Individualizing Automated Closed Loop Glucose Control through Pharmacokinetic Profiling in an Insulin-Only Bionic Pancreas

Principal Investigator:
Steven J. Russell, M.D., Ph.D.[1]

Co-Investigators:
Courtney Balliro BS, RN, CDE[1]
Rabab Jafri, MD[1]
Jordan Sherwood, MD[1]

[1]*Diabetes Research Center, Massachusetts General Hospital, Boston, Massachusetts.*

Address correspondence to Steven J. Russell, M.D., Ph.D., MGH Diabetes Center, 50 Staniford Street, Suite 301, Boston, MA 02114, email: sjrussell@mgh.partners.org, phone: 617-726-1848, fax: 643-0697, page: 617-726-2066.

Version 5, June 17, 2019

TABLE OF CONTENTS

I. Background and Significance

1.a. Background

Maintaining near-normal blood glucose (BG) levels (70--120 mg/dl) is a challenging and critically important task for people with diabetes. The Diabetes Control and Complications Trial (DCCT) Research Group definitively demonstrated that tight BG control can reduce long-term complications in patients with type 1 diabetes[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 requires a relentless daily effort to count carbohydrates, frequently monitor BG throughout the day and night, and administering a daily insulin regimen via multiple subcutaneous (SC) injections, or continuous SC infusion in a pump. The choice of insulin used in patients with diabetes is largely arbitrary, often based on what their insurance company will provide coverage for, as opposed to any clinical rationale. There is no currently available or straightforward way to identify if there is any clinically relevant difference between the insulins in any individual patient.

The SC route of administration for insulin also poses a challenge due to the delayed and attenuated absorption of the infused drug into the blood stream. However, the SC route is the only practical one due to risk of infection with intravascular catheters and logistical problems with intraperitoneal pumps. Delays in absorption after SC administration of insulin create the possibility of excessive insulin accumulation in the tissue which can result in delayed hypoglycemia, an event that must be safeguarded against in any practical glucose control system.

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 diabetes management and vastly improve glycemic control relative to the current standard of care. Use of the most appropriate insulin for any given individual in a bionic pancreas has the potential to achieve the best possible glucose control currently available.

I.b. 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, and potentially for patients with insulin dependent type 2 diabetes. 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. [3-10]

Our core technology is the insulin controller, which orchestrates all 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 the algorithm with a mathematical formulation for estimating the concentration of insulin in the blood we could predict future serum insulin concentrations. 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.

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 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 delivery even when the Dexcom CGM is offline. Specifically, when the Dexcom CGM is offline, the BP invokes the high-resolution "basal rate profile" that it had recently learned and stored when the Dexcom CGM was online. On the basis of what the system learned and stored about meal announcements when the Dexcom CGM was online, it is able to respond to meal announcements in the same manner when the Dexcom CGM is offline. Finally, it automatically responds to user-entered BG values when the Dexcom 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 Dexcom 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 diabetes 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--2017). Using the iPhone-driven BP system, we have conducted >160 outpatient experiments of 4--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 78 years old and in body mass between 21 and 133 kg. The robust adaptation capabilities of the BP are 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). We have tested the BP in bi-hormonal (insulin and glucagon), insulin only and glucagon only configurations. In all of our studies and all configurations, the BP has shown significant reductions in hypoglycemia compared to usual care[3-10].

In a previous study[5] we have shown that the pharmacokinetics of insulin lispro vary dramatically between different patients. Each of the three commercially available rapid acting insulin analogs contains amino acid substitutions in the B chain and are therefore immunologically distinct: In lispro, the order of Pro 28 and Lys 29 is reversed. Pro28 is replaced with Asp in aspart and Asn 3 is replaced with Lys and Pro 29 with Glu in glulisine. Most insulin treated patients with type 1 diabetes develop antibodies to insulin and insulin analogs are more immunogenic than human insulin[12-15]. There is ample evidence that even moderate titers of anti-insulin antibodies, common among people with type 1 diabetes, can delay the onset and prolong the action of insulin[16-20]. There is strong evidence for differential recognition of human vs. beef insulin (which vary by three amino acids) and human vs. pork insulin (which vary by only one amino acid). This is true even of highly purified mono-component beef and pork insulins. Analysis of antibodies to insulin by isoelectric focusing using radioactive human, beef, and pork insulin as probes revealed that some patients with type 1 diabetes had antibodies that were specific for beef or pork insulin but did not recognize human insulin[21]. Sulfation of beef insulin, which reduces the availability of antibody epitopes, has been shown to have a dramatically reduced half-life when

compared to non-sulfated beef insulin in patients with high serum insulin-binding capacity[10]. If insulin antibodies are responsible for much of the PK variation between different subjects, then different insulin analogs may have different PK characteristics in individual patients. Therefore, closed-loop control might be facilitated simply by switching from one commercially available insulin analog to another.

We have now developed insulin-specific assays to allow us to identify the absorption rates of each insulin in a single subject. We have completed analyses of samples from a protocol in which each of 20 subjects participated in 3 experiments during which they were given an injection of each rapid acting insulin simultaneously and plasma samples were taken at regular intervals. We used highly specific insulin assays to measure insulin aspart, insulin lispro, and regular human insulin in the plasma sample. We then extracted the PK parameters for each individual for each insulin.

In the majority of the subjects the absorption and clearance speeds of insulin lispro and insulin aspart were similar and faster than for regular human insulin. However, we found that many of the participants had quite different absorption and/or clearance rates for insulin lispro and insulin aspart. Specifically, of 22 total participants in the trial, 7 had a difference in mean Tmax between insulin lispro and insulin aspart that was ≥15 minutes. In 6/7 of these cases the difference favored insulin lispro while 1/7 cases favored aspart. In all but one participant, both lispro and aspart had a smaller Tmax than that of regular human insulin.

In 6/22 cases there was a difference in the T½max of >50% (or a numerically smaller but statistically significant difference). In 2/6 cases the advantage was to lispro and in 4/6 cases the advantage was to aspart. In every case both lispro and aspart had a smaller T½max than regular human insulin.

There were 14 participants who had a difference of more than 50% in the terminal half-life between lispro and aspart. In 8/14 the difference favored lispro and in 6/14 cases the difference favored aspart. In 9 of 22 participants regular human insulin had a faster clearance and numerically lower terminal half-life than either lispro or aspart.

These results suggest that for a surprising number of participants there are differences between the absorption and clearance rates of insulin lispro and insulin aspart. What is not yet clear is whether these differences in PK would result in differences in glycemic regulation. There are many factors beyond insulin PK that influence the effectiveness of glycemic regulation, the size of the differences in PK in some of the participants have the potential to significantly influence key parameters of glycemia, such as mean glucose and % time in the hypoglycemic range. It is more likely that such differences could be detected if more of the other factors that may influence glycemic regulation are neutralized, as is the case when glycemic regulation is automated. Therefore, use of the bionic pancreas may allow differences in glycemic regulation due to differences in insulin PK to be detected.

Additionally, the development of ultra-rapid insulins has the potential to further improve glycemic control achieved under closed loop by allowing the Bionic Pancreas to respond more efficiently to rising CGM glucose. Preliminary clinical studies of BC222 insulin lispro (Adocia) have shown increased insulin availability in the 30 minutes after a meal bolus and lower post-prandial glucose excursions, both via infusion pump or injections in type 1 and type 2 diabetes, when compared with insulin lispro (Humalog, Eli Lilly). This improved pharmacokinetic and pharmacodynamic profile of BC222 insulin lispro may provide superior glycemic control compared to both Humalog and Novolog, which may be of particular importance for those subjects who have altered absorption and clearance rates.

I. d. Fully Integrated Bionic Pancreas

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. The iLet has been 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 bihormonal configuration of the iLet includes a dual motor and drivetrain assembly, which independently actuates the delivery of insulin and/or glucagon from glass cartridges that are separately loaded into the BP housing. Each drivetrain 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. Our mathematical control algorithms, the CGM glucose engine (Dexcom, originally G4 AP version with 505 algorithm and now, the equivalent, G5 version), and the native user interface (UI) software, are all interconnected through a host controller software module and reside as embedded systems on printed circuit board assemblies contained within the device housing. Our touchscreen-enabled, menu-driven UI and onboard microprocessor 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 iLet BP system has dosing accuracy that is comparable to FDA-approved insulin pumps currently on the market.

The iLet BP system is set to an insulin-only, bihormonal, or glucagon-only configuration by manually selecting the configuration in the user interface. When in the bihormonal configuration, the control algorithm would occasionally and automatically invoke the same insulin-only dosing mode as in the insulin-only configuration during periods when the glucagon cartridge has not been loaded, is empty, or becomes empty during use, or if there is a pump occlusion detected in the glucagon fluid path. Whenever the control algorithm is in the insulin-only mode, the minimum glucose target is 110 mg/dl. The minimum glucose target in the bihormonal or glucagon-only mode, when the glucagon cartridge is available for dosing and the glucagon fluid path is patent, is 100 mg/dl. The default PK parameters in the algorithm use an insulin tmax of 65 minutes.

In addition to the iLet itself, the entire iLet BP system includes a glass insulin cartridge, a glass glucagon cartridge, pigtail adapters that connect the drug cartridges to infusion sets, and a self-monitored blood-glucose (SMBG) meter. The SMBG meter that we will use is the Contour Next One (Ascensia). This meter is the successor to the Contour Next SMBG meter (Bayer), which was found to be the most accurate meter assessed in all three blood-glucose ranges tested (< 70, from 70 to 179, and ≥ 180 mg/dl) in a comparative accuracy study involving 17 point-of-care glucose meters.

I. e. Rationale and Potential Benefits

It has generally been assumed that the PK characteristics of rapid-acting insulin analogs are equivalent. This has led to them being treated as a commodity by insurance companies, who generally have only one rapid-acting analog on formulary. However, it is clear from our data that in many individuals there are differences between the PK of insulin lispro and insulin aspart that are consistent across 3 different experiments on different days. If these differences in PK affect glycemic regulation, then better glycemic control may be achieved by identifying a preferred insulin analog for an individual. To determine this, we will test lispro and aspart in the context of the bionic pancreas. We will further examine the effect of PK differences on glycemic control using the experimental ultra-rapid BC222 insulin lispro in a third bionic pancreas study arm, without altering the default PK parameters. An uncontrolled Test Run period with 4 subjects using the iLet with BC222 lispro for three days will be completed prior to initiating outpatient use of BC222 lispro in the iLet to verify safety and feasibility. Data from this Test Run will be reviewed before the RCT period can begin.

II. Hypothesis and Specific Aims

We hypothesize that differences in the PK characteristics of rapid and ultra-rapid insulin analogs will lead to differences in glycemic outcomes when delivered by the *insulin-only* configuration of the bionic pancreas. Specifically, we predict that insulin analogs that have faster absorption (numerically lower Tmax and/or T½max) and insulin analogs that have faster clearance (numerically lower terminal half-life) will result in lower mean glucose and/or a lower percentage of time in the hypoglycemic range.

Aim 1: To conduct a randomized, single-blinded, cross-over study testing the *insulin-only* bionic pancreas in a home-use setting in up to 30 adult subjects (≥ 18 years of age) with type 1 diabetes comparing two commercially available rapid acting insulin analogs, insulin lispro (Humalog, Lilly) and insulin aspart (Novolog, Novo Nordisk.) A final insulin-only bionic pancreas arm will use the experimental ultra-rapid insulin BC222 insulin lispro (BC Lispro, Adocia). The focus will be on determining which fast-acting insulin would be best for use in the iLet bionic pancreas system.

Up to 30 subjects will participate in three 7-day study arms using insulin lispro, insulin aspart, and BC222 lispro in the bionic pancreas in random order. The co-primary outcomes will be mean CGMG and fraction of time spent with CGMG <54 mg/dl with comparisons made between arms for individual participants. Secondary analyses will include time in glycemic ranges (<50, <60, <70, 70-120, 70-180, >180, >250 mg/dl), coefficient of variation, mean postprandial excursion (difference in CGMG from the time of meal announcement to the peak CGMG in the first 4 hours after the meal announcement) for both mixed meal challenges, number of symptomatic hypoglycemic events, grams of carbohydrate consumed to treat hypoglycemia, and TDD of insulin, between arms for individual subjects.

III. Subject Selection

III. a. Inclusion Criteria

1. Age ≥ 18 years and have had clinical type 1 diabetes for at least one year
2. Diabetes managed using an insulin pump for ≥ 6 months
3. Have used a CGM for at least one cumulative month over the last 12 months
4. Prescription medication regimen stable for > 1 month, including any adjunctive anti-diabetic medications (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)
5. Willing to remain within a 250-mile radius of MGH. No air travel will be allowed, and subjects will still be expected to follow the visit schedule as described.
6. Willing to wear one Dexcom CGM sensor, and one leur-lock compatible infusion set that must be replaced every other day
7. Have a mobile phone they will have access to at all times during the study for making contact with study staff

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 long-acting basal insulin that would require an extended washout period.

III. b. Exclusion Criteria

1. Unable to provide informed consent (e.g. impaired cognition or judgment)
2. 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)
3. 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
4. Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the immediate future, or sexually active without use of contraception
    - Subjects must use acceptable contraception for the two weeks prior to the study, throughout the study and for the two weeks following the study.
    - Acceptable contraception methods include:
        - Oral contraceptive pill (OCP)
        - Intrauterine Device (IUD, hormonal or copper)

- Male condoms
- Female condoms
- Diaphragm or cervical cap with spermicide
- Contraceptive patch (such as OrthoEvra)
- Contraceptive implant (such as Implanon, Nexplanon)
- Vaginal ring (such as NuvaRing)
- Progestin shot (such as Depo-Provera)
- Male partner with a vasectomy proven to be effective by semen analysis

5. Current alcohol abuse (intake averaging > 3 drinks daily in last 30 days) or other substance abuse (use within the last 6 months of controlled substances other than marijuana without a prescription)
6. Unwilling or unable or to avoid 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 or other central nervous system depressants, even if by prescription, may be excluded according to the judgment of the principal investigator)
7. Renal failure requiring dialysis
8. Estimated Glomerular filtration rate <15 mL/min/1.73^2
9. Personal history of cystic fibrosis, severe pancreatitis, pancreatic tumor, pancreatectomy or any other pancreatic disease leading to diabetes mellitus.
10. 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)
11. Abnormal EKG consistent with coronary artery disease or increased risk of malignant arrhythmia including, but not limited to, evidence of active ischemia, prior myocardial infarction, proximal LAD critical stenosis (Wellen's sign), prolonged QT interval (> 440 ms). Non-specific ST segment and T wave changes are not grounds for exclusion in the absence of symptoms or history of heart disease. A reassuring evaluation by a cardiologist after an abnormal EKG finding may allow participation.
    - EKG is only required for participants ≥50 years old or with diabetes duration ≥20 years
    - For participants < 50 years of age and < 20 years since diagnosis: History of prolonged QT interval, malignant arrhythmia, or congenital heart disease
12. Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV
13. History of TIA or stroke
14. Seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants
15. Recent history of diabetic ketoacidosis (DKA) or severe hypoglycemia in the last 6 months. Severe hypoglycemia is defined as an event that required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma.
16. History of more than 1 episode of DKA requiring hospitalization in the last 2 years
17. History of more than 1 episode of severe hypoglycemia in the last year.
18. 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.
19. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference

20. Unable to completely avoid acetaminophen for duration of study
21. Established history of allergy or severe reaction to adhesive or tape that must be used in the study
22. History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
23. History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
24. Any diagnosed allergy to insulin lispro or insulin aspart
25. Lives in or frequents areas with poor Verizon wireless network coverage (which would prevent study staff from contacting subjects)
26. Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study

III. c. Source of Subjects

Subjects will be primarily recruited from those who completed our previously conducted Multiplex Pharmacokinetic Study (HRC protocol number 2010P001005), measuring the individual PK profile of each subject for each of the three rapid acting insulins. We will recruit up to 15 subjects who exhibited an atypical PK profile, with the largest differences between the insulin lispro and insulin aspart in either Tmax, T½max, or terminal half-life. Additionally, we will recruit up to 15 subjects who did not have a significant difference in Tmax, T½max, or terminal half-life between insulin lispro and insulin aspart. Most of these subjects will have met similar inclusion criteria to the ones for this study in the past, so we anticipate that most of them will meet inclusion criteria. Subjects in the Test Run will not be required to have shown significant difference in their PK and will be recruited from our general clinic population. However, they may be included in the RCT period provided they meet these recruitment goals.

We will post information about the trial along with contact information on our website www.bionicpancreas.org and on www.clinicaltrials.gov. We will consider include subjects who did not participate in the Multiplex Pharmacokinetic study in the "different PK group" if there is data from another source suggesting that they may have differences in PK with different insulins or they have high titers of anti-insulin antibodies, which we have previously found to correlate with slow PK for insulin analogs. We will consider including subjects who did not participate in the Multiplex Pharmacokinetic study in the "same PK group" if they have normal titers of anti-insulin antibodies.

IV. Subject Enrollment

IV. a. Number of Subjects

Four subjects will complete the Test Run period. It is expected that we will have up to 30 subjects complete the RCT portion of the study with a consistent protocol for a total of up to 34 subjects. We expect that the experiments and analysis can be accomplished over a period of 6-12 months. Up to 45 subjects 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).

For each subject there will be an adult who lives with them who will also be considered a participant in the study. They will receive some training regarding treatment of hypoglycemia and will consent to be a designated contact for the study participant. Up to two individuals may share this role, but they must be willing to carefully coordinate with each other and the subject so that one of them is clearly designated as having this responsibility at any given time, both must consent, and both must complete the required training. These designated contacts are also enrolled in the study, bringing the total enrollment to as many as 135 subjects.

Study staff will make alternative arrangements for any subject that is unable to identify a designated contact to ensure the safety of the subject throughout the duration of the study.

IV. b. Enrollment and Consent Procedures

Prospective participants and designated contacts will be briefed by a study staff member by phone or e-mail regarding the study procedure and the inclusion and exclusion criteria. Potential subjects will be sent an informed consent document by mail, fax, or e-mail.

Once potential subjects have had time to review the consent document, they will meet with a study provider (MD or NP) 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 or NPs, another staff MD or NP will answer questions and administer consent. Their designated contact will also have to meet with a study provider to hear what will be required of them if the subject participates in the study. Designated contact consent will be obtained in person or over the phone. Designated contact participants must have their own telephone in order to participate, either a personal cell phone or a household phone. If the designated contact's consent is obtained over the phone, two copies of the consent form will either be mailed or sent electronically to the designated contact (one to keep and one to return) and he/she will have the form in front of him/her during the phone consent process. The designated contact will return the signed consent form to the study staff either by mail or electronically, and the person obtaining informed consent will sign the document upon receiving it. All designated contacts will be trained in the symptoms of hypoglycemia and response to severe hypoglycemia, including the administration of glucagon. They will also be trained to recognize the symptoms of hyperglycemia, and when to contact study staff and local EMS. There will be separate consent documents for the subject and the designated contact. A licensed physician investigator will be available to speak with the subjects during the consent process in the event of an NP administering consent.

Study staff will answer any questions that the subjects and designated contacts 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 or designated contacts may choose to discontinue their participation at any time. If the designated contact chooses to discontinue their participation, another contact must be available, or study staff will make alternative arrangements to allow the subject to continue their participation in the study.

All enrollment and screening procedures and inclusion and exclusion criteria are the same for the Test Run and the RCT portion of the study.

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
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- History of exposure to non-human insulins or insulin analogs (type, timing, duration)
- Average total daily dose of insulin in the last 30 days

- Usage of CGM (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
- EKG (if > 50 years old or duration of diabetes > 20 years)
- Urine HCG (pre-menopausal females)
- Hemoglobin A1c
- Anti-insulin antibody titers
- Plasma, for future insulin antibody assays
- eGFR

V. b. Drugs

The study involves subcutaneous administration of insulin lispro (Humalog, Lilly), insulin aspart (Novolog, Novo Nordisk), and ultra-rapid insulin BC222 insulin lispro (Adocia). Humalog and Novolog are commercially available by prescription and are indicated for patients with diabetes, but not for use in a bionic pancreas.

BC222 insulin lispro is not FDA approved, and has never been tested in a bionic pancreas. BC222 insulin lispro incorporates Adocia's proprietary technology BioChaperone, which is designed to enable the acceleration of insulin absorption by promoting the insulin lispro hexamer dissociation in the subcutaneous tissue and increasing the vascular/capillary permeability. Adocia has conducted multiple Phase 1 clinical trials (including one under FDA IND 126132) comparing BC222 insulin lispro with the standard rapid acting insulins as well as additional ultra-rapid insulin Fiasp (faster acting insulin aspart, Novo Nordisk). A total of more than 280 subjects have been exposed to BC222 insulin lispro for up to 14-days, with no identified risks other than those known with insulin products.

The control system can administer bolus doses of insulin up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 µl] and a single meal-priming dose, which is triggered by the user, will not exceed 12 units [120 µl].

V. c. Devices

Infusion sets: Subjects will wear one FDA approved commercially available leur-lock compatible infusion set throughout the duration of the study. If an infusion set falls off or is clinically suspected of failing, it will be replaced with a new one. The infusion set will be changed at least every 48 hours.

Continuous glucose monitor (CGM) Sensor: One transcutaneous glucose sensor for the Dexcom G5 CGM will be inserted in the SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor. The whole assembly is held to the skin with an adhesive patch and communicates wirelessly via Bluetooth Low Energy with the Dexcom G5 application running on the iPhone 6S. If the G5 sensor fails for any reason during the experiment it will be replaced promptly. The G5 sensor will be replaced at least every 7 days.

IPhone 6s: The Dexcom G5 app is installed and run on a stock iPhone 6s running iOS 12. The Dexcom G5 app captures CGM glucose values and transmits the data via Bluetooth Low Energy to the bionic pancreas control algorithm running on the iLet.

iLet Bionic Pancreas: The iLet bionic pancreas has an integrated graphical user interface (GUI) and touchscreen display that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin delivered by the control algorithm. The GUI can also be used to input optional meal announcements, designating the size of the meal as "Large for Me" "Typical for Me", "Small for Me", or "Tiny for Me", and the mealtime as the "Start", "Middle", "End", or "Sleeping" periods of the day. 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 mealtime.

The default "usual" glucose target level for the bionic pancreas in the insulin-only mode is 120 mg/dl. A higher (130 mg/dl) or lower glucose target (110 mg/dl) can be set indefinitely as the "usual" target, or as "temporary" for a limited time with automatic expiration, or as "recurring" with automatic renewal and expiration times. When a temporary target is set, or when a recurring target period is on, upon expiration the target will revert to the currently chosen usual glucose target. Although our previous studies showed that the bionic pancreas decreased hypoglycemia and the need for carbohydrate interventions relative to usual care, this will allow participants to raise the glucose target for additional safety, particularly temporarily during periods when hypoglycemia may become problematic, such as when driving or otherwise unable to check or attend to their BG for a period of time, or during periods when hypoglycemia is more likely, such as during exercise. It may also be used to raise the mean BG if the mean is unnecessarily low and the user prefers to further reduce the risk of hypoglycemia. The use of this feature will be entirely optional – it will be presented to participants as an option that they may use or not, as they wish.

During periods when the CGM is offline, such as after a sensor is replaced and before the new sensor has been calibrated, the control algorithm will determine and direct the administration of insulin basal rates either based on the participant's weight in the first 24 hours of the experiment, or on the average of adaptively determined basal rates for that time of day once sufficient experience has been accumulated (i.e. 24 hours or more) by the control algorithm. The user will also be able to enter meal announcements in the GUI, in order to trigger automatically calculated meal boluses, in the same way as when the CGM was online. Finally, the user can trigger an automated correction bolus during such periods by entering a BG value in the GUI. The controller will administer insulin or decrease basal insulin as appropriate, in response to entered BG values during such CGM-offline periods, to a large extent as if the BG values were CGM values.

The device also displays visual alarms, sounds audible alarms, and generates vibration alarms for problems with the functioning of the bionic pancreas.

Ascensia Diabetes Care Contour Next One Glucose Meter: The Contour Next One glucometer is FDA approved and commercially available. Blood glucose measurements for Dexcom CGM calibrations and other required BG measurements will be obtained via finger stick with the Contour Next One in all study arms.

Precision Xtra Ketone Meter: The Precision Xtra ketone meter is FDA approved and commercially available. Blood ketone measurements will be obtained via fingerstick using the Precision Xtra ketone meter in all study arms.

V. d. Experimental Procedures and Data Collection

V. d. i. 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 to continue with the screening. Careful consideration will be given to ensure there are no medications or anything in their medical history that could affect their insulin absorption.
- A urine pregnancy test will be performed in pre-menopausal 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. An EKG will be performed in subjects who are either ≥50 years of age or who have had diabetes for ≥20 years.

- If the volunteer is not excluded based on historical criteria, blood pressure, EKG or urine pregnancy test, blood will be drawn for hemoglobin A1c, kidney function, anti-insulin antibody titers, and plasma, for future insulin antibody assays.
- Once all the laboratory results have been returned, a study MD or NP 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 3 months. The study staff should verbally confirm that there have been no health events that would make them ineligible at every study visit and rescreen subjects for eligibility if it has been greater than three months.
    - Subjects who screen for the Test Run are not excluded from the RCT portion of the study and may participate if they meet the recruitment goals. They do not have to rescreen for the RCT portion if it will take place within 3 months of their Test Run screening.

V. d. ii. Randomization of Study Visit Order

Once the subject has been enrolled and eligibility of subjects has been established, subjects will be randomized to one of the possible three visit orders. The Test Run period is not randomized; all subjects will only use the insulin-only iLet with BC222 lispro.

V. d. iii. General Study Policies for all Study Arms (including the Test Run):

- Subjects will remain within a geographic boundary established based on 250 miles from the designated base for study personnel at all times and will avoid any air travel.
- If the subject is sleeping at home, the designated contact (or one of the designated contacts, if two individuals are sharing the job) must also be at home. If the subject is traveling within the geographic boundary, the designated contact must go with them.
- Subjects and their designated contact will keep a charged mobile phone on their person (or at their bedside) at all times and will answer calls from the study staff.
- Study subjects will keep a Contour Next One glucometer easily accessible at all times in case a calibration is needed, and they will do all calibrations with this meter. They will keep a glucometer, fast-acting carbohydrates, and a glucagon emergency kit easily accessible at home in case their designated contact needs to use it.
- Subjects should use the study provided Contour Next One glucometer for all BG checks throughout the study. They are encouraged to check their BG at least four times a day, before meals and before bedtime. They will also be encouraged to check before exercise and at intervals during exercise, and for any symptoms of hypoglycemia. There are no restrictions on additional checks and subjects should check as often as they wish to confirm the accuracy of the Dexcom CGM and for safety.
- Subjects will wear leur-lock compatible infusion sets throughout the study.
- Subjects and their designated contact will not use any recreational drugs or drugs of abuse, other than alcohol. 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 may not take acetaminophen throughout the study due to potential interference with CGM sensing. Acetaminophen is known to interfere with the accuracy of the Dexcom CGM. Subjects will be instructed to contact study staff immediately if they inadvertently take acetaminophen or any drug containing acetaminophen (for example, combination cold medicines) for further instruction and guidance regarding use of the iLet.
- Subjects will not tamper with the bionic pancreas device in any way, including changing any settings.
- Subjects will keep their iPhone 6s charged, which will require charging at least once per day. In

addition, subjects will change the iLet batteries every two days and use only Lithium AAA batteries. Alkaline batteries should be avoided unless they are needed temporarily until lithium batteries can be placed.

- The bionic pancreas is not water resistant and therefore must be removed for showering. Subjects are urged to take appropriate precautions when they are disconnected from the bionic pancreas, including frequent BG checks and having carbohydrates readily available.
    - The Dexcom CGM transmitter is water resistant and can be left on for bathing and swimming.
    - Subjects may not remove the bionic pancreas for more than 1 hour at a time (e.g. for bathing) and may not remove it for more than 2 hours total in any 24-hour period.
- Any medical advice needed by the subjects during their participation, which is not directly related to BG control during the experiment, should be obtained by them in the usual manner with their primary care physician or endocrinologist.
    - If a subject develops an illness during the experiment, they can seek medical care as usual. As long as the subject is not hospitalized, the study can be continued. If the subject is unable to eat for a period exceeding one day, they must notify study staff so that the medical staff can assess the safety of continuing in the study.
- Subjects will be asked to report all hypoglycemia, carbohydrate interventions, any nausea and/or vomiting, any other adverse events, time spent exercising, and any unscheduled infusion set changes, alcohol use, and other questions through a daily email survey.
- Subjects may participate in any activities that they wish, as long as they abide by the policies above.
- There are no restrictions of any kind on diet or exercise in all three arms in the RCT portion of the study and the Test Run period, although subjects should attempt to maintain similar dietary habits and exercise habits during each arm of the study. The bionic pancreas must be kept dry during exercise.
- Subjects may choose to withdraw from the study at any time. If they withdraw from the study, they should contact a provider immediately who will help them transition to their own insulin regimen safely.

Test Run Policies Only

- Subjects in the Test Run period will be under supervision of study staff during the day. Subjects will be allowed to leave the clinic but will be restricted to the area immediately surrounding the clinic (e.g. within walking distance) and must be in contact with study staff regarding their location.
- While in the clinic, there will be no restrictions on physical activity and subjects will be encouraged to remain as physically active as they are in their normal life.
- Subjects will be required to check a BG at 1 and 2 hours after each meal announcement on all three days of the Test Run, including meal challenges and any other meal announcements delivered.
- Subjects will complete the meal challenges on days 2 and 3 of the Test Run period, following the same protocol as the RCT portion of the study.
- Subjects will be discharged from the clinic at the end of each day to home with a designated contact. During the first two nights at home, subjects will be instructed to check an overnight BG.

V. d. iv. Remote Monitoring

Local Alarms

- All alarm settings will be the same for the Test Run, the RCT portion of the study and during meal challenges.
- Alarms will sound and a visual alert will appear on the screen of the G5 mobile app when the CGM glucose is ≤ 70 mg/dl and the BP will alarm when the CGM glucose is ≤ 50 mg/dl.
    - Participants will be trained to test their BG with the study glucometer in response to such an alarm and take any necessary measures to treat hypoglycemia.

- Participants will be trained on troubleshooting for various scenarios that could lead to low threshold alarms. For instance, a threshold alarm could be due to true hypoglycemia, inaccurate CGM readings, or a compression artifact at the site of the sensor.
    - The first step for all glucose-related alarms will be to perform a fingerstick BG measurement.
    - If the BG measurement is not consistent with the fact that a threshold alarm has occurred, then the participant will assess the accuracy of the CGM, and the possibility of a compression artifact (they will be trained in the causes and recognition of these events). If a compression artifact is suspected, they will take steps to relieve the pressure on the transmitter. If no compression is suspected, the participant will calibrate the CGM.
    - If the BG measurement is consistent with a low threshold alarm, the participant will treat hypoglycemia with carbohydrate ingestion according to their usual practice. Study staff will recommend the standard of care, 15 grams of rapid acting carbohydrates and re-testing BG in 15 minutes. Study staff will recommend the participant continue to monitor their BG until it returns to normoglycemia, and to contact study staff with any questions or concerns.

- Alarms will sound and a visual alert will appear on the Dexcom CGM app if CGM glucose is > 250 mg/dl.
    - Participants will be trained to test their BG with the study glucometer (provided) and the ketone level with the study ketone meter (provided) in response to such an alarm and take necessary measures to treat the hyperglycemia.
    - Participants will be trained on troubleshooting for various scenarios that could lead to persistent or severe hyperglycemia. For instance, hyperglycemia could be due to true hyperglycemia (caused by a missed insulin dose or a failed infusion set for example) or inaccurate CGM readings.
    - The first step in responding to severe or persistent hyperglycemia according to the CGM will be to perform a fingerstick BG and ketone measurement.
        - If the BG measurement is not consistent with the CGM readings, the participant will calibrate the CGM.
        - If the BG measurement is consistent with the CGM readings:
            - Participants will be asked to investigate their insulin infusion set and consider replacing it, check for any occlusions along the insulin fluid path, and check to make sure that the insulin cartridge is not empty.
            - Study staff will recommend the participant continue to monitor their BG until it returns to normoglycemia, and to contact study staff with any questions or concerns.
    - If ketones $\geq$0.6 mmol/L are present:
        - Participants will be advised to change their pump infusion set and will be reminded that the BP should dose insulin accordingly.
        - Study staff will recommend the participant continue to monitor their ketone levels and BG every 60 minutes until ketones return to < 0.6 mmol/L and BG is < 180 mg/dl, and to contact study staff with any questions.
    - If participants experience persistent hyperglycemia lasting more than 2 hours, they will be instructed to contact study staff for consideration of infusion set replacement and/or correction insulin according to the above protocol.

Remote Monitoring

- All remote monitoring will be the same for the Test Run, the RCT portion of the study and during meal challenges.
- There will be at least one provider (MD or NP) on call at all times. Additional study staff members may assist with on-call duties. Subjects may contact study staff as necessary for help troubleshooting

any issues that may arise

- An alert will be generated if remote monitoring indicates that a participant is offline.
    - If there are no indications of device malfunction as the cause for lost connectivity, the glucose level is in safe range, and a participant chooses to remain in an area with poor network coverage, we will instruct the participant to check the BP display or CGM at least every 20 minutes for alert icons and to be aware that we are unable to monitor for severe lows or highs at this time.
    - We will call the participant every 2 hours to check on safety and device function until remote monitoring is restored.
- The remote monitoring system will generate an alarm if the CGM glucose is < 50 mg/dl for 15 minutes.
    - When an alert comes to the monitoring station, a study staff member will contact the participant on any of the provided phone numbers. If staff remains unable to contact the participant, they will call the designated contact on any of the provided phone numbers.
    - Study staff will verify the participants are aware of the hypoglycemia and taking action to treat it. Participants will be reminded of the protocol for hypoglycemia, and the study provider will ensure they understand and will follow study procedures. Participants will be encouraged to follow up with any questions or concerns. All contact with the participants in response to hypoglycemia alarms will be documented.
    - In the case of a low threshold alarm with no response from the participant and no success in locating them or their designated contact, the site principal investigator will be immediately informed. If remote monitoring shows ongoing hypoglycemia, a decision may be made to dispatch emergency medical services to the locations the participant is known to frequent.
    - Remote monitoring for hypoglycemia will be the same in all study arms.
- The remote monitoring system will generate an alarm if the CGM glucose is > 300 mg/dl for 90 minutes.
    - Participants will be reminded of the protocol for prolonged hyperglycemia, and the study provider will ensure they understand and will follow study procedures. Participants will be encouraged to follow up with any questions or concerns. All contact with the participants in response to hyperglycemia alarms will be documented.
    - Remote monitoring for hyperglycemia will be the same in all study arms.
- If there is a technical problem with the bionic pancreas that cannot be resolved over the phone, a member of study staff may be dispatched to the location of the subject to provide in-person assistance. The subject may be asked to come to the Diabetes Research Center or study staff may meet them in another public place. If this is not possible or would be too disruptive (i.e. in the middle of the night) the subject will be asked to take over their own glycemic control using their insulin pump until such time as a meeting can be arranged for in-person inspection of the device. This should occur in most cases within 12 hours. Staff will not go into subjects' houses or other non-public places; nor will they go to any place to meet the subject that is not public or where they do not feel safe.

V. d. v. Visit Procedures
Test Run Visit Procedures
Day 1:

- The body weight of the subject will be documented.
- A urine pregnancy test will be performed in female volunteers at the start of the Test Run. 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.
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.

- The subjects will place a Dexcom G5 sensor and study staff will confirm they are doing it properly.
- Study staff will provide supplies and review the study procedures. The BC222 Lispro will be provided. Study staff will supervise the setup of the iLet and infusion set.
- The control algorithm will be initialized only with the subject's weight. Diagnostics will be performed to ensure that the Dexcom CGM device is appropriately calibrated and that all the components of the bionic pancreas are in good communication with each other.
- The subject's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed.
- Subjects will remain in the clinic during the day under supervision of study staff, following the policies described above. At the end of the day, subjects will be discharged to home.

On Days 2 and 3, subjects will arrive to the clinic after fasting for 8 hours and begin the meal challenge, according to the protocol described below. At the completion of the 4-hour meal challenge, subjects will eat lunch and announce the meal to the bionic pancreas. Subjects will remain under supervision of the study staff during the day, following the policies described above. At the end of each day, subjects will be discharged to home. The visit procedures described below for days 1-7 of each arm of the RCT portion of the study will also be followed during the 3-day Test Run.

At the end of the third day, the Test Run will be stopped.

- The body weight of the subject will be documented
- Any changes to medications or medical history and any adverse events that may have occurred since the last study visit will be documented
- Anti-insulin antibody and plasma blood samples will be collected
- The Dexcom CGM sensor and all bionic pancreas infusion sites will be removed.
- All study devices, including the iLet BP and the study glucometer will be downloaded.
- Used and unused insulin vials will be returned.
- All equipment will be collected and cleaned. The Dexcom G5 transmitter will be cleaned using the validated cleaning and disinfecting procedures.
- Subjects will be reminded to bring their own pump, supplies and insulin to this visit.
- A provider (MD or NP) will review the last several hours of insulin dosing and assist the subject in resuming their usual care.

RCT Visit Procedures

Day 1 Visits:

- On arrival to the first study visit, subjects will answer the pre-study questionnaires.
- The body weight of the subject will be documented.
- A urine pregnancy test will be performed in female volunteers at the start of the first arm. 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.
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.
- The subjects will place a Dexcom G5 sensor and study staff will confirm they are doing it properly.
- Study staff will provide supplies and review the study procedures. The insulin the subject has been assigned to for that week will be provided. Study staff will supervise the setup of the iLet and infusion set.
- The control algorithm will be initialized only with the subject's weight. Diagnostics will be performed to ensure that the Dexcom CGM device is appropriately calibrated and that all the components of the bionic pancreas are in good communication with each other.
- The subject's own insulin infusion pump will be stopped and disconnected, and its infusion set will be

removed.

- Study staff will start the bionic pancreas and will verify that data streaming is working prior to the subject leaving the Diabetes Research Center.

Days 1-7:

- The subjects will calibrate the Dexcom CGM twice daily, preferably before breakfast and supper, using the Contour Next One.
    - Subjects will be advised to delay calibration if there is a steep rise or fall in the blood glucose (>2 mg/dl/min) or if there has been carbohydrate intake in the last 30 minutes. In the immediate aftermath of carbohydrate intake, it is possible for the BG to be rising without a change in interstitial fluid glucose. If a calibration is delayed for any of these reasons, it will be performed at the next opportunity.
    - Subjects may perform additional calibrations if the Dexcom CGM is inaccurate relative to a BG measurement as long as they do not calibrate within 30 minutes of food intake. Subjects will be discouraged from performing extra calibrations if the Dexcom CGM is within 15 mg/dl when the BG is ≤ 75 mg/dl and within 20% if the BG is >75 mg/dl at times when the rate of change is low. They will also be trained to understand that the apparent error can be higher than this when the BG is changing rapidly, and that it is typical for the Dexcom CGM to underestimate BG when the trend is upward and to overestimate BG when the trend is downward as a result of physiologic lag. Errors in these directions should typically not prompt extra calibrations unless they are very large (≥ 50%).
- If there is a technical fault with the bionic pancreas, study staff will troubleshoot this with the subject. If necessary, a staff member will meet the subject to assist with troubleshooting. This meeting may be delayed until morning if the problem occurs overnight - in this case, the subject will use their own pump until a meeting is possible. If necessary, the bionic pancreas control unit may be replaced.
    - When meeting subjects in an off-site location, the principal investigator will always be notified. A member of the clinical team (MD, NP or RN) will be dispatched if the problem is clinical in nature. If the principal investigator determines the problem to be purely technical, a trained engineer may be dispatched to assist the subject with troubleshooting their device.
    - If there is a complete failure of bionic pancreas operation and it is anticipated that restarting it will take more than an hour, subjects may take over their own BG control using their own insulin pump or with insulin injections until the bionic pancreas can be brought back online with the help of study staff. During the day, this should be rare. If the failure occurs at night, every effort should be made to correct the problem as soon as possible, which should almost always be possible within 12 hours.
    - If a Dexcom CGM sensor fails during the course of an experiment the system will provide basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated as Dexcom CGM data and may result in administration of insulin. The Dexcom CGM sensor will be replaced as soon as possible and normal bionic pancreas control will resume when the new sensor is calibrated.
- If the subject cannot be reached at night, then the designated contact will be called and asked to wake the subject so that troubleshooting can be performed.
- Subjects will be trained on troubleshooting for various scenarios that could lead to a low glucose threshold alarm. For instance, a low glucose threshold alarm could be due to true hypoglycemia, poor Dexcom CGM calibration, or a compression artifact at the site of the sensor.
    - The first step for all low glucose-related alarms will be to perform a finger stick BG measurement.
    - If the BG measurement is not consistent with the fact that a threshold alarm has occurred: the subject will assess the possibility of a compression artifact (they will be trained in the causes and recognition of these events). If a compression artifact is suspected, they will take steps to relieve the pressure on the transmitter. If compression is not suspected, they will calibrate the Dexcom

CGM as long as there has been no food or carbohydrate intake in the last 30 minutes. If a calibration is delayed for this reason, it will be performed at the next opportunity.
    - If the BG measurement is consistent with a low threshold alarm: the subject will treat hypoglycemia with carbohydrate ingestion according to their usual practice.
- Subjects will be asked to change their insulin infusion set and reservoir at least every other day throughout the study.
- Subject will also be instructed to change the iLet batteries during each insulin reservoir change.
- Subjects will be trained on troubleshooting for various scenarios that could lead to hyperglycemia. For instance, hyperglycemia could be due to true hyperglycemia or poor Dexcom CGM calibration.
    - The first step in responding to hyperglycemia according to the CGM will be to perform a finger stick BG measurement.
    - If the BG measurement is not consistent with the CGMG: the subject will calibrate the Dexcom CGM as long as there has been no carbohydrate intake in the last 30 minutes and there is no steep rise or fall in glucose (>2 mg/dl/min). If a calibration is delayed for this reason, it will be performed at the next opportunity.
    - If the BG measurement is consistent with the CGMG: the subject will investigate their insulin infusion site and consider replacing it, check for any occlusions along the insulin fluid path, and check to make sure that the insulin cartridge is not empty.
- Subjects will be asked and strongly encouraged to announce the three major meals of the day, but not snacks, to the bionic pancreas. The meal announcement will consist of choosing the type of meal (breakfast, lunch, dinner) and the size of the meal relative to typical meals for that subject (tiny, small, typical, large).

Meal Challenges

- During all study arms, subjects will be asked to complete two meal challenges at home to help identify any changes in glucose control on each insulin in response to a standardized meal and bolus.
- Meal challenges will be completed twice in each arm, and must be done during days 3-7, but not on the first 2 days of the arm.
- All meal challenges will be completed using a BOOST High Protein 8-ounce meal replacement drink. This will be provided to the subject at the beginning of each arm.
- Subjects will be asked to follow the protocol below:
    - Fast after 10:00 PM. Only water and non-caloric beverages will be allowed. Subjects will be instructed to follow the same protocols for any hypoglycemia or hyperglycemia that occurs during the fasting period. They will be asked to limit hypoglycemia treatment to simple, rapid-acting carbohydrates over complex carbohydrates wherever possible. Subjects will be encouraged to have a bedtime snack prior to initiating fasting as needed. They will be encouraged to contact study staff with any questions, and remote monitoring will remain in place.
    - Announce no meals on the BP after 10:00 PM.
    - After at least approximately 8 hours of fasting, all subjects will be required to check a fingerstick glucose immediately prior to beginning the meal challenge and use that glucose to calibrate their Dexcom G5 CGM.
    - Subjects will be instructed to announce the BOOST drink to the bionic pancreas immediately before drinking it. They will be instructed to announce the meal as tiny, small, typical, or large relative to their usual breakfast. They must use the same size meal announcement for each meal challenge they complete on the bionic pancreas.
    - Once they have calibrated their CGM and confirmed the appropriate insulin dose has been delivered by the iLet, subjects will immediately drink the provided 8-ounce BOOST high protein meal replacement drink.
    - Once they finish the BOOST, subjects will be asked to resume fasting for four additional hours,

until the meal challenge is complete. Water and non-caloric beverages are allowed. Subjects will be instructed to follow the same protocols for treating any hypoglycemia or hyperglycemia that occurs during the fasting period. They will be asked to limit hypoglycemia treatment to simple, rapid-acting carbohydrates over complex carbohydrates wherever possible.
    - We will ask subjects to check an additional blood glucose using the provided glucometer 1 hour, 2 hours and 4 hours after drinking the BOOST. Subjects will otherwise be allowed and encouraged to check their blood glucose as needed before, during and after the meal challenge. If they experience prolonged hyperglycemia, study staff may recommend they replace their infusion set. No corrections of insulin or other additional boluses or meal announcements may be taken during the meal challenge.
    - After 4 hours, the meal challenge is complete. At this time subjects are allowed to eat and bolus/announce meals at their discretion.
- Subjects will document when they did the meal challenges in each arm, including what day and time they drank each BOOST. Insulin doses given, CGM readings and fingerstick blood glucose readings will be collated from the device downloads at the end of each arm for analysis of these meal challenges.

Day 7/Day 1 Visits:

- At the end of the 7-day period, subjects will return to the clinic and answer the post questionnaires for the study arm.
- The body weight of the subject will be documented
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.
- All study devices, including the iLet BP and the study glucometer will be downloaded. The memory of the BP will be wiped and it will be re-initialized for the next study period. Diagnostics will be performed to ensure that the Dexcom CGM device is appropriately calibrated and that all of the components of the bionic pancreas are in good communication with each other.
- Used and unused insulin vials will be returned to prevent the subject from using the wrong insulin during the wrong week.
- Anti-insulin antibody and plasma blood samples will be collected.
- Subjects will have the option to begin the next arm of the study on the same day they complete the previous study arm.
    - If subject choose this option, they will start over with Day 1 procedures:
        - If the Dexcom CGM has not already been replaced, it will be replaced at this time.
        - Study staff will provide supplies, including the next week's insulin, and review the study procedures.
        - Study staff will supervise the setup of the iLet and infusion set. Participants will need to fill the iLet with a new reservoir and place a new infusion set at the start of each new study arm.
        - Study staff will start the bionic pancreas and will verify that data streaming is working prior to the subject leaving the Diabetes Research Center.
    - If subjects choose to not continue directly to the next arm of the study, the Dexcom CGM sensor will be removed, all bionic pancreas infusion sites will be removed, subjects will put their own pump back on, and they will be discharged.
        - A provider (MD or NP) will review the last several hours of insulin dosing and assist the subject in resuming their usual care.
        - The next arm of the study will be scheduled to begin up to 14 days from the end of the previous study arm.

Final Day 7 Visit:

- At the end of the 7-day period, subjects will return to the clinic and answer the post questionnaires for the study arm.

- The body weight of the subject will be documented
- Any changes to medications or medical history and any adverse events that may have occurred since the last study visit will be documented
- Anti-insulin antibody and plasma blood samples will be collected
- The Dexcom CGM sensor and all bionic pancreas infusion sites will be removed.
- All study devices, including the iLet BP and the study glucometer will be downloaded.
- Used and unused insulin vials will be returned.
- All equipment will be collected and cleaned. The Dexcom G5 transmitter will be cleaned using the validated cleaning and disinfecting procedures.
- Subjects will be reminded to bring their own pump, supplies and insulin to this visit.
- A provider (MD or NP) will review the last several hours of insulin dosing and assist the subject in resuming their usual care.

V. d. vi. Response to Hypoglycemia

- The response to hypoglycemia is the same for the Test Run, the RCT portion of the study and before, during and after the meal challenges.
- The Dexcom G5 app will generate a local low glucose threshold alarm if the subject's CGM value is ≤70 mg/dl and the iLet BP will generate an alarm for a CGMG <50 mg/dl.
- In all study arms subjects are encouraged to check their BG for any symptoms of hypoglycemia.
- Subjects are encouraged to treat hypoglycemia according their usual practice or according to the "rule of 15s": take 15 grams of rapid acting carbohydrate and recheck in 15 minutes, then repeat as needed.
- The designated contact will be trained in the signs and symptoms of hypoglycemia and the protocols for treating it. They will also be trained in the use of the glucagon rescue kit. If they should find the subject unresponsive they are to use the glucagon rescue kit and call 911.
- Subjects may contact a study provider (RN, MD or NP) for advice at any time, and may contact the troubleshooting support team, as they wish. Subjects will be assisted in checking the bionic pancreas for any malfunction and correcting 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 brought to the subject's location by study staff.
- If a subject experiences a seizure or unconsciousness associated with hypoglycemia in the study, his or her participation in the study will be discontinued.

V. d. vii. Response to Hyperglycemia

- The response to hyperglycemia is the same for the Test Run, the RCT portion of the study and before, during and after the meal challenges.
- The Dexcom G5 app will generate a local high glucose threshold alarm if the subject's CGM value is > 250 mg/dl. Subjects will be instructed to check their insulin infusion site and their bionic pancreas for normal operation any time BG is greater than 250 mg/dl. If there is any suspicion of insulin infusion set malfunction, the site should be replaced.
- Subjects may contact a study provider (MD or NP) for advice at any time, and may contact the troubleshooting support team, as they wish. Subjects will be assisted in checking the bionic pancreas for any malfunction and correcting 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 brought to the subject's location by study staff.
- If a subject experiences diabetic ketoacidosis requiring hospitalization during the study, his or her participation in the study will be discontinued.

V. d viii. Response to Other Medical Needs

If the subject experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will see their personal physician. 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. ix. Monitoring of Bionic Pancreas Performance

Collaborators from Beta Bionics will be readily available by phone for consultation at all times during the course of each experiment. Their team of engineers will train study staff on the appropriate use of the iLet and provide support as needed.

V. d. x. Supervision by Study Staff

A study provider (MD or NP) will be on call at all times during the course of all study arms. All trained staff will have the capability of remotely viewing glucose information to facilitate troubleshooting with subjects and decide whether additional assistance is needed. Subjects in the Test Run period will be under close supervision by study staff during the day on each of the three days.

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
- History of exposure to non-human insulin or insulin analogs (type, timing, duration)
- Usage of CGM (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
- EKG if applicable
- Hemoglobin A1c
- Anti-insulin antibody titers
- Plasma, for future insulin antibody assays
- Urine HCG (pre-menopausal females)
- eGFR

VI. a. 2. All Study Arms (including the Test Run period):

- CGMG (CGM glucose) every five minutes from the Dexcom CGM
- All fingerstick BG measurements taken by the subject (meter download)
- Insulin total daily dose from bionic pancreas download
- Timing of meal announcements and size of meals announced from bionic pancreas download

- Day, time, fingerstick BG measurements, CGMG readings, and insulin doses from each meal challenge
- Time subjects were not under bionic pancreas control
- List of technical faults associated with the bionic pancreas including cause and resolution
- Body weight after each study arm
- Anti-insulin antibody titers and plasma after each study arm
- Date of last menstrual period
- Information collected from the daily email survey and phone calls including but not limited to hypoglycemia, carbohydrate interventions, any nausea and/or vomiting, any other adverse events, time spent exercising each day, exercise intensity, and exercise exposure (time X intensity), any unscheduled infusion set changes or Dexcom CGM sensor changes, and alcohol intake.
- Data from questionnaires about attitudes and expectations regarding the bionic pancreas at baseline and on day 7 of each arm (RCT portion the study only).

VI. b. Study Endpoints

Statistical comparisons will be made between insulin analogs within a single participant. Three pairwise comparisons will be made between arms.

Data from the uncontrolled Test Run period will be reviewed to verify safety before proceeding with the RCT portion of the study. Descriptive statistics will be compiled based on the same analyses planned for the RCT portion of the study but no formal statistical analyses will be done. This period has no control and is intended to verify the iLet with BC222 lispro is safe and operating as expected prior to initiating outpatient experiments in a larger cohort.

VI. b. 1. Co-Primary endpoint analyses

The co-primary outcomes will be mean CGMG and fraction of time spent with CGMG <54 mg/dl.

VI. b. 2. Secondary endpoint analyses

Secondary analyses will include:

- Fraction of time spent within each of the following ranges:
  - < 50 mg/dl
  - < 60 mg/dl
  - < 70 mg/dl
  - 70-120 mg/dl
  - 70-180 mg/dl
  - >180 mg/dl
  - >250 mg/dl
- Within day coefficient of variation (CV)
- Mean postprandial excursion (difference in CGMG from the beginning of the meal challenge to the peak CGMG in the 4 hours after the meal) for both mixed meal challenges
- Number of symptomatic hypoglycemic events per day
- Grams of carbohydrate consumed to treat hypoglycemia per day
- TDD of insulin

VI. b. 3. Other Outcomes

- Mean number of meal announcements per day
- CGM Reliability index, calculated as percent of possible values actually recorded by CGM
- CGM MARD from Dexcom G5 CGM versus time-stamped BG values from meter downloads (any other BG values will not be considered)
- Percentage of days with mean CGM glucose < 154 mg/dl (estimated average glucose corresponding to

an A1c of 7%)

- Mean postprandial AUC (4 hours following each meal challenge) for both mixed meal challenges
- Mean number of daily BG measurements
- Number of severe hypoglycemic events (subject unable to self-treat, requiring the assistance of another person)
- Mean daily basal insulin dose
- Mean daily bolus insulin dose
- List of technical faults associated with the bionic pancreas including cause and resolution

The primary analysis of the designated endpoints will be calculated on an intention-to-treat basis. In cases where an arm was not completed we will use the available data from that arm in the data analysis. We will calculate percentages, means standard deviations (and medians and interquartile ranges as appropriate), and ranges in descriptive analyses. We will use paired t-test for comparison of means for normally distributed outcomes and the Wilcoxon Signed Rank test for comparisons of medians on non-normally distributed outcomes. In a secondary analysis we will look for any period effect and any interaction between treatment and period, although no such interaction is predicted and there is probably insufficient power to identify a small interaction. We may, in exploratory analyses, also stratify subjects for secondary analyses of the pre-specified endpoints by the following characteristics: sex, age, usual care insulin total daily dose, body mass index, baseline A1c, and use of CGM in usual care.

VI. c. Power Analysis

As this study is exploratory in nature, no formal power analysis has been performed. From our insulin specific data collected in our previous study, we identified 7 out of 22 had a difference in tmax, 6 out of 22 had a difference in t1/2max and 14 out of 22 had a difference in terminal half-life. We'd like to recruit all 22 of these subjects to participate in this study. Given the occurrence rate of different PK profiles, we believe this will still capture significant information. The sample size of 4 for the Test Run period is a convenience sample with no statistical implications.

We previously showed in a multicenter, outpatient, random-order crossover trial (n=39, 11 days each arm) that the bionic pancreas (BP) reduced group mean CGM glucose (141±10 vs. 162±29 mg/dl, p<0.0001) and percent of time spent <60 mg/dl (0.6±0.6% vs. 1.9±1.7%, p<0.0001) relative to usual care (UC) with pump ± CGM (El-Khatib FH, et al. Lancet. 2017; 389:369–80). We applied a statistical approach to these data that we will use in this study for comparisons within subjects to determine how many individuals saw benefit for each outcome. We compared the average CGM glucose and average time <60 mg/dl between the BP and UC arms for each patient using autoregressive time series models to determine significance of differences. We found that 72% of subjects had a statistically significant reduction in mean CGM glucose, 51% had significant reduction in time <60 mg/dl, 44% had a significant reduction in both, and 97% had a significant reduction in at least one outcome. These analyses provide a new prospective on the efficacy of the BP emphasizing the benefit to individuals rather than the group as a whole. Subjects least likely to benefit were those who had extremely tight glycemic control and minimal hypoglycemia under UC.

VII. Risks and Discomforts

Subjects may experience mild discomfort associated with the insertion of the infusion set and the Dexcom sensor into the SC tissues. This is expected to be the same as their usual care.

There is a risk of hypoglycemia. This risk is expected to be less than the risk during the subjects' lives outside the trial based on data from earlier trials. All of our previous studies have shown that hypoglycemia is significantly reduced in all configurations of the bionic pancreas when compared with usual care. Based on our experience,

we believe that the risk of hypoglycemia will be less than or equal to the risks that they are exposed to on a daily basis while living with type 1 diabetes outside of the trial.

Even though no increase in hypoglycemia was observed in subjects with T1D using BC222 inuslin lispro under MDI or open-loop regimen, there may be an increased risk of hypoglycemia with the ultra-rapid BC222 insulin lispro, which is expected to have a faster onset than rapid acting analogs. Subjects will be trained on the recognition and treatment of hypoglycemia, and the risk of using an ultra-rapid insulin will be explained to them. We anticipate the bionic pancreas will adapt to the faster pharmacokinetic profile of BC222 insulin lispro, and that hypoglycemia will not be higher than what the insulin-only bionic pancreas is able to achieve with rapid-acting insulin. We believe that the risk of hypoglycemia is further mitigated by keeping the PK parameter settings of the iLet at 65 minutes, despite the possibility BC222 is faster than that. The Test Run period using BC222 lispro in the iLet in a supervised setting will be completed and reviewed for safety prior to initiating any outpatient experiments using BC222 lispro.

There is a risk of hyperglycemia. This risk is expected to be similar to or less than the risk during the subjects' lives outside of the trial based on data from earlier trials in subjects with type 1 diabetes.

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 than they typically achieve.

Subjects are expected to benefit in all arms of the study from the formal involvement of a designated contact who will serve as a backup to respond to any overnight threshold alarms to which the subject does not respond.

The data obtained may be used to improve diabetes care, and the bionic pancreas, by identifying the advantages of individualizing insulin use based on a personalized PK profile. If participants are able to easily identify a type of insulin that can optimize their glycemic control, they could have better outcomes regardless of their insulin delivery method. This study is a necessary step in making individualized insulin prescriptions based on PK parameters a reality. In addition, this study will provide useful data in preparing the bionic pancreas to become available to people with type 1 diabetes. Wide availability of the bionic pancreas could improve the care in adults and children with 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, Dexcom CGM data will be collected in various ways. Dexcom CGM data, calibration data, and insulin dosing data will be automatically stored in the bionic pancreas device (from which it will be downloaded at intervals) and wirelessly streamed to the cloud where it will be stored to provide redundancy in data storage and mitigate the risk of data loss. 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 subject's 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 may be shared with collaborators at Beta Bionics and Adocia but only in a form in which all personally identifiable information has been removed (e.g. combined database including BG values, CGM values, and record of insulin delivered by the device). 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. The DSMB will be responsible for overseeing the transition from the Test Run period to the RCT portion of the study. They will be informed of any events described in the stopping criteria below that occur in the Test Run period. If there are no events for DSMB review, then the RCT portion of the study will be initiated prior to their review of the data.

Additionally, the DSMB will be informed in the event of any severe or unexpected adverse events in the RCT portion of the study. The DSMB will have unblinded access to the drug assignments to assess whether adverse events are associated with insulin administration. 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.

The participation of individual subjects will be discontinued if they experience:

- Subjects experience one episode of diabetic ketoacidosis (DKA) requiring hospitalization
    - Hyperglycemic events will be classified as DKA if the following are present:
        - Symptoms including but not limited to polyuria, polydipsia, nausea or vomiting
        - Serum ketones > 1.5 mmol/L or large/moderate urine ketones
        - Either arterial blood pH <7.30 or venous pH < 7.24, or serum bicarbonate < 15
        - Treatment provided in a healthcare facility
- Subjects experience one episode of severe hypoglycemia, defined as requiring the assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon or other resuscitative actions. This means the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is sufficient evidence that the event was induced by a low plasma glucose concentration.
- The investigator believes it is unsafe for the participant to continue in the study
- A participant becomes pregnant

- The participant requests that the study be stopped

If more than 1 subject must be withdrawn from the study for DKA requiring hospitalization or seizure or unconsciousness associated with hypoglycemia 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 concurrent 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 Definitions and Reporting Guidelines

Definitions

An **adverse event** is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Hypoglycemic events are recorded as Adverse Events (severe hypoglycemic event) if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

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

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

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

The PI and co-investigators will review any adverse events after each experiment to determine severity (serious or non-serious), expectedness (expected or unexpected) and relatedness (related, possibly related or unrelated). The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study intervention.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Related: There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study

intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

Possibly Related: Possibly related to the research means there is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)). Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures

Not Related: Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

Serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death
- is life threatening (places the subject at immediate risk of death from the event as it occurred)
- requires inpatient hospitalization or prolongation of existing hospitalization; • results in a persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Guidelines

Any serious adverse events or unexpected but related or 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 and to the BU IRB. Collaborator Ed Damiano is the sponsor of the Investigational Device Exception (IDE) for the bionic pancreas to be used in this trial. Adocia is the sponsor for the Investigational New Drug (IND) application for BC222 insulin lispro to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE and IND.

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.

Test Run participants will be compensated $50 per day. The total compensation for a subject who completed the Test Run would be $175. Parking expenses will be paid for up to $30 per subject per day. Subjects who are unable to complete the Test Run or choose to stop participation will receive prorated compensation for the portion of the study visits that they complete. Test Run designated contacts will be compensated $50 to complete the screening/consent visit. They will be compensated $50 for completing the study. The total compensation for a Test Run designated contact would be $100.

Study participants will be compensated $50 for completing each study visit. Thus the total compensation for a subject who completed the study would be $225. Parking expenses will be paid for up to $30 per subject for each visit. Subjects who are unable to complete the study or chose to stop participation will receive prorated

compensation for the portion of the study visits that they complete. Designated contacts for subjects will be compensated $50 to complete the screening/consent visit. They will be compensated $50 for completing the study. Thus, the total compensation for a designated contact would be $100.

Subjects who complete both the Test Run and the RCT portion of the study will be compensated up to $375. Designated contacts who complete both the Test Run and the RCT portion of the study will be compensated up to $150. If re-screening is required between the Test Run and the RCT, subjects and designated contacts will be compensated for the additional screening visit, bringing the total compensation up to $400 and $200 respectively.

XI. References

1. The Diabetes Control and Complications Trial research Group (DCCT) (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N. Engl. J. Med. 329, 977–986.
2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group (2005) Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. N. Engl. J. Med. 353, 2643–2653.
3. El-Khatib, F. H., Jiang, J., Gerrity, R. G. & Damiano, E. R. (2007) Pharmacodynamics and stability of subcutaneously infused glucagon in a type 1 diabetic swine model in vivo. Diabetes Technol. & Ther. 9, 135-144
4. El-Khatib, F. H., Jiang, J. & Damiano, E. R. (2007) Adaptive closed-loop control provides blood-glucose regulation in vivo using dual subcutaneous of insulin and glucagon infusion Diabetes Sci. & Technol. 2, 181-192.
5. El-Khatib, F. H., Russell, S. J., Nathan, D. M., Sutherlin, R. G., Damiano, E.R. (2010) A Bi-Hormonal Closed-Loop Blood Glucose Control Device for Type 1 Diabetes. Science Translational Medicine 2, 27ra27.
6. Russell, S.J., El-Khatib, F.H., Nathan, D. M., Magyar, K. L., Jiang, J., Damiano, E.R. (2012) Blood glucose control in type 1 diabetes with a bi-hormonal bionic endocrine pancreas. Diabetes Care 35, 2148-55.
7. El-Khatib, F.H., Russell, S.J., Magyar, K.L., Sinha, M., McKeon, K., Nathan, D.M., Damiano, E.R. (2014) Autonomous and continuous adaptation of a bi-hormonal bionic pancreas in adults and adolescents with type 1 diabetes. J. Clin. Endocrin. Metab. Early Release, http://dx.doi.org/10.1210/jc.2013-4151.
8. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon, K, Goergen L, Balliro C, Hillard M, Nathan DM, Damiano ER. Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes. New England Journal of Medicine 2014; 371 (4), 313-325.
9. SJ Russell, MA Hillard, CA Balliro, KL Magyar, R Selagamsetty, M Sinha, K Grennan, D Mondesir, L Ehklaspour, H Zheng, ER Damiano, FH El-Khatib. Randomized Outpatient Trial Comparing Day and Night Glycemic Control between a Bionic Pancreas and Conventional Insulin Pump Therapy in Preadolescent Children with Type 1 Diabetes. The Lancet Diabetes and Endocrinology 2016; 4:233-43.
10. FH El-Khatib, CA Balliro, M Hillard, K Magyar, L Ekhlaspour, M Sinha, D Mondesir, A Esmaeili, C Hartigan, MJ Thompson, S Malkani, JP Lock, DM Harlan, P Clinton, E Frank, DM Wilson, D DeSalvo, L Norlander, T Ly, BA Buckingham, J Diner, M Dezube, LA Young, A Goley, MS Kirkman, JB Buse, H Zheng, RR Selagamsetty, ER Damiano, SJ Russell. Home Use of a Bihormonal Bionic Pancreas versus Insulin Pump Therapy in Adults with Type 1 Diabetes: a Multicentre Randomised Crossover Trial. The Lancet 2017; 389(10067):369-380.
11. Garcia, A., Rack-Gomer, A.L., Bhavaraju, N.C., Hampapuram, H., Kamath, A., Peyser, T., Facchinetti, A., Zecchin, C., Sparacino, G., Cobelli, C. (2013) Dexcom G4AP: an advanced continuous glucose monitor for the artificial pancreas. Journal of Diabetes Science and Technololgy 7, 1436-45.
12. Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH, Jr. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. Diabetes Care 2003; 26(1):89-96.
13. Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rastam J. Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. Diabetes Care 2002;25(5):876-82.
14. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004; 27(10):2363-8.
15. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med

2008;25(4):442-9.
16. Francis AJ, Hanning I, Alberti KG. The influence of insulin antibody levels on the plasma profiles and action of subcutaneously injected human and bovine short acting insulins. Diabetologia 1985;28(6):330-4.
17. Van Haeften TW, Heiling VJ, Gerich JE. Adverse effects of insulin antibodies on postprandial plasma glucose and insulin profiles in diabetic patients without immune insulin resistance. Implications for intensive insulin regimens. Diabetes 1987;36(3):305-9.
18. Bolli GB, Dimitriadis GD, Pehling GB, et al. Abnormal glucose counterregulation after subcutaneous insulin in insulin-dependent diabetes mellitus. N Engl J Med 1984;310(26):1706-
19. Davidson JK, DeBra DW. Immunologic insulin resistance. Diabetes 1978;27(3):307-18.
20. Van Haeften TW, Bolli GB, Dimitriadis GD, Gottesman IS, Horwitz DL, Gerich JE. Effect of insulin antibodies and their kinetic characteristics on plasma free insulin dynamics in patients with diabetes mellitus. Metabolism 1986; 35(7):649-56.
21. Thomas JW, Virta VJ, Nell LJ. Heterogeneity and specificity of human anti-insulin antibodies determined by isoelectric focusing. J Immunol 1985;134(2):1048-52.

XII. Appendices

XII. a. Appendix A: Verizon Network Coverage Map

Figure 1: Nationwide Verizon Network Coverage Map (https://ss7.vzw.com/is/image/VerizonWireless/network-lp-marq-6-d-05152017?&scl=2)

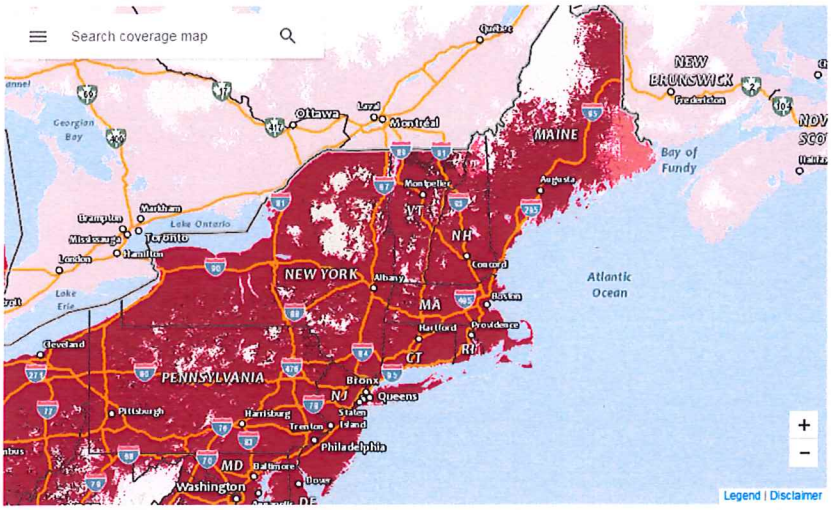

Figure 2: Detailed Verizon Network Coverage Map (https://www.verizonwireless.com/featured/better-matters/)