (even if they must return to CHOP for further testing) at the completion of the study. If for some reason, the subject cannot complete the study at the time of study visit, they will still receive the time and inconvenience compensation. This compensation will be in the form of a pre-paid bank card.

9.6.3 Gifts

Gifts will not be distributed to research subjects nor their parents/legal guardians.

10 SPONSORSHIP AND FUNDING

The BP system will be provided by Edward Damiano, Ph.D. and, per the requirements of The Children's Hospital of Philadelphia's IRB, Dr. Damiano is listed as a Funder for this study. As Dr. Damiano's group also holds the FDA's Investigational Device Exemption, he is also listed as the Sponsor of the study. Dr. Damiano nor his group will be providing financial support for this study beyond that of providing the BP devices and requisite training to the CHOP study staff.

Zealand Pharma A/S will be providing financial support for this study.

11 PUBLICATION

The investigators intend to present the results at national conferences and to publish the results in peer-reviewed medical journals.

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