The iLet Introduction Study: A feasibility study of the iLet, a fully integrated bihormonal bionic pancreas

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I. Background and Significance

I. a. Background and Rationale

Maintaining near-normal blood glucose (BG) levels (70--120 mg/dl) is a challenging and critically important task for people with type 1 diabetes (T1D). The Diabetes Control and Complications Trial (DCCT) Research Group definitively demonstrated that tight BG control can reduce long-term complications (1, 2). The likelihood and severity of nephropathy, retinopathy, neuropathy, macrovascular disease, and skin disorders is reduced in proportion to reductions in glycated hemoglobin (HbA1c), which is closely correlated with long-term average BG levels. Risks for such complications are elevated by three- to five-fold with diabetes. On the other hand, tight BG control through conventional intensive insulin therapy increases the likelihood of episodic hypoglycemia, which carries acute risks, including convulsions, seizures, coma, and death. Conventional therapy also requires a relentless daily effort to count carbohydrates, frequently monitor BG throughout the day and night, and administer a daily insulin regimen.

A more reliable method for achieving consistent BG control consists of an integrated artificial or bionic pancreas (BP) system, consisting of a continuous glucose monitor (CGM), an infusion pump, and a control algorithm that actuates the pump based on CGM glucose data. Such a system can automate and ease the burden of T1D management and vastly improve glycemic control relative to the current standard of care.

I. b. Bi-hormonal Bionic Pancreas System

We 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 T1D. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

Our 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. We 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 MPC 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 MPC 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 of the insulin-only control algorithms of which we are aware, the adaptive basal insulin algorithm obviates the need for 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). Our adaptive meal dose controller obviates the need for 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. Our 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.

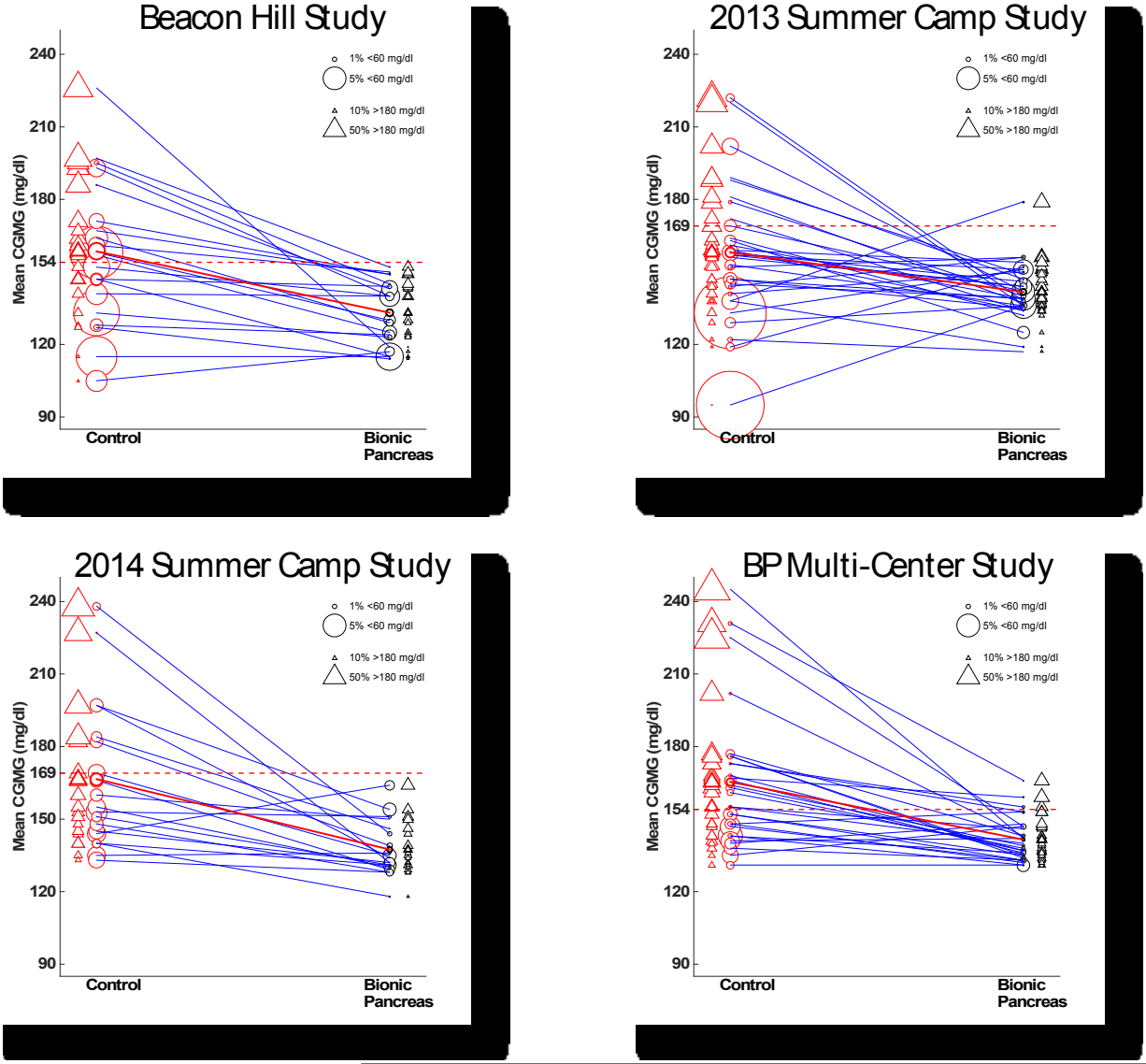
Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet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

able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM 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 CGM 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 T1D that comprehensively manages glycemia across a broad range of individual needs and a across a large spectrum of circumstances and challenges to glycemic control.

I. c. Preliminary Studies

Our BP hardware platform has evolved over the years from a laptop-driven system, which we used in all of our inpatient studies (between 2008--2012), to the first truly mobile wearable iPhone-driven platform, which we have used in all of our outpatient studies thus far (between 2013--2015). Using the iPhone-driven BP system, we 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 BU testing the BP in a diabetic swine model of T1D (3-4), and all of the inpatient clinical trials in the Clinical Research Center at MGH testing the BP in adults and adolescents with T1D (5-7) set the stage for the outpatient studies that followed. In November 2012 we obtained FDA approval to conduct our first outpatient study testing our 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 CGM 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 1 (8). Results are summarized in the plots and table of Figure 1.



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <60 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <60 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	*p*-value (BP versus Control) for: Mean CGM glucose level	*p*-value (BP versus Control) for: % of CGM glucose values <60 mg/dl	*p*-value (BP versus Control) for: % of CGM glucose values 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=39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

Figure 1. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the BP and control arms. Mean CGM glucose levels for each subject under usual care (shown as a red circle on the left) is connected with the subject's mean CGM 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 CGM glucose values < 60 mg/dl, and the size of the triangle is proportional to the percentage of CGM 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 CGM glucose level and percentage of CGM glucose values < 60 mg/dl) for the BP are highlighted in red for each of the four studies.

In April 2013, we obtained FDA approval to conduct our 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 CGM 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. Results are summarized in the plots and table of Figure 1 (8). In April 2014 we obtained FDA approval to conduct our 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 (9).

In April 2014, we obtained FDA approval to conduct our first multi-center study, which was also our 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 (BPMC) 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. Results are summarized in the plots and table of Figure 1.

I. d. Rationale and Potential Benefits

Our experiments to date in human subjects with type 1 diabetes 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. Despite current technical limitations of the pump and CGM components, we have shown that a bi-hormonal bionic endocrine pancreas is capable of achieving good BG control automatically with minimal hypoglycemia during eleven continuous days in the face of unrestrained meals and exercise and with trivial patient input (optional announcement of meals).

The bionic pancreas BG control system we have developed is able to provide automatic BG regulation and reduce hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG 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 type 1 diabetes.

Our current bionic pancreas system utilizes an iPhone running the control algorithm and Dexcom G4 CGM combined in a customized control unit, which then communicates via Bluetooth to two tandem t:slim insulin pumps. Naturally, connection is lost between these four devices at multiple times throughout the day, which has the potential to impact blood glucose control due to missing CGM values or missed doses. In addition, the troubleshooting required to repair these connections can be a burden on the wearer. Integrating these parts into one combined device would eliminate the need to maintain constant connections, optimizing blood glucose control, ease of use and quality of life.

We have designed, built, and tested our first-generation working prototype BP system, which we refer to as the iLet, and which consists of a dual-chamber autonomous infusion pump integrated with a CGM receiver and printed circuits that run the control algorithm. The current study is designed to test the iLet BP in human subjects for the first time in comparison with our iPhone-based system to establish equivalence between the two systems (primarily in terms of functionality, user safety, accuracy, and component reliability), and allow us to move forward with larger studies using the iLet BP (where comprehensive efficacy through continuous full daily use will be established).

The iLet BP is capable of using a new formulation of glucagon that is non-aqueous and is much more stable. This formulation, produced by Xeris pharmaceuticals, is stable for at least 2 years at room temperature. However, this formulation is not compatible with plastics used in the Tandem t:slim pump and standard infusion sets. The iLet BP and its new infusion set have been designed to be fully compatible with the Xeris glucagon formulation.

A custom infusion set is required for this bihormonal system, to prevent future consumers from being able to accidentally swap their insulin and glucagon reservoirs and infusion sets, which could be potentially fatal. Previous experiments have demonstrated flaws in the infusion set design, requiring human experiments to be suspended and modifications to the infusion set be made. We believe the current infusion set has addressed

these flaws by incorporating an anti-coring heel and a tri-beveled needle, and this sub-study is designed to isolate and study the infusion set function before further experiments using the iLet BP are conducted.

II. Hypothesis and Specific Aims

We hypothesize that the iLet BP will be non-inferior to the iPhone-based BP in dose administration and blood glucose control while subsequently improving user satisfaction with the device. We also hypothesize that Xeris glucagon in the iLet BP will be non-inferior to Lilly glucagon in the iLet BP in both infusion site reactions and occlusions.

In the Infusion Set Sub-Study, we hypothesize that the iLet infusion set will be non-inferior to the Contact Detach infusion set in plasma insulin levels, blood glucose control, and user experience.

The specific aims of this study are:

Aim 1. To conduct an outpatient study testing the safety and efficacy of the iLet BP versus our iPhone-based BP in up to 10 adult (≥ 18 years of age) subjects with type 1 diabetes in the fasted state, after a meal, and during and after exercise.

The study for this Aim will consist of two 8-hour study arms in random order: one with the iPhone-based BP and one with the iLet BP. Subjects will arrive fasting and remain fasted until the lunch meal. They will exercise on a stationary bike bpm for approximately 30 minutes with a heart rate from 120–140, starting at least 2 hours after lunch. The primary outcome will be the average percent dose amounts of both insulin and glucagon calculated by the control algorithm that are successfully delivered by the pump. Important secondary outcomes will include other metrics of device function (plasma insulin and glucagon levels will be measured every 30 minutes throughout the experiment) and measures of glycemic regulation, including mean CGM glucose and hypoglycemia exposure (% time <60 mg/dl).

Aim 2. To conduct an outpatient study testing the safety and efficacy of the iLet BP with Lilly glucagon versus Xeris glucagon in up to 10 adult (≥ 18 years of age) subjects with type 1 diabetes

To achieve this second Aim we will conduct an additional, third 8-hour study arm with the iLet BP using Xeris glucagon, which will be compared to the 8-hour study arm with the iLet BP using Lilly glucagon. The data from Aim 1 will be analyzed prior to initiation of the Aim 2 visit. If the performance of the iLet BP in the studies of Aim 1 visits is as expected, we will proceed to the visits of Aim 2. Subjects will arrive fasting and remain fasted until the lunch meal. They will exercise on a stationary bike bpm for approximately 30 minutes with a heart rate from 120–140, starting at least 2 hours after lunch. The primary outcome will be the average percent of glucagon calculated by the control algorithm that is successfully delivered by the pump. Important secondary outcomes will include infusion site reactions at the glucagon site, subject reported nausea, glucagon exposure (plasma insulin and glucagon levels will be measured every 30 minutes throughout the experiment), and measures of glycemic regulation, including mean CGM glucose and hypoglycemia exposure (% time <60 mg/dl).

Aim 3. To document the satisfaction of subjects with the iLet BP device with the goal of optimizing user interaction with the iLet.

Questionnaires will be administered at the beginning of the study and at the end of each arm to gather data on attitudes towards bionic pancreas usability, BG control, quality of life and treatment satisfaction. The primary analysis will include data from the first 2 arms (iPhone BP and iLet BP with Lilly glucagon) so that the analysis will be focused entirely on the performance of the BP platform and not the glucagon. A structured phone interview will be conducted with each participant after they have completed all of the visits to compare their experiences. This information will be used to make the best choices about how the final version of the bionic pancreas should be configured.

Aim 4. To conduct an in-clinic study comparing the performance of an investigational infusion set designed for use with the iLet Bionic Pancreas versus an FDA approved infusion set in up to 10 adult subjects with type 1 diabetes in both the fasted and post-prandial states.

This sub-study is designed to isolate the performance of the modified iLet infusion set, and is a necessary step towards continuing human experiments using the iLet Bionic Pancreas. The study will consist of two 5-hour study visits in random order: one with an FDA approved 6 mm steel cannula (Contact Detach) luer-lock compatible infusion set and one with the investigational steel cannula luer-lock compatible infusion set developed for use with the iLet Bionic Pancreas.

III. Subject Selection

III. a. Inclusion Criteria

- Age ≥ 18 years and have had clinical type 1 diabetes for at least one year
- Diabetes managed using an insulin pump for ≥ 6 months
- 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 principal investigator)
- Infusion Set Sub-Study:
    - Age ≥ 18 years
    - Type 1 diabetes for at least one year
    - Diabetes managed using an insulin pump

No subjects will be excluded on the basis of 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.

III. b. Exclusion Criteria

- Unable to provide informed consent (e.g. impaired cognition or judgment)
- Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory, unable to speak and read English)
- Current participation in another diabetes-related clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the subject
- Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the immediate future, or sexually active without use of contraception
- Current alcohol abuse (intake averaging > 3 drinks daily in last 30 days), use of marijuana within 1 month of enrollment, or other substance abuse (use within the last 6 months of controlled substances other than marijuana without a prescription)
- Unwilling or unable to refrain on the study days from:
    - acetaminophen in any form
    - use of marijuana
    - use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study (use of beta blockers will be allowed as long as the dose is stable and the subject does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator)
- History of liver disease that is expected to interfere with the anti-hypoglycemia action of glucagon (e.g. liver failure or cirrhosis). Other liver disease (i.e. active hepatitis, steatosis, active biliary disease, any tumor of the liver, hemochromatosis, glycogen storage disease) may exclude the subject if it causes significant compromise to liver function or may do so in an unpredictable fashion.
- Renal failure on dialysis
- Personal history of cystic fibrosis, pancreatitis, pancreatic tumor, or any other pancreatic disease besides type 1 diabetes
- Any known history of coronary artery disease including, but not limited to, history of myocardial

infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)

- Congestive heart failure (established history of CHF, lower extremity edema, paroxysmal nocturnal dyspnea, or orthopnea)
- History of TIA or stroke
- Seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants
- History of hypoglycemic seizures (grand-mal) or coma in the last year
- History of pheochromocytoma: fractionated metanephrines will be tested in patients with history increasing the risk for a catecholamine secreting tumor:
    - Episodic or treatment refractory (requiring 4 or more medications to achieve normotension) hypertension
    - Paroxysms of tachycardia, pallor, or headache
    - Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
- History of adrenal disease or tumor
- Hypertension with systolic BP ≥160 mm Hg or diastolic BP ≥100 despite treatment
- Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation.
- Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference
- History of adverse reaction to glucagon (including allergy) besides nausea and vomiting
- History of severe milk allergy
- Established history of allergy or severe reaction to adhesive or tape that must be used in the study
- Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) anti-diabetic medications
- Use of parenteral diabetes medications other than insulin (e.g. amylin mimetics or GLP-1 receptor agonists)
- Chronic use of drugs with strong anticholinergic actions, including over-the-counter products (intermittent use is allowed as long as the drug is not taken on the day of experiments)
- Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study
- Hemoglobin <12 g/dl
- Any subjects who develops an exclusionary condition during the study will be withdrawn
- Infusion Set Sub-Study:
    - Unable to provide informed consent (e.g. impaired cognition or judgment)
    - Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of their insulin pump, impaired memory, unable to speak and read English)
    - Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the immediate future, or sexually active without use of contraception
    - Hemoglobin < 11 g/dl
    - Unable to establish IV access, or subject reports difficult IV access in the past

History of allergy or severe reaction to adhesive or tape that must be used in the study

III. c. Source of Subjects

Volunteers who fit the selection criteria will be considered as candidates for this study. We will contact individuals who have previously inquired about participation in our studies and have asked us to have their contact information kept on file. In addition, advertisements for the study may be posted at the MGH Diabetes Center and other places, and may be distributed in the weekly broadcast email of research studies seeking volunteers. A letter may be sent to adult endocrinologists in the Boston metropolitan as well as selected nearby endocrinologists informing them of the study and asking them to refer any eligible patients who might be interested. We will post information about the trial along with contact information on our website

www.bionicpancreas.org and on www.clinicaltrials.gov.

IV. Subject Enrollment

IV. a. Number of Subjects

It is expected that we will have up to 10 subjects complete the study with a consistent protocol. We expect that the experiments can be accomplished over a period of 6 months. Up to 20 subjects with type 1 diabetes will be enrolled. The upper bound is based on the expectation that some volunteers will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or subject withdrawal).

It is expected that we will have up to 10 subjects complete the Infusion Set Sub-Study with a consistent protocol. We expect that the experiments can be accomplished over a period of 6 months. Up to 20 subjects with type 1 diabetes will be enrolled. The upper bound is based on the expectation that some volunteers will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or subject withdrawal).

The total enrollment for the study, including the infusion set sub study will be up to 40 subjects.

IV. b. Enrollment Procedures

Prospective participants will be briefed by a study staff member by phone or secured e-mail (using the “Send Secure” encryption) regarding the study procedure and the inclusion and exclusion criteria. Potential subjects will be sent an informed consent document by mail, fax, or secured e-mail. Subjects will be discouraged from discussing medical issues by non-secure e-mail, according to institutional policy.

IV. c. Consent Procedures

Once potential subjects have had time to review the consent document, they will meet with a study MD that will explain the study, answer any questions, and administer informed consent. In the event that a volunteer is a patient of one of the study MDs, another staff MD will answer questions and administer consent.

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 may choose to discontinue their participation at any time.

V. Study Procedures

V. a. Screening data

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female volunteers
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- 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)
- Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Height and weight
- Blood pressure
- Urine HCG (pre-menopausal females)
- Hemoglobin A1c

- Fractionated plasma metanephrines (if testing is indicated by history)
- Hemoglobin
- Infusion Set Sub-Study:
    - Age
    - Sex
    - Race and ethnicity
    - Date of last menstrual period in female volunteers
    - Date of diabetes diagnosis
    - Medical, surgical and social history, allergies and review of systems relevant to inclusion and exclusion criteria
    - Medications (prescription and non prescription)
    - Type of insulin used in pump
    - Average total daily dose in the last 30 days (from pump history)
    - Height and weight
    - Blood pressure
    - Urine HCG (pre-menopausal females)
    - Hemoglobin
    - Hemoglobin a1c

V. b. Drugs

The study involves subcutaneous administration of *insulin lispro (Humalog, Lilly)*, which is commercially available by prescription and is indicated for patients with type 1 diabetes, but not for use in a bionic pancreas.

The study also involves subcutaneous administration of *Lilly glucagon.* Lilly glucagon is commercially available by prescription and is indicated for patients with type 1 diabetes in severe hypoglycemia, but not for use in a bionic pancreas.

The study also involves subcutaneous administration of *Xeris glucagon*. Xeris glucagon has the same active pharmaceutical ingredient as Lilly glucagon, but is dissolved in a different vehicle at a higher concentration. Xeris glucagon in dissolved in a non-aqueous solvent that is composed primarily of dimethyl sulfoxide (DMSO) at a concentration of 5 mg/ml, while Lilly glucagon is dissolved in an aqueous vehicle at a concentration of 1 mg/ml. DMSO is listed by the FDA as an inert ingredient and is a component of several approved drug formulations. Xeris glucagon is stable at room temperature for two years (see the Investigator Brochure in Appendix A). The age of the Xeris glucagon at the time of administration will depend on when the experiments are done, but we will complete all of them within the already determined window of stability.

Xeris has performed pre-clinical toxicology study up to 28 days in length in rats, and found the No-observed-adverse-effect-level (NOAEL) to be 1 mg/kg/day in both male and female rats. In our studies, we expect to deliver less than 0.33 mg/day to our subjects (over 8 hours), which is greater than 240-fold below the NOAEL in an 80 kg subject. Therefore, we are confident that one day of administration will safe in human subjects for a one day study.

Human studies with Xeris glucagon have included phase 1 through phase 3 studies intended to support the use of Xeris glucagon for the emergency treatment of severe hypoglycemia. The most commonly reported AE with Xeris glucagon was pain at the injection site, and this occurred more often than with the comparator (Lilly glucagon). However, edema and erythema occurred infrequently and were not different between Xeris glucagon and Lilly glucagon. This study involved administration of 0.5 mg or 1 mg of Xeris or Lilly glucagon as a single injection.

Other studies have provided information on infusion site reactions when delivering smaller quantities of Xeris glucagon as a single injections. In one study study, 0.075 mg of Xeris glucagon was delivered as a single injection, with no comparator arm. In that study, a burning sensation at the injection site was the most common reaction, occurring in 58% of subjects and numbness at the injection site occurred in 17% of subjects. There were no instances of well defined erythema in any subjects (n=12) administered this dose. In another study, small doses of Xeris glucagon or Novo glucagon (0.3, 1.2, and 2.0 mcg/kg) were administered as a single injection using an Omnipod patch pump. In this study, infusion site erythema and edema were the most common

AEs, and these occurred more commonly with Xeris than Novo glucagon (47% vs. 11% and 32% vs. 6%, respectively). Most cases were mild and transient for both formulations.

The bionic pancreas administers a maximum 0.08 mg per injection, and does this rarely. More typical doses of glucagon are in the range of 0.005-0.04 mg per dose. We do not have data on the tolerability of doses in this size range, nor on intermittent dosing at a single site, as will occur in this study. The incidence of other AEs with Xeris glucgaon in human studies were low and were not different between Xeris and Lilly glucagon.

Both the iPhone-based and iLet bionic pancreas systems could administer isolated insulin–glucagon doses once every 5 minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 µl of U-100 insulin] in both systems, and a single meal-priming dose, in response to a meal announcement made by the user, will not exceed 12 units [120 µl of U-100 insulin]. A single bolus of glucagon will not exceed 80 µg [80 µl of 1 mg/ml Lilly glucagon, 16 µl of 5 mg/ml Xeris glucagon]. The t:slim insulin pumps used in the iPhone-based bionic pancreas are capable of administering as little as 0.5 µl (0.05 units of U-100 insulin or 0.5 µg of 1 mg/ml Lilly glucagon) in single programmable bolus doses. The iLet bionic pancreas is capable of administering as little as 0.11 µl (0.011 units of U-100 insulin or 0.55 µg of 5 mg/ml Xeris glucagon).

It is expected that the mean total daily dose of glucagon will be <1.0 mg daily as in previous studies. The mean daily glucagon dose in our previous 11 day outpatient study was 0.51 mg/day (range 0.20-0.90 mg/day). The recommended dose of glucagon for adult patients suffering from severe hypoglycemia is 1 mg as a single injection. Mean glucagon levels in our 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. We expect that glucagon exposure will be the same on both bionic pancreas models.

V. c. Devices

V.c.1. iPhone-based Bionic Pancreas

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 provided. Note that components of the standard infusion sets are not compatible with DMSO, and therefore this pump cannot be used to pump Xeris glucagon.

Continuous glucose monitors: One transcutaneous glucose sensor for the DexCom G4 Platinum (10) will be inserted in the subcutaneous tissue 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 G4 receiver. If the G4 sensor fails for any reason during the experiment it will be replaced promptly.

Bionic Pancreas Control Unit: The control unit consists of a stock iPhone 4S and a DexCom G4 Platinum receiver connected with a custom hardware interface and placed back-to-back in a custom enclosure. The G4 receiver converts the raw wireless signal from the transmitter into an estimated BG signal that is sent via a hardwired connection to the iPhone.

The iPhone runs iOS 6 in “Guided Access” mode, where the only app accessible to the subject is the Beta Bionics app, which runs the control algorithm. The home screen, where typical user options reside, is password protected. Access to other functions on the iPhone (primarily the Settings options) is separately password protected and only accessible to the study staff. This prevents accidental activation of other apps that could interfere with the function of the bionic pancreas. The control algorithm app has a graphical user interface (GUI) that displays the current CGM glucose, a graphical history of the 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 course of the trial to meet a target of 75% of the insulin needs for that size and type of meal.

The target glucose level will be programmed to 100 mg/dl by the study engineers prior to the start of each experiment. This will be locked for each arm of the study; the subject will be unable to accidentally change or tamper with this setting.

The GUI can be used to manage meal boluses and correction boluses during periods when the 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 based on the subject's weight. The controller will also administer insulin and/or glucagon as appropriate in response to any entered BG values, just as if they were CGM values.

The GUI also displays visual alarms associated with an audio signal if communication is dropped between the CGM transmitter and the bionic pancreas control unit or between the control unit and the two insulin pumps.

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

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 BTLE protocol by the iPhone 4S. Note that components of the t:slim pump are not compatible with DMSO, and therefore this pump cannot be used to pump Xeris glucagon.

V.c.2. iLet Bionic Pancreas

Infusion set: A novel, dual cannula infusion set has been designed specifically for use with the iLet, and is compatible with DMSO, which is present in the Xeris glucagon formulation. Subjects will wear dual channel tubing that will be attached to a single dual-cannula infusion set with two steel cannulae, one for insulin infusion and the other for glucagon infusion. Subjects will wear two (one for insulin, one for glucagon) of these infusion sets, each with only one steel cannula.The entire fluid path, including tubing and infusion set, will be compatible with the DMSO in the Xeris glucagon formulation. They are also compatible with all aqueous insulin and glucagon formulations, including insulin lispro (Humalog) and Lilly glucagon. The tubing and infusion sets will have undergone sterilization prior to being delivered in a sealed pouch.

Continuous glucose monitors: One transcutaneous glucose sensor for the DexCom G4 Platinum (10) will be inserted in the subcutaneous tissue 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 bionic pancreas. If the G4 sensor fails for any reason during the experiment it will be replaced promptly.

Bionic Pancreas Control Unit: The iLet is being built according to Class III medical device standards, adheres to a comprehensive and robust quality system, and is fully compliant with ISO 13485 standards and document control practices. The iLet is a fully-integrated dual-hormone BP system that integrates the CGM technology (currently the Dexcom G4 Share system) as well as two independent motor–drivetrain pumping assemblies, which independently actuate the delivery of insulin and glucagon from pre-filled cartridges that are separately loaded into the iLet housing. Each drivetrain assembly utilizes a lead screw, which is driven by a precision micromotor, a gear case assembly, and a motor controller unit, in a manner similar to what is commonly found in most insulin infusion pumps on the market today. The iLet has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market. The iLet has a built-in Bluetooth Low Energy (BTLE) radio also allows automatic communication with the paired CGM, as well as the Nova StatStrip Xpress blood-glucose (BG) meter (Nova Biomedical). The iLet does not contain a cellular nor a WiFi radio, and does not accept input data from another mobile device (e.g. smartphone), other than the paired CGM and BG meter(s).

Our mathematical control algorithms (which are the same as those used in the iPhone-based Bionic Pancreas), the CGM glucose engine (DexCom), and the native user interface (UI) software, are all interconnected through controller framework software and reside as embedded systems on printed circuit boards contained within the device housing. Our touchscreen-enabled, menu-driven UI and onboard processor provide a comprehensive and standalone platform, which allows the iLet to operate independently of smartphones or other devices and without the need for internet support during routine operation. The GUI of the iLet BP has the same user options and capabilities of the iPhone BP, including having its home screen password protected and its settings options only accessible to study staff via a separate password.

V.c.3. Other study devices

Nova Biomedical StatStrip Xpress Glucose Meter: The StatStrip Xpress glucose meter is an FDA approved glucose meter that is commercially available. Blood glucose measurements for CGM calibration will be obtained

via fingerstick with the StatStrip Xpress in all study arms if the IV and/or YSI fail.

Yellow Springs Instrument (YSI) 2300 STAT PLUS: The YSI Model 2300 STAT PLUS Glucose and Lactate Analyzer is a laboratory instrument that is intended for use in clinical care. It provides quick measurements of glucose in whole blood, plasma or serum and will be used as to measure plasma glucose during the visit. This device will be stored at the Diabetes Research Center when not in use, and study staff will follow proper maintenance and quality assurance procedures.

Exercise bike: the study will utilize a stationary exercise bike (ergometer) for the exercise portion of the visit. This bike will be stored at the Diabetes Research Center when not in use.

V.c.4. Infusion Set Sub-Study devices:
The Infusion set sub-study will use the following devices:

Infusion sets: The Infusion Set Sub-Study will use two different infusion sets. One will be the FDA approved Contact Detach, which is leur-lock compatible and uses a 29 gauge 6 mm steel cannula. This will be compared with the leur-lock compatible infusion set designed for use with the iLet Bionic Pancreas, that also uses a 29 gauge 6 mm steel cannula.

Insulin pump: subjects will wear their own leur-lock compatible insulin pump, or will be switched to a study provided leur-lock compatible infusion pump for the duration of the experiment.

Yellow Springs Instrument (YSI) 2300 STAT PLUS: The YSI Model 2300 STAT PLUS Glucose and Lactate Analyzer is a laboratory instrument that is intended for use in clinical care. It provides quick measurements of glucose in whole blood, plasma or serum and will be used as to measure plasma glucose during the visit. This device will be stored at the Diabetes Research Center when not in use, and study staff will follow proper maintenance and quality assurance procedures.

V. d. Experimental Procedures and Data Collection

V. d. 1. Screening Visit

- 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.
- A urine pregnancy test will be performed in female volunteers. If the test is positive the volunteer will be informed of the result and the visit will be ended.
- Height, weight and blood pressure will be measured.
- Blood will be drawn for hemoglobin A1c. Plasma fractionated metanephrines may be obtained if indicated by history.
- Once all of the results have been returned, a study MD will review the case report form to determine subject eligibility. If subjects are not eligible to continue in the study the results of abnormal tests will be reported to the subjects and to a health care provider of their choosing.
- Subjects who have been screened and are eligible can participate without having to be re-screened for a period of one year. The study staff should verbally confirm that there have been no health events that would make them ineligible if the interval between screening and participation is longer than 3 months.
- Subjects who participated in Aim 1 and/or Aim 2 will be eligible to participate in Aim 4, but will have to be rescreened if it has been more than 1 year.

V. d. 2. Visit Order: Once the subject has been enrolled and eligibility of subjects has been established, the order of the visits using Lilly glucagon with the iPhone based system and the iLet system will be randomized in blocks of two subjects. The experiments of Aim 2 (iLet BP with Xeris glucagon) will be performed after the first two visits.

The order of the visits for the Infusion Set Sub-Study of Aim 4 will be randomized in blocks of two subjects, separately from the visits for Aim 1 and Aim 2.

V. d. 3. Training Visit: A training visit will take place before the first bionic pancreas visit. Subjects will be

trained in the insertion and calibration of the Dexcom G4 sensor, insertion of infusion sets, use of the two bionic pancreas systems and study policies and procedures. Study staff will verify that the subjects have understood the material and are competent to participate safely in the study.

A training visits is not required for the Infusion Set Sub-Study.

V. d. 4. Bionic Pancreas Visits

- Up to 2 subjects may participate at the same time.
- Each subject will participate in the bionic pancreas visit three times: once with the iPhone-based BP, once with the iLet BP using Lilly glucagon and once with the iLet BP using Xeris glucagon.
- The night before the visit, subjects will place a Dexcom G4 CGM sensor that is provided by the study team, and calibrate the sensor when prompted using the provided Nova Biomedical Statstrip Xpress meter. Subjects will be instructed to call if they encounter any difficulty with their CGM.
- We will tell subjects, both verbally and through an email that we will send them on the eve of their participation, that they are expected to take carbohydrates if needed to treat hypoglycemia, or indeed to avoid impending hypoglycemia, even if they are fasting. Furthermore, we will tell them that if they anticipate problems in the period between the time that they wake up and the time that they will arrive at the Diabetes Research Center for the start of the experiment, that they are encouraged to set a lower temporary basal rate on their pumps.
- We will remind subjects, both verbally and through an email that we will send them on the eve of their participation, that they are expected bring all of their diabetes management supplies that would normally use to manage their diabetes, including their own insulin pump, a vial of the specific insulin analog they use, a spare reservoir, at least two spare infusion sets, a glucometer, glucose strips, lancets, glucose tabs/juice, and a continuous glucose monitor if they have one. These supplies will in any case be needed at the end of the study period for re-initiation of their own pump therapy before they leave the Diabetes Research Center.
- If a subject arrives on the morning of a visit with a BG of >300 mg/dl, the experiment will not be initiated on that day and will be rescheduled. A study physician will evaluate the subject, provide assistance to the subject in bringing their BG back towards the target range, and make sure that they are medically safe before they leave.
- If the participating subject is hypoglycemic at any time after arrival, they will be treated with oral carbohydrates (15 g every 15 minutes until their BG is >70 mg/dl), and the study will start as normal.
- In the case of severe hypoglycemia that occurs before the study start, the experiment with not be initiated, and the principle investigator will determine whether the study visit should be re-scheduled or whether the participation of the subject should be ended. The subjects own physician will be informed of any severe hypoglycemic event.
- Subjects will be responsible for their own medications other than insulin during the experiment. Any medical advice needed by the subjects during their participation that is not directly related to BG control should be obtained from them in their usual manner. The trial is an outpatient trial that will be facilitated by their proximity to MGH but they will not be admitted to MGH for the experiment and will not be under the care of MGH physicians except as specifically pertinent to study procedures. Subjects may take over-the-counter medications that they wish during the trial, with the exception of any medication containing acetaminophen as that may cause interference with CGM sensing. If the subject develops an illness during the experiment and their own physician is not at MGH, they will have the option of going to the MGH Walk-in Clinic or a non-study associated MGH physician who may agree to see them. As long as the subject is not hospitalized, the study can be continued.
- During the experiment, subjects will not use any recreational drugs or drugs of abuse. The need to take prescription drugs that dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder appropriate decision-making may be grounds for exclusion from the trial or discontinuation of participation, a decision that will be made by the principal investigator.
- Subjects will not tamper with the bionic pancreas, including changing any settings
- Subjects may not remove the bionic pancreas during the experiment unless the bionic pancreas failed or they are withdrawing from the experiment.

Visit Procedures:

- Subjects will arrive at the visit having fasted since 12:00 AM the night before. They will be asked to

arrive at least 1 hour before starting the bionic pancreas. Upon arrival to the visit, the body weight and blood pressure of the subject will be documented.

- A urine pregnancy test will be performed in female volunteers. If the test is positive the volunteer will be informed of the result and the visit will be ended. The date of the last menstrual period will also be documented, along with usual cycle length, for female subjects.
- Study staff will review any changes in medical history or medications since the last study visit, and obtain an updated medication list.
- A 20 gauge or smaller peripheral I.V. will be placed.
- Study staff will assist the subject to calibrate their CGM, review the study procedures again and assist with the set up of the bionic pancreas system, including inserting and priming infusion sets.
- The control algorithm will be initialized only with the subject's weight. Diagnostics will be performed to ensure that the CGM device is appropriately calibrated and that all of the components of the bionic pancreas systems are in working order.
- The subject's own insulin infusion pump will be stopped and disconnected
- 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 or at 9:00 AM. The starting time will be considered Hour 0.
- Plasma BGs will be taken off of the IV and measured using the YSI every 15 minutes. Study staff will perform any additional BG check for symptoms of hypoglycemia. There are no restrictions on additional checks.
- The insulin and glucagon infusion sites will be assessed by study staff every 15 minutes for the presence of any moisture and evidence of displacement of the site. The infusion site will be replaced if there is any suspicion of it failing.
- 5 ml plasma samples will be taken and processed every ~30 minutes throughout the experiment for later analysis of insulin and glucagon levels.
- If the IV or YSI fail, capillary BGs using the Nova Biomedical Stat Strip Xpress will be used.
- Additional calibrations will be performed at any of the blood glucose checks throughout the day if the CGM value does not meet the ISO standard (< 15 mg/dl difference for BG values < 75 mg/dl, < 20% absolute difference for BG values > 75 mg/dL) at the time of the BG measurement AND it is a good time to calibrate (the CGM trend arrow is flat and there has been no carbohydrate intake in the last 30 minutes or glucagon boluses in the last 15 minutes).
- Subjects will be asked to rate any nausea and/or infusion site pain on 10 cm visual analog scales (VAS) at the beginning of the study once the infusion sites have been placed but no drug has yet been administered, then every 2 hours during the study and at the end of the study. Study staff will also evaluate their infusion sites to document any erythema or edema at the same times.
- After approximately 3-4 hours of closed loop control, the subjects will be permitted to eat lunch. The content of their meal will not be restricted in any way, with the exception that the number of carbohydrates should be in the "typical" range for them at lunch, and that they must eat the same meal at approximately the same time during both visits. Practically speaking, this means that they must have the same lunch that can be delivered or brought to the DRC. Subjects will select meals that will have a typical amount of carbohydrates for a lunch-time meal and will announce their meals to the bionic pancreas by selecting the "typical" option in the meal announcement screen.
- After lunch is completed, the subjects will not be allowed any carbohydrate intake (non-caloric drinks will be permitted) until the study is completed, to allow the bionic pancreas to control the post-prandial blood glucose without further interruption.
- Approximately 2 hours after lunch is completed (Hour 5-6 of the experiment), subjects will exercise on a stationary bike with a heart rate from 120-140 beats per minute (bpm) for a total of 4,000 heart beats (approximately 30 minutes). Subjects will rate their exercise intensity using the Borg scale every 5 minutes, with the target intensity level between 12 and 14. Heart rate will be measured every 5 minutes.
- BG measurements using the YSI will be obtained off of the IV line every 10 minutes during exercise. If the BG is < 80 mg/dl, BG measurements will be obtained off of the IV line every 5 minutes.
    - Carbohydrates will be given for any BG < 50 mg/dl according to the following protocol: Dextrose (g) = BSA (m^2)/[1.7 m^2 (women) or 1.9 m^2 (men)] *15g
    - Repeat treatments will be given at 15 minute intervals as long as BG remains < 50 mg/dl.
    - Heart rate will be measured every 5 minutes during exercise
    - Subjects will be asked to rate the intensity of their exercise every 5 minutes using the Borg Scale

- If there is an interruption in the Dexcom CGM output, study staff will assist the subject in recovering CGM data streaming. If this requires replacement of the CGM sensor, BGs will continue to be checked every fifteen minutes per protocol. These blood glucoses will be entered into the bionic pancreas, which will treat them as CGM values and dose insulin and/or glucagon appropriately. If the CGM sensor fails a second time, the subject may be asked to repeat that arm of the experiment because of the effect that repeated sensor replacements may have on study outcomes.
- If there is a complete failure of the bionic pancreas operation, subjects will take over their own blood glucose control using their personal insulin pump until the bionic pancreas can be brought back online. If bionic pancreas control cannot be promptly resumed (e.g. within 30 minutes), the subject may be asked to repeat that experiment day.
- Subjects may choose to withdraw from the study at any time. If they withdraw from the study, they should alert a provider immediately.
- The maximum amount of blood loss per visit will be about 120 ml. The maximum amount for the entire study will be about 360 ml.
- After 5:00 PM (at least 8 hours on the bionic pancreas), the bionic pancreas will be stopped and the subject will replace their personal insulin pump.
- Whenever a subject reinitiates their own insulin pump therapy, a study physician will assist the study participants in safely transitioning from control by the bionic pancreas to control using their own insulin pump.
- The bionic pancreas and glucose meters will be collected and downloaded.
- A study MD will review the last several hours of insulin and glucagon dosing and assist the subject in resuming their usual care. They will be instructed to call study staff with any questions, issues or concerns.
- A structured phone interview will be conducted with each participant after they have completed their participation in all bionic pancreas visits. The aim of the interview will be to subjectively compare their experiences with the two systems. This interview will be recorded and de-identified, and will be shared with collaborators.

V. d. 5. Infusion Set Sub-Study Visit Procedures:

- Subjects will arrive at the visit having fasted since 12:00 AM the night before.
- A urine pregnancy test will be performed in female volunteers. If the test is positive the volunteer will be informed of the result and the visit will be ended. The date of the last menstrual period will also be documented, along with usual cycle length, for female subjects.
- Study staff will review any changes in medical history or medications since the last study visit, and obtain an updated medication list. Their current pump settings, including basal rates, carbohydrate ratios and correction factor will be documented.
- A 20 gauge or smaller peripheral I.V. will be placed for monitoring plasma glucose and insulin levels.
- Subjects will be provided with the rapid-acting insulin they usually use.
    - For subjects wearing their own leur-lock compatible pump, a new reservoir will be filled with insulin lispro, new tubing will be primed and a new infusion set will be placed (either Contact Detach or iLet infusion set). The cannula will be primed as recommended by the manufacturer.
    - For subjects using the study provided pump, their pump settings will be programmed into the study pump. A new reservoir will be filled with insuln lispro and new tubing will be primed. A new infusion set (either Contact Detach or iLet infusion set) will be placed. The cannula will be primed as recommended by the manufacturer.
- A t=0, baseline plasma samples will be drawn for insulin levels, and a baseline blood glucose level will be obtained.
- Subjects will remain fasted for 90 minutes, while their pump (or the study pump) delivers their usual basal rate for this time of day. Non-caloric beverages and black coffee will be allowed.
    - During this time, blood will be drawn from the IV for plasma glucose levels at least every 30 minutes. Blood will be drawn more frequently as needed for hypoglycemia.
    - During this time, Blood will be drawn for plasma insulin levels every 30 minutes.
- A t=90, a 0.1 u/kg dose of insulin will be administered through the pump. Subjects will eat a breakfast of their choice containing carbohydrates appropriate to the insulin dose based on their own carbohydrate ratio and correction factor.
    - After breakfast is completed, subjects will not dose any further insulin and will resume fasting

until the experiment is completed.

- For 2 hours after the insulin injection (t=90 to t=210), blood will be drawn for plasma glucose and plasma insulin levels every 20 minutes.
    - Blood will be drawn for plasma insulin levels then every 30 minutes thereafter until the end of the experiment.
- For the last hour and a half (from 2 to 3.5 hours after injection, t=210 to t=300), blood will be drawn for plasma glucose at least every 30 minutes and for plasma insulin levels every 30 minutes.
- The infusion set site will be assessed for pain, skin reactions, and evidence of failure immediately after insertion, at 1 hour intervals during the experiment, and at the end of each experiment. The participant will complete a short survey evaluating the user experience related to the infusion set at the end of the experiment.
- Three and a half hours after the meal bolus has been given the experiment will end (t=300). The IV will be removed, subjects will switch back to the usual infusion set (and/or pump if applicable) and they will be discharged. Subjects will be advised by a study provider on re-initiation of their own insulin regimen.
- Their basal rates, insulin dose and meal will be the same during both experiments.
- Hypoglycemia will be treated with oral carbohydrates as needed.

V. d. 6. Response to Hypoglycemia

- Subjects are encouraged to check their BG for any symptoms of hypoglycemia.
- Subjects will be permitted to take 15 grams of carbohydrates for any capillary BG value less than 60 mg/dl. Study staff will ensure proper functioning of the bionic pancreas and infusion set, and will encourage the subject to wait for the bionic pancreas to treat the low blood sugar for as long as they feel comfortable.
- Subjects will be required to take 15 grams of carbohydrates for any plasma BG value less than 50 mg/dl. Blood glucose will continue to be checked every 15 minutes per protocol, with increased frequency during exercise. Treatment will be repeated if subsequent BG values are still < 50 mg/dl after 15 minutes. All carbohydrate treatments for hypoglycemia will be documented by study staff (amount and time).
- Study staff will check the infusion site and the bionic pancreas for normal operation any time hypoglycemia occurs. If there is any suspicion of infusion set malfunction, the site should be replaced. Study staff will check the bionic pancreas for any malfunction and correct any problems that are found.
- 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 may be started.
- If a subject experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the study will be discontinued.
- In the Infusion Set Sub-Study:
    - Hypoglycemia will be treated at the subject's discretion using oral carbohydrates.
    - If a subject experiences a seizure or unconsciousness associated with hypoglycemia, his or her participation in the sub-study will be discontinued.

V. d. 7. Response to Hyperglycemia

- Study staff will check the infusion site and the bionic pancreas for normal operation any time BG is greater than 300 mg/dl. If there is any suspicion of infusion set malfunction, the site should be replaced. Study staff will check the bionic pancreas for any malfunction and correct any problems that are found.
- If the BG remains > 300 mg/dl for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/l, the experiment will be stopped and rescheduled. The subject will be provided with insulin and a syringe to give an injection based on their correction factor.
- If no correctable fault is found, but there is doubt regarding the correct function of the bionic pancreas system, the experiment may be stopped and the arm rescheduled.
- If a subject experiences diabetic ketoacidosis, his or her participation in the study will be discontinued.
- In the infusion set sub-study:
    - Study staff will check the infusion site for normal operation and any signs of failure hourly throughout the experiment and any time the BG is greater than 300 mg/dl. If there is any suspicion of infusion set malfunction, the site should be replaced.

- If the BG remains > 300 mg/dl for 2 hours despite troubleshooting, blood ketones will be measured. If the blood ketone result is >1.5 mmol/l, the experiment will be stopped and rescheduled. The subject will be provided with insulin and a syringe to give an injection based on their correction factor.
- If no correctable fault is found, but there is doubt regarding the correct function of the infusion set, the experiment may be stopped and the arm rescheduled.

V. d. 8. Response to Nausea/Vomiting

If significant nausea (e.g. that prevents the subject from eating normally) or any vomiting occurs, study staff will notify the study provider. Study staff will assist the subject in troubleshooting, such as checking the BG and the calibration of the CGM (excessive glucagon dosing may occur if the CGM is reading lower than the true BG). 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.

V. d. 9. Response to Infusion Site Reaction

If moderate or severe pain and/or edema/erythema occur at an infusion site(s), we will move the infusion set. If moderate or severe pain continues at the original site for more than 15 minutes after the infusion set removal, or if moderate or severe pain and/or edema/erythema occurs at the new site we will stop the study and remove all infusion sets. We will continue to monitor the subjects for resolving of any reactions that occur as long as is necessary, despite the end of the study session. This may include direct monitoring at the Diabetes Research Center and/or follow-up with the patient by telephone and/or return visit the following day or as long as necessary to document full resolution of any local reactions.

V. d. 10. Response to Other Medical Needs

If the subject experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will be instructed to follow up with their primary care provider, or may choose to see a non-study physician at MGH. If the subject experiences urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they should visit a walk-in clinic or emergency room, or if necessary call 911.

V. d. 11. Monitoring of Bionic Pancreas Performance

A study MD or RN will check on device functioning frequently throughout each experiment. The bionic pancreas developers will be readily available by phone for consultation at all times during the course of each experiment to remotely assist with any technical problems that arise, but will not be present at the experiment or interact with subjects.

V. d. 12. Supervision by Study Staff

A study MD will be on call at all times during the course of each experiment. An RN or MD will accompany the study subjects at all times.

VI. Biostatistical Analysis

VI. a. Data Collected

VI. a. 1. Prior to start of experiment:

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female subjects
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use

- Type of insulin used in pump
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days as available (from pump history)
- Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings)
- Height and weight
- Blood pressure
- Hemoglobin A1c
- Urine HCG (pre-menopausal females)
- Fractionated plasma metanephrines (if indicated by history)

VI. a. 2. During study visits:

- CGMG (CGM glucose) every five minutes from the DexCom G4 Platinum CGM
- All BG measurements taken
- Insulin total daily dose
- Glucagon total daily dose
- Timing and content of the meal eaten and carbohydrate amount
- Timing of meal announcement and size of meal announced
- Timing and glucose values at calibrations
- Timing and amount of carbohydrates taken for hypoglycemia
- Time subjects were not under bionic pancreas control for any reason
- List of technical faults associated with the bionic pancreas including cause and resolution
- Nausea on a visual analog scale at study start, every 2 hours, and at study end
- Infusion site pain at study start (after insertion and before any drug administration), every 2 hours, and at study end
- Infusion site reaction according to the Draize scale at study start (after insertion and before any drug administration), every 2 hours, and at study end
- Infusion site appearance every 15 minutes (presence/absence of moisture, evidence site has been displaced)
- Timing of any infusion site replacements
- Subject reports of symptoms of any other complaints
- Timing of exercise and duration
- Volunteer reported Borg scale score for exercise intensity every 5 minutes during exercise
- Heart rate during exercise from Polar heart rate monitor every 5 minutes
- Plasma insulin levels every 30 minutes throughout the experiment
- Plasma glucagon levels every 30 minutes throughout the experiment

VI. a. 3. During the Infusion set Sub-Study:

At Screening:

- Age
- Sex
- Race and ethnicity
- Date of last menstrual period in female volunteers
- Date of diabetes diagnosis
- Medical, surgical and social history, allergies and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non prescription)
- Type of insulin used in pump
- Average total daily dose in the last 30 days (from pump history)
- Height and weight
- Blood pressure
- Urine HCG (pre-menopausal females)
- Hemoglobin
- Hemoglobin a1c

During Study Visits:

- Insulin analog given
- Basal rates for the duration of the experiment, and carbohydrate ratio and correction factor used for the meal bolus
- Timing and content of the meal eaten, including carbohydrate count
- Timing and amount of insulin dose given for the meal
- Plasma glucose levels at least every 30 minutes, more frequently in the low range
- Plasma insulin levels every 20-30 minutes (assayed with Mercodia Iso-insulin ELISA)
- Total insulin given throughout the experiment
- Timing and amount of any carbohydrates taken for hypoglycemia
- Infusion site assessments including pain, skin reactions, appearance of site, and any evidence of leaks
- Timing of any infusion site replacements
- Subject reports of symptoms of any other complaints
- User satisfaction with both infusion sets

VI. b. Study Endpoints

VI. b. 1. Primary endpoint analyses

Aim 1: This will be generated from the bionic pancreas data during each arm:

- Average percent dose amounts calculated by the bionic pancreas control algorithm that are successfully delivered by the pump (aggregate of both insulin and glucagon doses).

Aim 2:
This will be generated from the bionic pancreas data during each arm:

- Average percent dose amounts calculated by the bionic pancreas control algorithm that are successfully delivered by the pump (glucagon doses).

Aim 4: Insulin Area Under the Curve in the 3.5 hours following the insulin bolus

VI. b. 2. Secondary endpoint analysis – Infusion Set Sub-Study

- During the initial 90 minute fasted period:
  - AUC
  - Mean insulin levels
  - Difference between insulin levels at baseline and at 90 minutes
- After the insulin dose:
  - Tmax
  - T½max
  - Cmax
  - AUC in the first 30 minutes
  - AUC in the first 60 minutes
  - AUC in the first 90 minutes
  - Terminal half-life
- Difference between the fasted PG value and the PG value at 90 minutes
- Difference in PG prior to the meal and peak post-prandial glucose
- PG AUC in the 3.5 hours following the meal
- Number of infusion sites replaced for clinically suspected failure
- Local skin reactions
- Infusion site pain
- User satisfaction

VI. b. 3. Secondary endpoint analyses – Bionic Pancreas Function:
This will be generated from the bionic pancreas data during each visit:

- Average percent insulin dose amounts calculated by the bionic pancreas control algorithm that are successfully delivered by the pump.

- Average percent glucagon dose amounts calculated by the bionic pancreas control algorithm that are successfully delivered by the pump.
- Average percent dose amounts successfully issued to the pump by the bionic pancreas control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available).
    - Average percent insulin dose amounts successfully issued to the pump by the bionic pancreas control algorithm that are successfully delivered by the pump.
    - Average percent glucagon dose amounts successfully issued to the pump by the bionic pancreas control algorithm that a successfully delivered by the pump.
- Average percent dose amounts calculated by the bionic pancreas control algorithm that are successfully issued to the pump by the bionic pancreas (calculated doses are not issued unless the pump is accessible and its delivery channel is available).
    - Average percent insulin dose amounts calculated by the bionic pancreas control algorithm that are successfully issued by the bionic pancreas.
    - Average percent glucagon dose amounts calculated by the bionic pancreas control algorithm that are successfully issued by the bionic pancreas.
- Average percent of 5 minute steps during which the bionic pancreas is functioning nominally in all respects based on real-time CGM data (new CGM glucose reading captured, dose calculated, dose issued to pumps,
- Average percent of 5 minute steps during which the bionic pancreas is functioning nominally with or without a new CGM glucose reading captured (dose calculated, dose issued to pumps). If a CGM signal is not available, the dose calculated may be based on weight-based or historical basal rates.
- CGM reliability index, calculated as percent of possible values actually recorded by CGM.
- CGM MARD versus time-stamped BG values from YSI.
- List of technical faults associated with the bionic pancreas including cause and resolution.

VI. b. 4. Secondary endpoint analyses – Glycemic:

- All of following metrics will be generated from the DexCom G4 Platinum CGM data during each bionic pancreas visit.
    - Mean CGM glucose.
    - 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 CGM glucose < 154 mg/dl (estimated average glucose corresponding to an A1c of 7%).
- Number of severe hypoglycemic events (subject unable to self-treat, requiring the assistance of another person).

<u>During Exericse</u>

- Number of subjects discordant for reaching a BG < 60 mg/dl (measured with YSI) for > 2 consecutive plasma glucose measurements
- Area between the glucose curve and 60 mg/dl calculated from BG measurements
- Area between the glucose curve and 60 mg/dl calculated from CGM data
- Time from start of exercise to first BG measurement < 60 mg/dl
- Time from start of exercise to first CGM measurement < 60 mg/dl

VI. b. 5. Secondary endpoint analyses – Non-glycemic

- Glucagon total delivery per kg of body mass.
- Insulin total delivery per kg of body mass.
- Number of episodes of symptomatic hypoglycemia.
- Number of carbohydrate interventions for hypoglycemia.
- Total grams of carbohydrate taken for hypoglycemia.

- Difference in mean nausea from VAS during the study (mean of measurements every 2 hour and at study end) vs. baseline at study start.
- Difference in Infusion site pain from VAS during the study (mean of measurements every 2 hour and at study end) vs. baseline at study start. Note that in the iLet infusion set the infusion catheters are 1 cm apart, so it may not be possible to differentiate whether a sensation is coming from the insulin or glucagon infusion catheter. Subjects will be asked to use their best judgment and to provide scores for both catheters.
- Difference in local erythema and edema according to the Draize scale (mean of measurements every 2 hour and at study end) vs. baseline at study start. Note that in the iLet infusion set the infusion catheters are 1 cm apart, so it may not be possible to differentiate whether a skin reaction is coming from the insulin or glucagon infusion catheter. Subjects will be asked to use their best judgment and to provide scores for both catheters.
- Number of unscheduled infusion set replacements.
- Number of unscheduled CGM sensor changes.

During Exercise

- Grams of oral carbohydrates given to the subject to treat hypoglycemia
- Total glucagon dosing by bi-hormonal bionic pancreas from the start of exercise until the end of the visit

The primary analysis of the designated endpoints will be calculated on an intention-to-treat basis. In cases where an arm was not completed (and that arm was not repeated according to protocol criteria) we will use the available data from that arm in the data analysis. We will only include arms that were started by the subject.

We will use the Shapiro-Wilk test to determine the normality of the residuals for each comparison and calculate percentages, means or medians, and standard deviation and/or ranges as appropriate in descriptive analyses. We will use paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively. In a secondary analysis we will look for any period effect and any interaction between treatment and period, although no such interaction is predicted for the primary outcome, and there is probably insufficient power to identify a small interaction.

VI. c. Power Analysis

The power analysis is based on data from previous studies using the iPhone-based BP. The following table shows the percentage of time that that the insulin and glucagon pumps were available to deliver doses calculated by the bionic pancreas. When pumps were not available, this was typically due to loss of communication between the iPhone and the t:slim pumps, but could also be due to pump occlusion or inadequate drug in the reservoir, among many other possible reasons.

Table 1. Time that pumps were available in previous bionic pancreas studies

Study	insulin		Glucagon	
	Mean	SD	Mean	SD
Beacon Hill	96.5	2.7	95.9	2.3
Camp1	93	2.7	92.2	2.3
Camp2	95.1	2.5	93.9	3.1
Multi-center	96.1	2.5	95.9	2.5
Mean	95.2	2.6	94.5	2.6
Min	93.0	2.5	92.2	2.3
Max	96.5	2.7	95.9	3.1
ttest (insulin vs. glucagon)			0.044	

The glucagon pump was unavailable a greater percentage of the time than the insulin pump in the iPhone-based BP. This could be due to more frequent reservoir changes (the glucagon reservoir had to be changed every day, while the insulin reservoir was changed every other day – the pumps were unavailable during the reservoir change process), greater number of occlusions in the glucagon tubing and infusion sets, or possibly other, unknown factors.

We anticipate that the iLet BP will be much more reliable in terms of delivering calculated doses because it does not rely on wireless communication between the device running the control algorithm and the pumps. In the iLet, the control algorithm and pumps are integrated into a single device. Nonetheless, there may still be times that the pump is unavailable or that the full dose is not delivered (e.g. due to temporary loss of communication between components due to software issue, tubing occlusion, or inadequate drug in the reservoir). Therefore, we anticipate that the percentage of the dose amount calculated that are delivered will be substantially greater, but not 100%.

We have modeled the power to detect a difference between the iPhone-based and iLet BPs based on an aggregate rate of pump unavailability of the iPhone-based BP (including both the insulin and glucagon pumps) of 96±2.5%, which is close to the maximum reliability that we observed in the more reliable insulin pump across the 4 previous studies. We then calculated the power based on different possible reliabilities of the iLet internal pumping systems, based on 2-fold, 5-fold, and 10-fold reductions in pump unavailability, corresponding to availabilities of 98±2.5%, 99.2±2.5%, and 99.6±2.5%, respectively. Under these assumptions, the sample sizes required for each of these possible outcomes to achieve a power of 80% with an alpha of 5% using a 2-sided test are 25 subjects, 10 subjects, and 8 subjects respectively. We expect a reduction of at least 5-fold in pump unavailability (and 10-fold would not be surprising), so 10 subjects should provide sufficient power to detect a difference. The standard deviations are assumed to be unchanged in these calculations, although it is likely that the standard deviations would also be reduced if the pump becomes more reliable - this means that the sample size estimates are likely conservative.

As the Infusion Set Sub-Study is a pilot study of the modified infusion set, no formal power calculations have been done for this portion of the study.

VI. d. Criteria for Success of the Study

The main criteria for the success of the study will be that we observe a significant improvement in the primary outcome measure (and the related secondary reliability measures) in the iLet vs. the iPhone-based BPs, and no significant difference in the glycemic control measures. It is possible that improved reliability may actually improve glycemic control measures, but the sample size may not be sufficient to detect any such difference. A secondary criterion for success of the study will be that we observe no statistical difference in safety-related outcomes (occlusions, infusion site reactions or pain, nausea) between Xeris and Lilly glucagon.

The main criteria for the success of the infusion set sub-study will be that we observe no significant difference in the performance of the iLet infusion set when compared with the Contact Detach. Achieving a non-inferior result would allow us to move forward in future testing of the iLet infusion set with the iLet bionic pancreas in outpatient trials.

VII. Risks and Discomforts

Subjects may experience mild discomfort associated with the insertion of the infusion sets and sensor into the SC tissues. The risk of 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 will be inserted and a CGM sensor will be inserted, which may not be used in usual care.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Due to frequent monitoring of glucose and direct supervision by an RN or MD at all times, the risk of a hypoglycemic episodes leading to significant harm to volunteers is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk is expected to be less than the risk during the subjects' lives outside of the trial based on data from earlier trials.

There is a risk of headache, nausea, or vomiting in subjects due to the administration of exogenous glucagon. This risk has been low in prior studies, and we expect it to remain so in this trial given its short duration. In our previous studies we found no significant difference between daily nausea scores (10 cm visual analog scale) on the bionic pancreas vs. usual care. We found the same in a study in which patients controlled their own insulin pump and got glucagon or placebo delivered by the bionic pancreas (randomized by day). In that study there was no difference in VAS nausea and subjects correctly guessed their treatment assignment on a given day only

42% of the time (less than chance). Therefore, the glucagon appears to be very well tolerated.

There is a risk of skin irritation at the site of the Xeris glucagon infusion. Based on previous studies using larger doses of Xeris glucagon, we expect any infusion site reactions to be mild and transient.

The risks of intravenous lines remaining in place for about 8 hours include thrombosis and phlebitis of the peripheral vein. Subjects may experience discomfort with insertion of the peripheral intravenous line.

There is a risk of risk of dizziness or lightheadedness from blood loss. However, typical blood loss will be less than 200 ml per visit. Furthermore, subjects will be disqualified from participation if they have a hemoglobin < 12 g/dl.

VII. a. Infusion Set Sub-Study risks:

Subjects may experience mild discomfort associated with the insertion of the infusion sets into the SC tissues. The risk of discomfort due to insertion of infusion sets is not expected to be greater than in their lives outside the trial.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Due to frequent monitoring of glucose and direct supervision by an RN or MD at all times, the risk of a hypoglycemic episodes leading to significant harm to volunteers is expected to be substantially lower than their risk during their usual therapy.

There is a risk of hyperglycemia. This risk may be higher than their usual lives outside the trial due to the use of an investigational infusion set.

The risks of intravenous lines remaining in place for about 5 hours include thrombosis and phlebitis of the peripheral vein. Subjects may experience discomfort with insertion of the peripheral intravenous line.

There is a risk of risk of dizziness or lightheadedness from blood loss. However, typical blood loss will be less than 100 ml per visit. Furthermore, subjects will be disqualified from participation if they have a hemoglobin < 11g/dl.

VIII. Potential Benefits

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 compared to their usual diabetes care during their participation.

The data derived from this study will allow us to evaluate the robustness and effectiveness of the new bionic pancreas control system. The data obtained will be used to further improve the iLet BP and will allow us to expand to larger outpatient trials using the new device.

This study is a necessary step in preparing the bionic pancreas to become available to people with type 1 diabetes. Wide availability of the bionic pancreas could improve the care adults and children with type 1 diabetes.

Subjects will be financially compensated for participating in the study.

VIII. a. Infusion Set Sub-Study Potential Benefits

The data derived from this study will allow us to evaluate the robustness and effectiveness of the new iLet infusion set. The data obtained will be used to further improve the iLet BP and will allow us to expand to larger outpatient trials using the new device.

This study is a necessary step in preparing the bionic pancreas to become available to people with type 1 diabetes. Wide availability of the bionic pancreas could improve the care adults and children with type 1 diabetes.

Subjects will be financially compensated for participating in the study.

IX. Data and Safety Monitoring

IX. a. Monitoring of Source Data

During the experiment, CGM 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 at intervals). All of the 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.

Study staff will be encouraged to raise any concerns they may have or problems they have identified at any time. The PI, in consultation with the co-investigators, will decide a course of corrective action, and resolution or progress will be assessed no later than the next meeting.

An audit of procedures, regulatory documentation, and a sample of subject files will be performed by a member of the Diabetes Research Center at least biannually. The audit will be conducted by a staff member who is not directly involved in the conduct of the study. This audit will include a review of regulatory documentation, such as IRB and FDA correspondence, and a review of subject files, including a review of consents, case report forms, and other data from study visits.

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.

The study data will be shared with collaborators at Beta Bionics, Inc. but only in a form in which all personally identifiable information has been removed (e.g. combined database including BG 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.

IX. b. Safety Monitoring

This study is considered moderate risk. An external Data and Safety Monitoring Board will oversee the conduct of the study and review its results on a regular basis. Additionally, the DSMB will be informed in the event of any severe or unexpected adverse events. The DSMB will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. A final DSMB meeting will convene after the completion of the study. Safety and efficacy data will also be reported to the FDA in compliance with applicable regulations.

As noted above, the participation of individual subjects will be discontinued if they experience:

- Seizure or unconsciousness associated with hypoglycemia
- Persistent nausea and vomiting thought to be related to glucagon dosing
- Persistent moderate or severe pain, edema or erythema at an infusion site
- Diabetic Ketoacidosis

If more than 1 subject must be withdrawn from the study for these reasons, the study will stop and a vote of the DSMB will be required to restart it. All serious and unexpected events will be reported to the DSMB 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 intercurrent 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.

IX. c. Adverse Event Reporting Guidelines

The PI and co-investigators will review any adverse events after each experiment. Any serious or unexpected but possibly related adverse events will be communicated to the PI as soon as possible and within 48 hours of the time they are detected. Adverse events will be reported promptly to the Partner's IRB. Collaborator Ed Damiano is the sponsor of the Investigational Device Exception (IDE) for the bionic pancreas to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE.

X. Subject Compensation

Financial compensation will be provided to all subjects who complete the screening visit. Subjects will be paid $25 for completing the screening visit whether or not they are eligible to participate in the study. Study participants will be compensated $150 for completing the three study visits. Thus the total compensation for a subject who completed the study would be $175. Parking expenses will be paid for up to $30 per subject, and lunches will be paid for up to $100 per subject (50 dollars per lunch). Subjects who are unable to complete the study or chose to stop participation will receive prorated compensation at a rate of $50 per completed day. In addition to the monetary compensation, the cost of the subjects lunch meals during their participation in the study will be covered by study funds.

X. a. Infusion Set Sub-Study Compensation:
Financial compensation will be provided to all subjects who complete the screening visit. Subjects will be paid $25 for completing the screening visit whether or not they are eligible to participate in the study. Study participants will be compensated $50 for completing each study visit. Thus the total compensation for a subject who completed the study would be $125. Parking expenses will be paid for up to $30 per subject, and breakfast will be paid for up to $40 per subject (20 dollars per meal).

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XII. Appendices

A. Xeris Investigator Brochure – see attached

B. List of Abbreviations

ADA	American Diabetes Association
AE	Adverse Event
BG	Blood Glucose
BP	Blood Pressure
BP	Bionic Pancreas
BPMC	Bionic Pancreas MultiCenter
BTLE	BlueTooth Low Energy
BU	Boston University
CGM	Continuous Glucose Monitor
CHF	Congestive Heart Failure
DCCT	Diabetes Control and Complications Trial
DMSO	dimethyl sulfoxide
DPP-4	Dipeptidyl peptidase-**4**
DSMB	Data Safety and Monitoring Board
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-**1** receptor agonists
GUI	Graphical User Interface
HbA1c	Hemoglobin A1c
HCG	Human Choriogonad….
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
MARD	Mean Absolute Relative Difference
MD	Doctor Of Medicine
MEN2A	Multiple Endocrine Neoplasia, type 2A
MEN2B	Multiple Endocrine Neoplasia, type 2B
MGH	Massachusetts General Hospital
MPC	Model-Predictive Control
NOAEL	No Observed Adverse Effect Level
PI	Principal Investigator
PK	Pharmacokinetics
RF	Radio Frequency
RN	Registered Nurse
SC	Subcutaneous
SGLT-2	Selective sodium-glucose transporter-2 inhibitors
T1D	Type 1 Diabetes
UI	User interface
VAS	Visual Analog Scale
YSI	Yellow Spring Instrument