The Insulin-Only Bionic Pancreas Bridging Study

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Acronym	Abbreviation For
ADA	American Diabetes Association
ADE	Adverse Device Effect
AOC	Area Over the Curve
AUC	Area Under the Curve
BG	Blood Glucose
BP	Bionic Pancreas
BPMC	Bionic Pancreas Multi-Center
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
CV	Coefficient Variation
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EKG	Electrocardiogram
FDA	Food and Drug Administration
FDR	False Discovery Rate
GCP	Good Clinical Practice
GUI	Graphical User Interface
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
HCG	Human Chorionic Gonadotropin
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IOBP	Insulin-only Bionic Pancreas
IQR	Interquartile Range
IRB	Internal Review Board
JCHR	Jaeb Center for Health Research
LBGI	Low Blood Glucose Index
MDI	Multiple Daily Injections
MODD	Mode of Daily Difference
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NYHA	New York Heart Association
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled/Clinical Trial
RBM	Risk-Based Monitoring
SC	Subcutaneous

Acronym	Abbreviation For
SD	Standard Deviation
TIA	Transient Ischemic Attack
T1D	Type 1 Diabetes
UC	Usual Care
UADE	Unanticipated Adverse Device Effect
UI	User Interface

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDDK Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date: _____
Signature

CHAPTER 1: INTRODUCTION

1.1. Background and Rationale

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

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

Recent years have seen the development of several competing strategies for automated or semi-automated management of glycemia. One large difference between competing designs is whether they use insulin alone (insulin-only) and rely on the user treating with carbohydrates if the blood glucose falls too low, or insulin and glucagon (bihormonal) and use glucagon to automatically prevent and treat hypoglycemia, with carbohydrate treatment used only if glucagon treatment is not successful.

Glucagon is an endogenous hormone that binds with high affinity to its cognate receptor. Glucagon is quantitatively the most important counter-regulatory hormone in normal glucose control physiology. In healthy individuals without T1D, glucagon levels rise during exercise, and in the late-postprandial period as glucose levels return to the normal range after a small hyperglycemic excursion. The production of glucagon is dysregulated early in the course of T1D and glucagon production in response to threatened hypoglycemia is lost. Therefore, people with T1D are functionally glucagon deficient.

An important challenge for automated glucose control is that the physiologic need for insulin can change rapidly, but insulin is slowly absorbed when delivered subcutaneously. Even “rapid-acting” insulin analogs such as insulin lispro (Humalog) have a mean time-to-peak of ~70 minutes. This means that if the need for insulin decreases rapidly, such as in the case of exercise, there is already insulin-on-board that cannot be withdrawn. In contrast to insulin, glucagon is absorbed quickly, with a time-to-peak of ~15-20 minutes. Therefore, small doses of glucagon can be given to counter the effects of excess insulin that has already been delivered and cannot be withdrawn, and can prevent hypoglycemic events that could not be prevented by suspending insulin delivery alone.

The use of glucagon provides the BP with a powerful tool to automatically prevent and treat hypoglycemia, but it does present two challenges. First, exogenous glucagon must be shown to be safe when administered in micro-doses intermittently on a chronic basis. A second challenge to the use of glucagon is that a form of glucagon that is stable near body temperature for at least

several days in a pump must be available. When we first began developing our BP, there was no stable form of glucagon available; however, several companies have now developed stable analogs (Zealand, Eli Lilly) and stable formulations (Xeris, Adocia). The clinical programs for the Zealand analog are sufficiently advanced that we are now using it in the BP in preliminary studies, and we expect it to be qualified for pivotal studies by the end of 2018. A third challenge is that, as with subcutaneously administered insulin, replacement of glucagon by subcutaneous administration cannot perfectly mimic normal physiology, and peripheral levels must be higher than normal to generate adequate liver exposure for effectiveness. In our last inpatient study of the BP in adults and adolescents during over 2,300 patient-hours of exposure, frequent blood sampling showed that the aggregate mean glucagon levels were in the normal fasted range (<150 pg/ml by the Millipore radioimmunoassay) between 61% and 91% of the time. Based on these results, we expect that the doses of glucagon used by the bihormonal BP will be safe. However, a stable glucagon is not qualified for chronic use at this time and there will inevitably be additional cost associated with use of a second drug.

Given the various advantages and disadvantages of using glucagon, we have developed a BP system that can be used in either a bihormonal, insulin-only, or glucagon-only mode.

1.2. Bihormonal BP System

We have developed an autonomous, self-learning BP that requires only the participant'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. Our BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors.

Our core technology is our insulin controller, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics. We were the first to incorporate insulin pharmacokinetics (PK) into our algorithm, by augmenting it with a mathematical formulation for estimating the concentration of insulin in the blood and predicting its future concentration. It is essential to compensate for the slow absorption rate of SC insulin analogs (peak time in blood of 30–90 min, clearance in 4–8 hr), and to enable the algorithm to refrain from stacking and overdosing insulin. Furthermore, our MPC algorithm automatically adjusts its insulin-doing aggressiveness continuously and in real time to different insulin needs between individuals and variable needs within the same individual. Running in parallel with our 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, our adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her “basal-rate profile”. Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g. circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g. hormonal changes that occur during puberty or menopause). Our adaptive meal dose controller obviates the need for the user to set, or even know, his or her “carbohydrate-to-insulin ratios”, as it makes automatic adjustments based on dosing history for similar meal announcements made on previous days, and customizes the dose for each individual and for time of day. Our BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It could occur preemptively even if glucose is above range and

it includes a feedback term to account for the pending effects of recent glucagon doses. The amount of glucagon dosed also feeds back on the insulin controller, so that large amounts of glucagon dosing decrease the aggressiveness of the insulin controller.

Taken together, these mathematical algorithms provide a universal framework for a glycemic control strategy that requires no quantitative input from, or participation by, the user (besides entering body weight to initialize the system), but which automatically adapts insulin and glucagon dosing to meet the individual needs of each user. Another challenge we have met is enabling our technology to remain completely autonomous in managing insulin and glucagon delivery even when the CGM is offline. Specifically, when the CGM is offline, our BP invokes the high-resolution "basal rate profile" that it had recently learned and stored when the CGM was online. On the basis of what the system learned and stored about meal announcements when the CGM was online, it is able to respond to meal announcements in the same manner when the CGM is offline. Finally, it automatically responds to user-entered BG values when the CGM is offline by issuing a correction dose of insulin or glucagon based on what it learned about the user's insulin and glucagon needs when the CGM was online. Thus, our BP never relies on, or burdens the user with, the determination of dosing decisions, which inevitably vary in quality and reliability among different users. The BP provides a turnkey solution for people with T1D that comprehensively manages glycemia across a broad range of individual needs and a across a large spectrum of circumstances and challenges to glycemic control.

1.3. Insulin-Only BP System

The BP can also operate in an insulin-only mode. During operation in this mode, all of the other features of the BP operate as usual except that glucagon is not given. In addition, the lowest glucose target that can be chosen by the user (towards which the insulin controller drives down the blood glucose levels) is increased from 100 mg/dl in the bihormonal system to 110 mg/dl in the insulin-only system. This works to reducing the aggressiveness of insulin dosing in the insulin-only system relative to its bihormonal counterpart, with the aim of keeping the amount of hypoglycemia low even at the potential cost of raising the mean glucose level achieved by the insulin-only system. The intended use for such a system would be to provide glycemic control for people with type 2 diabetes who require insulin therapy, and early technology adopters with type 1 diabetes.

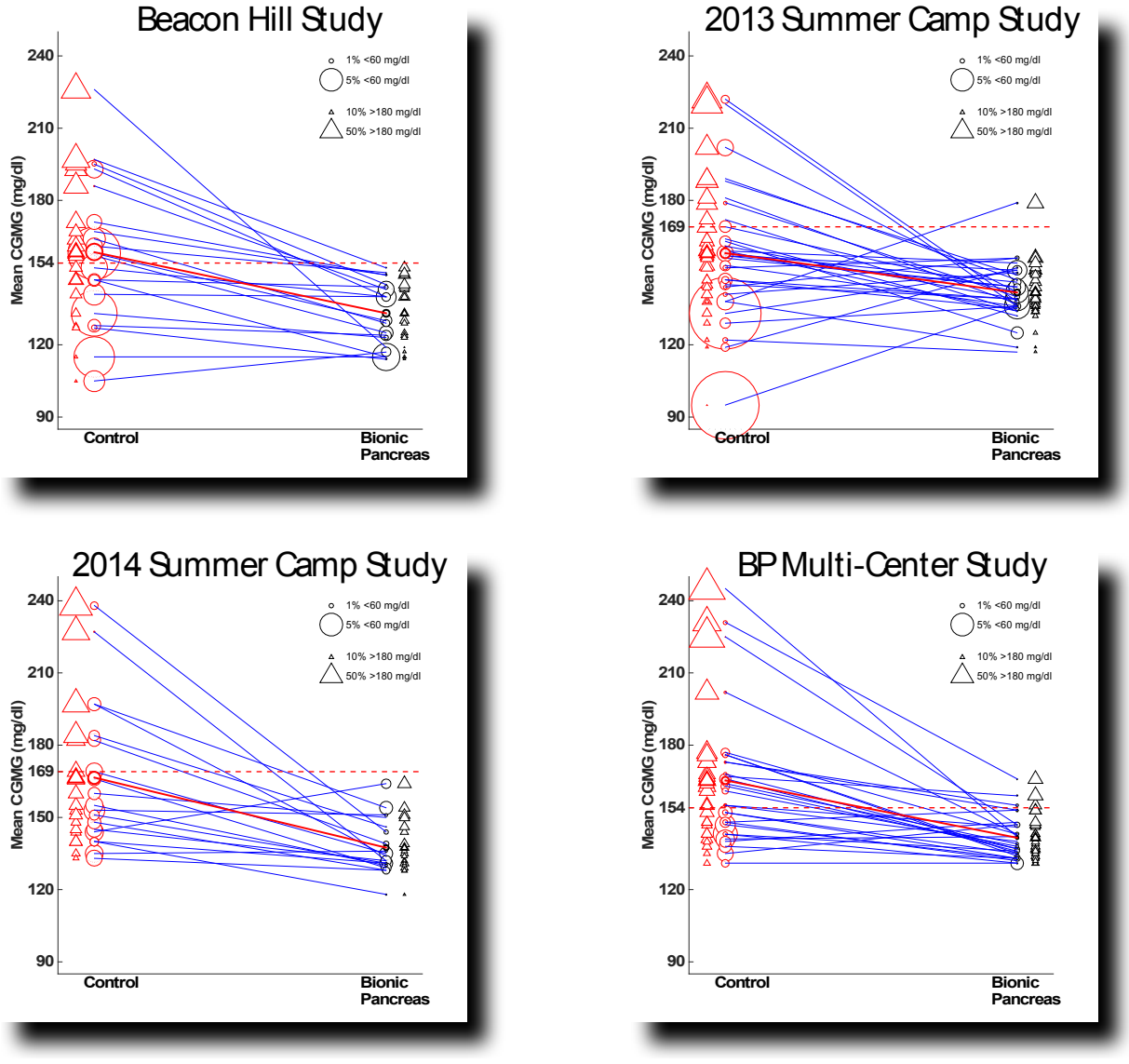
1.4. Glucagon-Only BP System

The BP can also operate in a glucagon-only mode. During operation in this mode, all of the other features of the BP operate as usual except that insulin is not given. The intended use for such a system would be to treat glycemic disorders associated with chronic hypoglycemia (such as congenital hyperinsulinism, insulinoma syndrome, chronic hypoglycemia in post-bariatric surgery patients, etc.).

1.5. 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 2013–2016). Using our iPhone-driven BP system, we have conducted >110 outpatient experiments of 5–11 days in duration in each participant (> 800 patient days or > 2 patient years of data), and across participants ranging in age between 6 and 76 years old and in body mass between 21 and 133 kg. The robust adaptation capabilities of our BP are evident in the fact that the average total daily dose of insulin among these participants varied by over 13-fold (from 11 to 145 units/day).

All of our preclinical studies at BU testing our BP in a diabetic swine model of T1D (between 2005 and 2009), and all of our inpatient clinical trials in the Clinical Research Center at MGH testing our BP in adults and adolescents with T1D (between 2008 and 2012) have set the stage for the outpatient studies that followed. In November 2012 we obtained FDA approval to conduct our first outpatient study testing our bihormonal BP in adults 21 years or older with T1D. This study, which we referred to as the Beacon Hill Study, followed a random-order cross-over design in which 20 adults with T1D participated in 5 days on our iPhone-based BP and 5 days of usual care. In the usual care control period the participants used conventional insulin pump therapy (and their own CGM if they had one), and they wore a CGM with blinded display and muted alarms. In the BP period, participants kept to a three-square-mile geographic area centered around the Beacon Hill neighborhood in Boston. They ate as they chose at local restaurants, and exercised at will with access to two gyms. Analysis was pre-specified to focus on Days 2–5, since glycemic control is more representative of BP performance after most of the adaptation by the BP occurs on Day 1. Results are summarized in the plots and table of Figure 1.



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <60 mg/dl (%)	Bionic Pancreas (BP) % of CGM glucose levels 70–180 mg/dl (%)	Control Mean CGM glucose level (mg/dl)	Control % of CGM goucose values <60 mg/dl (%)	Control % of CGM goucose values 70–180 mg/dl (%)	*p*-value (BP versus Control) for: Mean CGM glucose level	*p*-value (BP versus Control) for: % of CGM glucose values <60 mg/dl	*p*-value (BP versus Control) for: % of CGM glucose values 70–180 mg/dl
Beacon Hill (n=20, 5-day experiments)	≥21	133	1.5	80	159	3.7	59	<0.001	0.020	<0.001
2013 Summer Camp (n=32, 5-day experiments)	12–20	142	1.3	76	158	2.2	65	0.004	0.192	<0.001
2014 Summer Camp (n=19, 5-day experiments)	6–11	137	1.2	81	168	2.8	58	0.004	0.001	<0.001
BP Multi-Center (n=39, 11-day experiments)	≥18	141	0.6	78	162	1.9	62	<0.001	<0.001	<0.001

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

In April 2013, we obtained FDA approval to conduct our first outpatient study testing our bihormonal BP in adolescents 12–20 years old with T1D. This study, which we referred to as the 2013 Summer Camp Study, followed a random-order cross-over design in which 32 adolescents with T1D participated in 5 days on our BP and 5 days of supervised camp care in the control period. In the control period the participants used conventional insulin pump therapy (and their own CGM if they had one), and they wore the BP without pumps and with blinded display and muted alarms for remote monitoring. Participants were monitored remotely according to identical criteria in all periods for proper device functioning and CGM glucose <70 mg/dl lasting more than 15 minutes, which would prompt study staff to call the participant and make sure they were treated. Participants were fully integrated into normal camp activities without restrictions on diet or exercise. The study used the same iPhone-based BP that was used in our Beacon Hill Study. The mean HbA1c of all 32 participants at baseline (pre-study) was 8.2%, which corresponds to a mean BG of 189 mg/dl. Results are summarized in the plots and table of Figure 1.

In April 2014 we obtained FDA approval conduct our first outpatient study testing our bihormonal BP in pre-adolescents 6–11 years old with T1D. This study, which we referred to as the 2014 Summer Camp Study, was similar in design to our 2013 Summer Camp Study. Results are summarized in the plots and table of Figure 1.

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

In July 2015 we obtained FDA approval to perform our first study testing the BP at different static

glucose targets (“set-points”), including in both the bihormonal and insulin-only configurations. In this study, which we referred to as the MGH Set-point Study, 20 adults participated in 7 periods, each lasting 3 days. This study was the first to explore modifying the glucose target towards which the BP attempts to drive the glucose level. In all of our previous studies, the target glucose was 100 mg/dl. Since this was the first study to test the BP in a configuration without glucagon, the insulin-only periods initially used significantly elevated glucose targets of 130 mg/dl and 145 mg/dl (not shown). We subsequently obtained approval to test glucose targets of 120 mg/dl and 110 mg/dl in December 2015. Results for the insulin-only and control periods are summarized in Figure 2. The conclusion of this study was that *the insulin-only system was safe, with minimal hypoglycemia,* with the 120 mg/dl glucose target appearing to be a good compromise between mean glucose, amount of hypoglycemia, and insulin utilization.

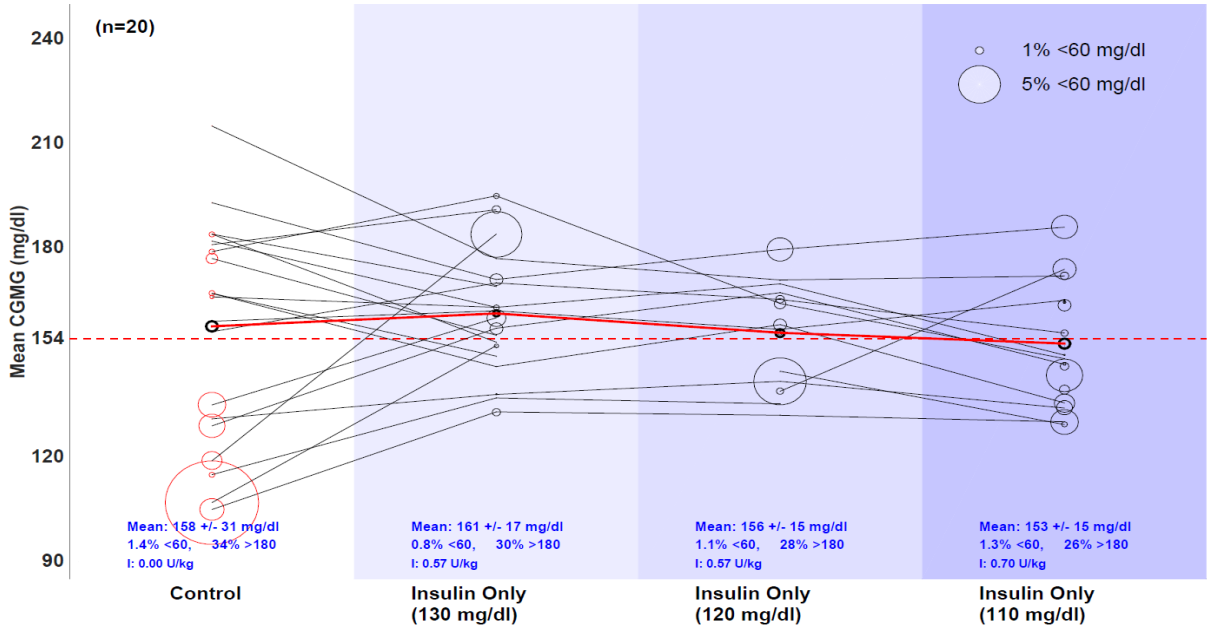


Figure 2 Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP (set-points 130, 120, and 110 mg/dl) and comparator periods. Mean CGM glucose levels for each participant in each period (shown as a red circles) are connected by black lines. For each participant, the circle diameter is proportional to the percentage of CGM glucose values < 60 mg/dl. The heavy circles and lines represent the group means. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal for each age group tested, which corresponds to 154 mg/dl (HbA1c <7%) for adults.

In July 2015 we obtained FDA approval to perform our first study investigating a feature that allowed the target glucose to be determined automatically by the BP, an additional level of adaptation to the individual participant. In this study, which we call the Stanford Insulin-only Study, 16 adults participated in a week of usual care followed by another week on the insulin-only BP. Participants were monitored remotely according to identical criteria in both periods for proper device functioning and CGM glucose <50 mg/dl lasting more than 15 minutes, which would prompt study staff to call the participant and make sure they were treated. The first week was a control period in which participants managed their own conventional insulin pump therapy (using their own CGM if they had one) and wore the BP without pumps and with blinded display and muted alarms for remote monitoring. In the second week, the BP was initiated with target glucose of 130 mg/dl, which could be lowered to 115 mg/dl if certain criteria were met. All but one participant was

kept at a target of 130 mg/dl, and one was lowered to 115 mg/dl, for an overall average target of 129 mg/dl. During this week the mean CGM glucose achieved was 159 mg/dl. There was only 0.8% time <60 mg/dl in the static set-point week. This was non-significantly lower than the 2.3% observed in the usual care period. Results are summarized in Figure 3.

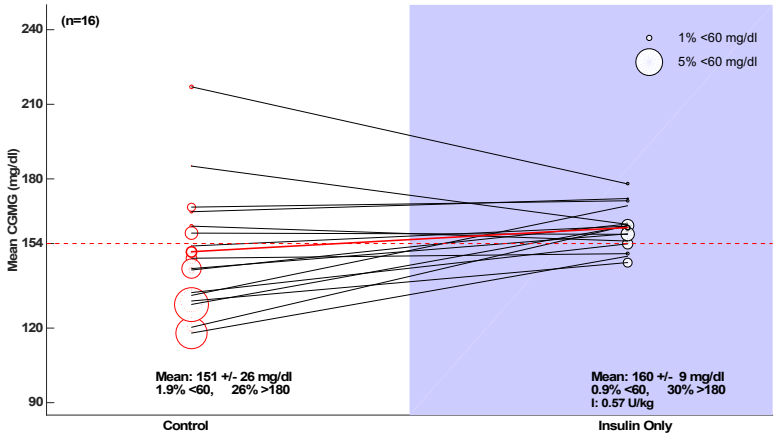


Figure 3 Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control periods. Mean CGM glucose levels for each participant under usual care (shown as a red circle on the left) is connected with the participant's mean CGM glucose level on the BP (shown as a black circle on the right). For each participant, the circle diameter is proportional to the percentage of CGM glucose values < 60 mg/dl. The heavy circles and lines represent the group means. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal for each age group tested, which corresponds to 154 mg/dl (HbA1c <7%) for adults.

This provided further reassurance that the insulin-only configuration of the BP is safe and effective.

1.6. Fully Integrated Insulin-Only, Glucagon-Only, and Bihormonal BP

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.

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.

The bionic pancreas will make recommendations for MDI dosing (for those on MDI therapy) AND for CSII dosing (for those on CSII therapy). We have shown in our previous outpatient and home-use studies in adult and pediatric participants with T1D that the total daily dose of insulin used by the bionic pancreas is consistent with usual care. The bionic pancreas has three insulin controllers running in parallel: a basal insulin controller, which continually adapts to each individual's basal metabolic need for insulin, an MPC controller, which provides control doses that are required above and beyond basal insulin, and a meal-announcement controller, which continually adapts to the individual's prandial insulin needs. The bionic pancreas provides a daily readout with updated estimates of daily basal insulin (in terms of a daily long-acting dose for MDI users and a basal rate regimen for CSII users), prandial insulin (for breakfast, lunch, and dinner) and correction doses. Thus, we hypothesize that the bionic pancreas can effectively provide a recommendation of these quantities for both MDI and CSII users. This bridging study will be the first test of this hypothesis.

1.7. Faster Insulin Aspart, an Ultra-rapid Insulin Analog Formulation

Faster insulin aspart or Fiasp is a formulation of insulin aspart (sold as Fiasp in both the United States and in Europe) that contains nicotinamide (also known as niacinamide or vitamin B3) and L-arginine hydrochloride (an amino acid). The addition of nicotinamide is intended to result in a faster initial absorption of insulin aspart following SC injection or infusion. The addition of L-arginine hydrochloride should support stabilization of the Fiasp formulation. The active substance (i.e. insulin aspart) in Fiasp and Novolog is identical and therefore, once systemically absorbed, it has the same biological action at the insulin receptor as that of Novolog.

Since one of the important limitations of automated closed-loop glucose control is the delay in absorption of insulin, the use of Fiasp may allow improved glycemic control with the bionic pancreas. To date, there have been no published studies of the effect of an ultra-rapid insulin on the performance of an artificial pancreas.

1.8. Senseonics Eversense Continuous Glucose Monitoring System

The Senseonics Eversense CGM is the first implantable CGM. The Senseonics Eversense CGM is currently being marketed in select European countries, and the pre-market approval has been submitted to the FDA in the US. As a part of the FDA review, an FDA Advisory Committee voted 8-0 that the system was safe, effective, and that the benefits outweighed the risk. The BP can

operate using both the Dexcom G5 CGM system or the Senseonics Eversense CGM system as the glucose value input to the algorithm. All functionality of the device and the algorithm remains the same, regardless of which CGM is the driving system.

We conducted a head-to-head comparison between the Dexcom G5 CGM and the Senseonics Eversense CGM as an adjunctive study to a previous bionic pancreas study, and found Senseonics Eversense to have modestly, but statistically significantly, better accuracy than the Dexcom G5. From this, we concluded it would be safe to integrate this system with our bionic pancreas in the same manner we have integrated the Dexcom.

One of the limitations of the Dexcom CGM system is the short sensor life of 7 days, increased to only 10 days with the new G6 system. The Senseonics Eversense CGM sensor is implanted in the subcutaneous tissue of the upper arm and can operate for up to 90 days. The most recently approved model of the Senseonics Eversense CGM system in Europe can operate for up to 180 days. The option to use a longer lasting sensor of equivalent or superior accuracy would appeal to many potential users of a closed loop system. To date, there have been no published studies using the Senseonics Eversense CGM sensor in a closed loop system.

CHAPTER 2: SYNOPSIS OF INSULIN-ONLY BP BRIDGING STUDY

2.1. Study Objectives

- To serve as a transitional study, bridging to larger and longer outpatient pivotal studies using the insulin-only configuration of the bionic pancreas
- To assess the efficacy, safety, and reliability of the insulin-only configuration of the bionic pancreas in regulating glycemia using Humalog, or Novolog, in adult and pediatric participants and using Fiasp in adult participants in a short-term, outpatient study under real-world conditions;
- To assess safety of the insulin-only configuration of the bionic pancreas using Humalog, Novolog, and Fiasp (adults only), particularly with respect to severe hyperglycemia and hypoglycemia;
- To assess the impact of the insulin-only configuration of the bionic pancreas on quality of life and treatment satisfaction among study participants, their caregivers and/or family members;
- To document the interaction of the participants with the insulin-only configuration of the bionic pancreas device for human factors analysis, with the goals of identifying any problems with the user interface or instruction manual for the device that could lead to unsafe use of the device or an adverse event.
- To assess the efficacy, safety, and reliability of the insulin-only configuration of the bionic pancreas in the transition from autonomous glycemic control to either multiple daily injection therapy or insulin pump therapy.
- To assess the efficacy, safety, and reliability of the insulin-only configuration of the bionic pancreas using the Senseonics Eversense CGM as the input CGM in adult participants in a short-term outpatient study under real-world conditions.

2.2. Protocol Synopsis

Study Design

Test-Run Period: Prior to beginning the Adult RCT Period, 8 adults ≥ 18 years old with T1D will participate in the Test-Run Period. The Test-Run Period will consist of an uncontrolled, 7-day

pilot study (at MGH) testing the iLet in the insulin-only configuration using the iLet pigtail adapter and iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, the Dexcom G5 CGM, and the insulin analog that they use for their usual care (either Humalog or Novolog). Participants will be followed with round-the-clock, remote, telemetric monitoring for hyperglycemia (> 300 mg/dl for ≥ 90 minutes) and hypoglycemia (< 50 mg/dl for ≥ 15 minutes). All 8 adult participants will have a designated contact, who will serve as an emergency contact person in the event study staff are unable to reach the participant. The Test-Run Period will be completed before the Adult RCT Period starts. If any events described in the study stopping criteria (section 8.7) occur during the Test-Run Period, the data for the Test-Run Period will be reviewed by the DSMB to determine if the RCT Period will commence. If there are no events for DSMB review during the Test-Run Period, the RCT Period will proceed prior to review of the data by the DSMB.

Pediatric Transitional Study Session: Prior to beginning the Pediatric RCT Period, 20 pediatric participants from three clinical sites (Colorado, Nemours, and Stanford) will take part in the Pediatric Transitional Study Session to assess the efficacy, safety, and reliability of the insulin-only configuration of the bionic pancreas in regulating glycemia in pediatric subjects in a more supervised setting prior to beginning the true outpatient study. The Pediatric Transitional Study Session will consist of a multi-center, two-period, random-order, cross-over, pilot study in 20 pediatric participants 6–17 years old with T1D (~ 6 adolescent participants at Colorado 12–17 years old, ~ 6 pre-adolescent participants at Nemours 6–11 years old, and ~ 8 pediatrics subjects at Stanford 6-17 years old). Insulin therapy for each participant will be administered (i) in one period using the iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, the Dexcom G5 CGM, and the insulin analog that they use for their usual care (either Humalog or Novolog), and (ii) in the other period using the participant's own usual care (UC), where each participant will wear a Dexcom G5 CGM. Both experimental periods will be followed by round-the-clock, remote, telemetric monitoring for hyperglycemia (> 300 mg/dl for ≥ 90 minutes) and hypoglycemia (< 50 mg/dl for ≥ 15 minutes). The two experimental periods will each span 5 days, including 4 nights (e.g. Monday–Friday). A washout period of ~ 3 days in duration will separate the two experimental periods of the Pediatric Transitional Study Session.

Both study periods will be conducted in the same clinically supervised setting during each of the 5 days and at home under parental supervision or other overnight companion who is available to serve as an emergency contact during each of the 4 nights. Parents/guardians must be present (i.e. in the house or building) while the participant is home and sleeping and will serve as the contact person for overnight alerts. During the daytime in the Pediatric Transitional Study Session, participants of each cohort will be with the clinical study staff at each of the three clinical sites and will engage in common activities such that meals and activities can be well-characterized and supervised. For further quantification of stress due to exercise, activity monitors will be worn by all of the participants in both periods of the study. In terms of physical activity, diet, and remote monitoring for hypo- and hyperglycemia, parity will be maintained between both study periods.

All 20 pediatric participants in the Pediatric Transitional Study Session will use insulin pump therapy for their usual diabetes management. The Dexcom G5 CGM will serve as the input CGM to the iLet for all 20 pediatric participants. The cohort of 6 adolescent participants at Colorado and 6 pre-adolescent participants at Nemours, and 8 participants at Stanford might overlap or might not overlap in time. The Pediatric Transitional Study Session will be completed before the Pediatric RCT Period starts. If any events described in the study stopping criteria (section 8.7) occur during the Pediatric Transitional Study Session, the data for the Pediatric Transitional Study

Session will be reviewed by the DSMB to determine if the RCT Period will commence. If there are no events for DSMB review during the Pediatric Transitional Study Session, the RCT Period will proceed prior to review of the data by the DSMB.

Adult RCT Period: The Test-Run Period will be completed and the data will be reviewed to verify safety prior to beginning the Adult RCT Period. The Adult RCT Period will consist of a multi-center, three-period, random-order, cross-over, feasibility study in 36 adult participants ≥ 18 years old with T1D (18 participants at MGH and 18 participants at Stanford).

Four adult participants at MGH will have a Senseonics Eversense CGM sensor implanted and will participate in a 3-day supervised Test Run. All 4 adult participants will have a designated contact, who will serve as an emergency contact person in the event study staff are unable to reach the participant. This Senseonics Eversense Test Run Period will be completed and data will be reviewed to verify safety prior to beginning the Adult RCT Period at MGH using the Senseonics Eversense CGM sensor as the input to the iLet. All 18 adult participants at MGH will have a Senseonics Eversense CGM sensor implanted prior to the initiation of the Adult RCT Period by the clinical PI at MGH (Dr. Steven Russell) or by a study physician under his supervision. These subjects will use the Senseonics Eversense CGM as the input to the bionic pancreas instead of the Dexcom G5.

All 18 adult participants at Stanford will use the Dexcom G5 CGM as the input to the bionic pancreas. All other aspects of the Adult RCT Period will remain the same across the two sites.

Insulin therapy for each participant will be administered (i) in one period using the iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the insulin analog that they use for their usual care (either Humalog or Novolog), (ii) in another period using the iLet in the insulin-only configuration using the iLet pigtail adapter, the Contact Detach infusion set, and faster insulin aspart (Fiasp) in PumpCart, where the pharmacokinetic (PK) parameter for t_{max} used by the insulin-dosing algorithm will be set to the same value as is used for Humalog and Novolog (65 minutes), and (iii) in a third period using the participant's own usual care (UC), where each participant will wear a CGM. All three experimental periods will be followed by round-the-clock, remote, telemetric monitoring for hyperglycemia (> 300 mg/dl for ≥ 90 minutes) and hypoglycemia (< 50 mg/dl for ≥ 15 minutes). The three experimental periods will each have a duration of 7 days. Washout periods of approximately 7 days in duration will follow the first and second experimental periods of the Adult RCT Period. The washout period could be as short as 5 days or as long as 9 days, depending on scheduling of study visits. Of the 36 adult participants, 9 at MGH and 9 at Stanford will use MDI therapy for their usual diabetes management; the remaining 18 will use insulin pump therapy. The participants in Stanford Adult RCT Period will wear the Dexcom G5 CGM and the participants in the MGH Adult RCT Period will wear the Senseonics Eversense CGM. This will allow us to collect further comparative accuracy data on both the Senseonics Eversense and the Dexcom G5 in the outpatient setting using the Ascensia Contour Next One meter as the reference. The cohort of 18 participants at MGH and 18 participants at Stanford might run simultaneously, might overlap, or might not overlap in time. The Adult RCT Period may take place weeks or months after the Test-Run Period, so the cohort for the Adult RCT Period may include all, some, or none of the participants from the cohort of the Test-Run Period.

Pediatric RCT Period: The Pediatric Transitional Study Session will be completed and the data will be reviewed to verify safety prior to beginning the Pediatric RCT Period. The Pediatric RCT Period will consist of a multi-center, two-period, random-order, cross-over, feasibility study in 20 pediatric participants 6–17 years old with T1D (10 participants at Colorado and 10 participants at

Nemours). Insulin therapy for each participant will be administered (i) in one period using the iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, the Dexcom G5 CGM, and the insulin analog that they use for their usual care (either Humalog or Novolog), and (ii) in the other period using the participant's own usual care (UC), where each participant will wear a Dexcom G5 CGM. Both experimental periods will be followed by round-the-clock, remote, telemetric monitoring for hyperglycemia (> 300 mg/dl for ≥ 90 minutes) and hypoglycemia (< 50 mg/dl for ≥ 15 minutes). The two experimental periods will each have a duration of 7 days. A washout period of approximately 7 days in duration will separate the two experimental periods of the Pediatric RCT Period. The washout period could be as short as 5 days or as long as 9 days depending on scheduling of study visits. Of the 20 pediatric participants, 5 at Colorado and 5 at Nemours will use MDI therapy for their usual diabetes management; the remaining 10 will use insulin pump therapy. The Dexcom G5 CGM will serve as the input CGM to the iLet for all 20 pediatric participants. The cohort of 10 participants at Colorado and 10 participants at Nemours might run simultaneously, might overlap, or might not overlap in time. The Pediatric RCT Period may take place weeks or months after the Pediatric Transitional Study Session, so the cohort for the Pediatric RCT Period may include all, some, or none of the participants from the cohort of the Pediatric Transitional Study Session.

Post-Study Transition to Usual Diabetes Management: For 48 hours after the last period of the RCT Period in both adults and pediatric participants is completed, there will be a small Post-Study Transition period. All adult and pediatric participants who complete the RCT Period on an intervention period will transition to their usual care (CSII or MDI) regimen following the recommendations of the bionic pancreas for 48 hours.

Insulin Usage During Usual Diabetes Management: Those who use Humalog (CSII or MDI) for their usual diabetes management will use Humalog in the iLet during the RCT Period, and those who use Novolog (CSII or MDI) or Fiasp (adults, MDI only) for their usual diabetes management will use Novolog in the iLet during the RCT Period except for the period in the adult RCT Period for which Fiasp is specified. Those who use glulisine for their usual diabetes management will be excluded from participating in the study.

Participant Training: Training on the use of the iLet BP system will be provided to all participants (and caregivers) prior to initiating the Test-Run Period at MGH, the Pediatric Transitional Study Session at all three sites, and the RCT Period at all four clinical sites. In particular, these skills sets will include (1) replacement of batteries, (2) installing the iLet ready-to-fill insulin cartridge or PumpCart, (3) priming the fluid path, (4) priming and inserting the Contact Detach infusion set, (5) replacement and calibration of a sensor, (6) entering an SMBG value into the bionic pancreas, (7) use of the meal-announcement feature, (8) use of temporary and recurring set points, (9) general use of the graphical user interface, and (10) troubleshooting the bionic pancreas (for occlusions, sensor drop-outs, alarms and alerts, etc.). Additional time will be allocated for training on the use of the iLet BP system for all participants who normally use MDI therapy for their usual care or are otherwise naïve to the use of sensor-augmented, insulin-pump therapy. It is noteworthy that whether or not the CGM is communicating with the iLet, there are no basal rates to adjust, carb-to-insulin ratios to know, or correction factors to calculate when the iLet is dosing insulin, so training of these particular skill sets will not be necessary for any of our participants.

Sites

The Test-Run Period in adults will be conducted by one site in the U.S. (MGH), the Pediatric Transitional Study Session will be conducted by three sites in the U.S. (Colorado, Nemours, and Stanford), and the RCT Period in adults and pediatrics will be conducted by all four sites (MGH,

Stanford, Nemours, and Colorado).

Major Eligibility Criteria

- Clinical diagnosis of type 1 diabetes for at least 12 months
- HbA1c level < 11.0%
    - At least 13 adult participants and 6 pediatric participants in the RCT Period must have an HbA1c level of 8–11%
    - At least 13 adult participants and 6 pediatric participants in the RCT Period must have an HbA1c level < 8%
- Using an FDA-approved insulin therapy (including Fiasp on MDI therapy for adults, Humalog or Novolog with CSII or MDI therapy; glulisine users will be excluded)
    - 18 adult participants and 10 pediatric participants must use MDI therapy to manage their diabetes
    - 18 adult participants and 10 pediatric participants must use CSII therapy to manage their diabetes
- The Adult RCT Period will enroll participants ≥ 18 years old
    - Approximately 9 participants in a young adult group (18–24 years old)
    - Approximately 27 participants in an adult group (≥ 25 years old)
- The Pediatric RCT Period will enroll participants 6–17 years old
    - 10 participants in a pre-adolescent group (< 12 years old)
    - 10 participants in an adolescent group (12–17 years old)

Additional eligibility and exclusion criteria are listed in section 3.2

Sample Size

- The Test-Run Period: 8 participants (age ≥ 18 years, MGH only)
- The Pediatric Transitional Study Session: 20 participants (~ 6 participants age 6–11 years at Nemours, ~ 6 participants age 12–17 years at Colorado, and ~ 8 participants age 12–17 years at Stanford)
- Adult RCT Period: 36 participants (age ≥ 18 years, 18 participants at MGH, 18 participants at Stanford)
- Pediatric RCT Period: 20 participants (age 6–17 years, 10 participants at Nemours, 10 participants at Colorado)

Treatment Groups

- The Test-Run Period: All participants will use the iLet in the insulin-only configuration with Humalog or Novolog (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) in one uncontrolled 7 day period.
- The Pediatric Transitional Study Session: All participants will use the iLet in the insulin-only configuration with Humalog or Novolog (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM)
- Senseonics Eversense Test Run (MGH only): 4 adults will use the iLet in the insulin-only configuration using Humalog or Novolog with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Senseonics Eversense CGM as the input to the iLet in an uncontrolled 3-day period.
- Adult RCT Period: Three-period, random-order, cross-over study into the following study periods:
    - (1) the iLet in the insulin-only configuration using Humalog or Novolog with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and either the Dexcom G5 or Senseonics Eversense CGM as the input depending on

the site
    - (2) the iLet in the insulin-only configuration using faster insulin aspart (Fiasp) in PumpCart with the iLet pigtail adapter, the Contact Detach infusion set, and either the Dexcom G5 or Senseonics Eversense CGM) as the input, depending on the site, where the pharmacokinetic (PK) parameter for t_{max} used by the insulin-dosing algorithm will be set to the same value for Fiasp as is used for Humalog and Novolog (65 minutes)
    - (3) UC (with the Dexcom G5 or the Senseonics Senseonics Eversense CGM depending on the site).
- Pediatric RCT Period: Two-period, random-order, cross-over study where assignment of study period order follows either (1) the iLet in the insulin-only configuration using Humalog or Novolog with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) in period 1 and UC (with the Dexcom G5 CGM) in period 2 or (2) UC (with the Dexcom G5 CGM) in period 1 and the iLet in the insulin-only configuration using Humalog or Novolog with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) in period 2.

Visit and Phone Contact Schedule

1. Screening Visit
    - Eligibility assessed, informed consent, and bloodwork including point-of-care/local HbA1c and eGFR.

1.5. Senseonics Eversense CGM sensor placement visit (MGH site only, prior to Senseonics Eversense Test Run and RCT Period only)

- The procedures of this visit will take place at least 24 hours before the first Startup visit, to allow the Senseonics Eversense sensor to complete its 24-hour warm up period after insertion. In order to test the performance of the full life of the Senseonics Eversense sensor the study team will endeavor to schedule these visits such that subjects have the sensor placed in a roughly even distribution (approximately 3 insertions per week) over the 6 weeks prior to the Startup Visit of the RCT Period

Each study period will follow the schedule below:

2. Startup visit (day 0)
    - The first start up period will include the completion of the baseline psychosocial questionnaires. See Chapter 7 for more details.
    - Every start up visit will include a review of medical history since the last study visit to ensure continued eligibility, and adverse event querying.
    - Test-Run Period: Reassess eligibility, place the Dexcom G5 CGM sensor, train, and initiate automated glycemic management with the iLet in the insulin-only configuration (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM)
    - Transitional Study Session: Reassess eligibility, place the Dexcom G5 CGM sensor, train, and initiate automated glycemic management with the iLet in the insulin-only configuration (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM)
    - Eversense Test Run: Reassess eligibility, assess sensor insertion site, train, and initiate automated glycemic management with the iLet in the insulin-only configuration (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Senseonics Eversense CGM)
    - Adult RCT Period: Reassess eligibility prior to randomization, place the Dexcom G5 CGM sensor where applicable, train and:
        - BP periods: Initiate automated glycemic management for the BP Periods with the

iLet in the insulin-only configuration (with the iLet pigtail adapter, the Contact Detach infusion set) using Humalog, Novolog (with the iLet ready-to-fill insulin cartridge), or Fiasp (in PumpCart)

- Pediatric RCT Period: Reassess eligibility prior to randomization, place the Dexcom G5 CGM sensor, training and:
  - BP periods: Initiate automated glycemic management for the BP Period with the iLet in the insulin-only configuration (with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) using Humalog or Novolog

3. Phone contacts to query for adverse events and proper device functioning will occur on:
   - Days 3 or 4 for each 7-day Adult and Pediatric RCT Periods and the 7-Day Test-Run Period
   - No phone contact during the Pediatric Transitional Study Session or the Senseonics Eversense Test Run since clinical study staff will be with the entire cohort every day of the study
4. Shutdown visits (Day 7 for the Test-Run Period in adults and for each period of the RCT Period in both adults and pediatric participants, Day 5 for the Transitional Study Session in pediatrics, Day 3 for the Senseonics Eversense Test Run)
   - Download data from study devices as follows:
     - Usual care: Dexcom G5 CGM, glucose meter, ketone meter, participant's personal insulin pump if applicable, and Senseonics Eversense CGM where applicable
     - BP: iLet BP, glucose meter, ketone meter, and Senseonics Eversense CGM where applicable
   - Psychosocial questionnaires will be completed at the end of each period. See Chapter 7 for more details.

4.5 Senseonics Eversense CGM sensor removal visits (MGH site of RCT Period only)
The Senseonics Eversense CGM may be removed on the final shutdown visit, after the Post-Study Transition Period is complete, or on a subsequent visit as schedules allow. The Senseonics Eversense CGM will be removed within the required 90 day window.

The Startup and Shutdown visit are repeated for each study period in the RCT period. There is only one Startup and Shutdown visit in the Test Run, the Senseonics Eversense Test Run and the Pediatric Transitional Study Session.

Participants randomized to a BP period using Humalog or Novolog for the final period of the RCT period will be discharged to their usual care following the dosing recommendations of the iLet for 48 hours in the Post-Study Transition Period. Remote monitoring will continue per the same protocol as the RCT Period. At the end of this period, participants will return to the research clinic and the CGM data will be analyzed for the safety and efficacy of the iLet dosing recommendations.

Outcomes

Primary Efficacy Outcomes

- Mean CGM glucose (Days 3–7 for the Adult Test-Run Period, Days 2–5 for the Pediatric Transitional Study Session, Days 3–7 for the RCT Period, Days 2-3 for the Senseonics Eversense Test Run)
- Time < 54 mg/dl according to CGM (Days 3–7 for the Adult Test-Run Period, Days 2–5 for the Pediatric Transitional Study Session, Days 3–7 for the RCT Period, Days 2-3 for the Senseonics Eversense Test Run)

Main Safety Outcomes

- Number of episodes of severe hypoglycemia
- Number of episodes of diabetic ketoacidosis (DKA)
- Other serious adverse events

The two primary outcome metrics (mean glucose and time <54 mg/dl) and three treatment group comparisons in the adult RCT Period [(2) BP with rapid insulin vs. (3) UC, (1) BP with analog insulin vs. (3) UC, and (2) BP with rapid insulin vs. (1) BP with analog insulin], combine for a total of six statistical comparisons.

To preserve the overall type 1 error, a hierarchical gatekeeping testing procedure will be used. If a comparison results in a statistically significant result ($p < 0.05$), then testing will proceed to the next one on the list. See Chapter 10 for additional information.

2.3. Schedule of Study Visits and Procedures during the 7-day Adult Test-Run Period and each of the 7-day Adult RCT Periods

Each Period of the Test-Run Period and the Adult RCT Period						
	Screening	**Senseonics Eversense Sensor Insertion**	**Day 0**	**Day 3 or Day 4**	**Day 7**	**Senseonics Eversense Sensor Removal**
Informed Consent	**X**					
Eligibility assessment	**X**		**X**			
Bloodwork: eGFR and HbA1c	**X**					
EKG[1]	**X**					
Body weight	**X**		**X**		**X**	
Urine pregnancy test[2]	**X**					
Physical exam	**X**					
Insertion of Dexcom CGM sensor[3]			**X**			
Insertion of Senseonics Eversense CGM sensor[4]		**X**				
Removal of Senseonics Eversense CGM sensor[5]						**X**
Psychosocial questionnaires[6]			**X**		**X**	
Data download					**X**	
Adverse event querying[7]		**X**	**X**	**X**	**X**	**X**

1 – An EKG is required for participants ≥ 50 years old and/or with a diabetes duration of ≥ 20 years

2 -- A urine pregnancy test will be conducted for women post-menarche and pre-menopause who are not surgically sterile.

3 –At Stanford during the RCT Period, a new Dexcom CGM sensor will be inserted at each day 0.

4 – At MGH during the RCT Period, Senseonics Eversense CGM sensor will be inserted during the period between Screening and Day 0, at least 24 hours before Day 0.

5 – At MGH during the RCT Period, Senseonics Eversense CGM sensor will be removed at the Final Shutdown visit, after the Post-Study Transition Period, or a later date, up to 90 days after insertion

6 – Questionnaires (see Chapter 7)

- Baseline questionnaires include: Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs), Diabetes Distress Scale (DDS), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE Survey. These will be completed by the participant on the first Startup visit only.
- Day 7 of each experimental period: Diabetes Treatment Satisfaction Questionnaire - Change (DTSQc),

Diabetes Distress Scale (DDS), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE survey, Bionic Pancreas User Opinion Survey (BPUOS) – BP period only
7-- Study physicians will follow up with subjects and query about any adverse events within 48 hours following Senseonics Eversense insertion and removal.

2.4. Schedule of Study Visits and Procedures during the Senseonics Eversense Test Run Period

Senseonics Eversense Test Run Period						
	Screening	**Senseonics Eversense Sensor Insertion**	**Day 0**	**Days 1-3**	**Day 3**	**Senseonics Eversense Sensor Removal**
Informed Consent	X					
Eligibility assessment	X		X			
Bloodwork: eGFR and HbA1c	X					
EKG[1]	X					
Body weight	X		X		X	
Urine pregnancy test[2]	X					
Physical exam	X					
Insertion of Senseonics Eversense CGM sensor[3]		X				
Daytime supervision by study staff			X	X	X	
Removal of Senseonics Eversense CGM sensor[4]						X
Data download					X	
Adverse event querying[5]		X	X	X	X	X

1 – An EKG is required for participants ≥ 50 years old and/or with a diabetes duration of ≥ 20 years
2 -- A urine pregnancy test will be conducted for women post-menarche and pre-menopause who are not surgically sterile.
3 –Senseonics Eversense CGM sensor will be inserted during the period between Screening and Day 1, at least 24 hours before day 1.
4 –Senseonics Eversense CGM sensor will be removed at the Final Shutdown visit or a later date, up to 90 days after insertion. Subjects who participate in the Eversense Test Run may also participate in the Adult RCT. They may use the

same sensor for the RCT Period, as long as it will not expire.
5 – Study physicians will follow up with subjects and query about any adverse events within 48 hours following Senseonics Eversense insertion and removal.

2.5. Schedule of Study Visits and Procedures during the 7-day Pediatric RCT Periods

Experimental Periods of Pediatric RCT Period				
	Screening	**Day 0**	**Day 3 or 4**	**Day 7**
Informed Consent	**X**			
Eligibility assessment	**X**	**X**		
Bloodwork: eGFR and HbA1c	**X**			
Body weight	**X**	**X**		**X**
Urine pregnancy test[1]	**X**			
Physical exam	**X**			
Insertion of Dexcom CGM sensor		**X**		
Psychosocial questionnaires[2]		**X**		**X**
Data download				**X**
Adverse event querying		**X**	**X**	**X**

1 -- A urine pregnancy test will be conducted for women post-menarche and pre-menopause who are not surgically sterile.
2 – Questionnaires (see Chapter 7)
Baseline questionnaires include: Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs), Diabetes Distress Scale (DDS), Problem Areas in Diabetes Survey (PAID), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE Survey. These will be completed by the participant on the first Startup visit only.
Day 7 of each experimental period of the Pediatric RCT Period: Diabetes Treatment Satisfaction Questionnaire - Change (DTSQc), Diabetes Distress Scale (DDS), Problem Areas in Diabetes Survey (PAID), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE survey, Bionic Pancreas User Opinion Survey (BPUOS) – BP period only

2.6. Schedule of Study Visits and Procedures during the 5-day Pediatric Transitional Study Session

Pediatric Transitional Study Session				
	Screening	**Day 0**	**Days 1-5**	**Day 5**
Informed Consent	**X**			
Eligibility assessment	**X**	**X**		
Bloodwork: eGFR and HbA1c	**X**			
Body weight	**X**	**X**		**X**
Urine pregnancy test[1]	**X**			
Physical exam	**X**			
Insertion of CGM sensor		**X**		
Psychosocial questionnaires[2]		**X**		**X**
Data download				**X**
Adverse event querying		**X**	**X**	**X**

1 -- A urine pregnancy test will be conducted for women post-menarche and pre-menopause who are not surgically sterile.

2 – Questionnaires (see Chapter 7)

- Baseline questionnaires include: Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs), Diabetes Distress Scale (DDS), Problem Areas in Diabetes Survey (PAID), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE Survey
- Day 5: Diabetes Treatment Satisfaction Questionnaire - Change (DTSQc), Diabetes Distress Scale (DDS), Problem Areas in Diabetes Survey (PAID), Hypoglycemia Fear Survey (HFS), Hypoglycemia Confidence, INSPIRE survey, Bionic Pancreas User Opinion Survey (BPUOS) – BP period only

2.7. General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic case report forms, which will be considered the source data.

A risk-based monitoring approach will be followed, consistent with the FDA “Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” (August 2013).

The protocol is considered a significant risk device study, due to the fact that the iLet BP system is experimental. Therefore, an IDE from the FDA is required to conduct the study.

CHAPTER 3: PARTICIPANT ENROLLMENT AND STUDY INITIATION

3.1. Study Population

Up to 240 individuals with type 1 diabetes may be screened and sign the informed consent form for the study so that a minimum of 8 will enter the Test-Run Period in adults, 20 will enter the Transitional Study Period in pediatrics, 4 will enter the Senseonics Eversense Test Run and a total of 56 will enter the RCT Periods between adults (36 subjects) and pediatrics (20 subjects). Screening will continue until the required number is reached. Adult participants in the Test Run and the Senseonics Eversense Test Run may also participate in the RCT Period.

No individuals will be excluded on the basis of gender or race. An equal gender distribution between males and females is anticipated.

The Test-Run Period will be conducted at a single site (MGH) and the Transitional Study Session will take place at three sites (Stanford, Nemours and Colorado). It is anticipated that 8 adult participants will be in the Test-Run Period and 20 pediatric participants in the Transitional Study Session. The Senseonics Eversense Test Run will include 4 adult participants at MGH only. The Adult and Pediatric RCT Period will be conducted at four sites in the United States. It is anticipated that each adult site (MGH and Stanford) will randomize approximately 18 participants into the Adult RCT Period and each pediatric site (Nemours and Colorado) will randomize approximately 10 participants into the Pediatric RCT Period. The maximum number of randomized participants at a site will be 40.

Individuals generally will be recruited from each site's existing patient population. Direct contacting of patients and advertisements including website postings may be used subject to Institutional Review Board approval.

3.2. Eligibility and Exclusion Criteria

Eligibility and exclusion criteria will be the same for both the adult and pediatric patient populations, and the same for the Test Run Period, the Pediatric Transitional Study Session, the Senseonics Eversense Test Run, and the Adult and Pediatric RCT Period. Exceptions to this are noted below.

3.3. Eligibility

To be eligible for the study, a participant must meet the following criteria:

1. Clinical diagnosis of type 1 diabetes for at least one year and using insulin for at least 1 year
2. Diabetes managed using an insulin pump for ≥ 3 months or with multiple daily injections (approximately 1/2 of participants should use a pump and approximately 1/2 should use MDI)
    - The Test Run Period, the Pediatric Transitional Study and the Senseonics Eversense Test Run Period will only enroll participants using an insulin pump.
3. Age ≥18 years (for Test-Run Period and Adult RCT Period); ≥6 years, up to 17 years (for Pediatric Transitional Study and Pediatric RCT Period)
    - *There is no upper age limit in the Adult RCT Period (instead the exclusion criteria are used to restrict the participants to those healthy enough to participate in the trial)*
4. HbA1c level <11.0%
    - *A point of care or local lab measurement is used to assess eligibility for screening.*
5. At least 3 SMBG meter tests daily on average or use of a CGM and 2 or more SMBG meter tests daily on average by history
6. For females, not currently known to be pregnant
    - *If female, sexually active, and at risk for pregnancy, must agree to use a highly effective form of contraception to prevent pregnancy while a participant in the study. A negative*

urine pregnancy test will be required for all women who are post-menarche and pre-menopause who are not surgically sterile. Participants who become pregnant will be discontinued from the study.

7. An understanding of and willingness to follow the protocol and sign the informed consent and assent where applicable
8. Pediatric Transitional Study Session, Adult Test Run, and Senseonics Eversense Test Run only: an adult (≥ 18 years of age) willing to serve as an emergency contact person throughout the study

3.4. Exclusion

Note: any laboratory testing needed to assess for eligibility is considered part of standard care as it is necessary as part of a participant's general medical management.

The presence of any of the following is an exclusion for the study:

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 BP, impaired memory)
3. Unable to speak and read English
4. Currently using for the first time a real-time CGM for < 1 month (Individuals who have been using CGM for 1 or more months are eligible)
5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system
6. Current use of insulin glulisine (Apidra) as part of usual diabetes home regimen
7. Current off-label use of faster-acting insulin aspart (Fiasp) in CSII therapy as part of usual diabetes home regimen
8. 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 participant
9. Pregnant (positive urine HCG), breast feeding, plan to become pregnant in the next 12 months, or sexually active and at risk for pregnancy without use of contraception
10. Current alcohol abuse (intake averaging >4 drinks daily in last 30 days) or other substance abuse (use within the last 3 months of controlled substances other than marijuana without a prescription)
11. 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 benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator)
12. Stage 4 renal failure (eGFR <30) or Stage 5 renal failure on dialysis (hemodialysis or peritoneal dialysis)
13. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy
14. Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. exercise of intensity up to 6 METS) despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting
15. Abnormal EKG consistent with increased risk of malignant arrhythmia including, but not limited to, evidence of active ischemia, proximal LAD critical stenosis (Wellen's sign), or prolonged QT interval (> 440 ms). Other EKG findings, including stable Q waves, are not grounds for exclusion as long as the participant is not excluded according to other criteria. 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*
16. For participants < 50 years of age and < 20 years since diagnosis: History of prolonged QT

interval, malignant arrhythmia, or congenital heart disease

17. Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV
18. History of TIA or stroke in the last 12 months
19. 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.
20. History of more than 1 episode of DKA requiring hospitalization in the last 2 years
21. History of more than 1 episode of severe hypoglycemia in the last year.
22. 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.
23. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference
24. Unable or unwilling to completely avoid acetaminophen for duration of study. Participants wearing the Senseonics Eversense CGM must also be willing and able to avoid tetracycline, sorbitol and mannitol for the duration of the study.
25. Established history of allergy or severe reaction to adhesive or tape that must be used in the study
26. History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
27. Current or planned use of SGLT2 inhibitors (prior use more than 3 months prior to enrollment is acceptable; SGLT2 inhibitors should not be initiated during the trial)
28. If using GLP1, pramlintide, or metformin must be on a stable dose for 3 months prior to enrollment (these agents should not be initiated during the trial)
29. Required use of 2 or more steroid bursts in the 6 months prior to the trial
30. Participants wearing the Senseonics Eversense CGM cannot be currently using systemic glucocorticoids at baseline or throughout the study.
31. History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
32. Any factors that, in the opinion of the site principal investigator or clinical protocol chair, would interfere with the safe completion of the study, including medical conditions that may require hospitalization during the trial

3.5. Informed Consent

Informed consent, and assent where applicable, and an authorization for release of personal information will be obtained according to IRB requirements prior to any data collection or study-specific procedures that are not part of the participant's routine care. The principal investigator at each site will be responsible for assuring that the informed consent and assent process is properly followed and that each study participant is well informed about the study and the participant's responsibilities.

3.6. Eligibility Assessment and Baseline Data Collection

Potential participants will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing to screen for exclusionary medical conditions. Participant exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria and lab results.

3.7. Historical Information and Physical Exam

A history will be elicited from the participant (and parents/guardians if applicable) and extracted from available medical records with regard to the participant's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies. A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

3.8. Screening Testing and Procedures

At the Screening Visit the following procedures will be performed:

- Informed consent/assent process
- Assessment of eligibility
- The following labs will be required:
    - eGFR
    - HbA1c assessment via fingerstick using DCA2000 or equivalent NGSP-certified point-of-care method or via venous blood sample at a local laboratory (value within 2 weeks prior to enrollment acceptable)
- Physical examination to include:
    - Height/weight and vital signs including measurement of blood pressure and pulse
    - Tanner staging for participants <18 years
- EKG (for participants ≥50 years old or diabetes duration ≥20 years)
- Urine pregnancy test for all premenopausal women who are not surgically sterile

Screening for the Adult RCT Period may start while the Test-Run Period is being conducted. However, the crossover phase of the Adult RCT Period cannot begin until the Test-Run Period and the subsequent review of the data for safety and feasibility has been completed. The crossover phase of the Adult RCT Period at MGH using the Senseonics Eversense CGM cannot begin until the Senseonics Eversense Test Run and the subsequent review of the data for safety and feasibility has been completed.

Similarly, screening for the Pediatric RCT Period may start while the Transitional Study Session is being conducted, however the crossover phase of the Pediatric RCT Period cannot begin until the Transitional Study Session and the subsequent review of the data for safety and feasibility has been completed.

Participants in the Test Run, the Senseonics Eversense Test Run, and the Pediatric Transitional Study Session may also participate in the RCT Period. Study staff will confirm they are still eligible to participate prior to enrolling them in the RCT Period.

CHAPTER 4: STARTUP VISITS

4.1. Timing of Visits

The Initial Startup Visit, or Senseonics Eversense Insertion visit where applicable, should occur within 30 days after the screening visit. Participants in the Test Run, the Senseonics Eversense Test Run, and the Pediatric Transitional Study Session may also participate in the RCT Period. Study staff will confirm they are still eligible to participate prior to enrolling them in the RCT Period.

In the three-period Adult RCT Period, there should be a minimum of 5 days, but no more than 9 days, between a Shutdown Visit and a subsequent Startup Visit. In the two-period Pediatric RCT Period, there should be a minimum of 5 days, but no more than 9 days, between a Shutdown Visit and a subsequent Startup Visit.

4.2. Testing and Procedures

The following will be completed at each Startup Visit:

- Review medical history since screening visit to verify that there have been no events that affect participant eligibility
- Verify that participant understands the protocol

4.3. Randomization

Test-Run Period

In the Test-Run Period, adult participants will all use the iLet in the insulin-only configuration and the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, and the Contact Detach infusion set for 7 days. The Dexcom G5 CGM will serve as the input CGM to the iLet.

Pediatric Transitional Study Session

In the Pediatric Transitional Study Period, pediatric participants will all use the iLet in the insulin-only configuration and the iLet pigtail adapter, iLet ready-to-fill insulin cartridge, and the Contact Detach infusion set across ~ 5 days. The Dexcom G5 CGM will serve as the input CGM to the iLet.

Senseonics Eversense Test Run Period

In the Senseonics Eversense Test Run Period, adult participants will all use the iLet in the insulin-only configuration and the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, and the Contact Detach infusion set for 3 days. The Senseonics Eversense CGM will serve as the input CGM to the iLet.

RCT Period

In the RCT Period, participants for whom eligibility has been verified will complete each of the following phases with the order randomly assigned:

- Adult RCT Period: (i) the iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the insulin analog that they use for their usual care (either Humalog or Novolog), (ii) the iLet in the insulin-only configuration using the iLet pigtail adapter, the Contact Detach infusion set, and faster insulin aspart (Fiasp) in PumpCart, where the pharmacokinetic (PK) parameter for t_{max} used by the insulin-dosing algorithm will be set to the same value as is used for Humalog and Novolog (65 minutes), and (iii) the participant's own usual care (UC), where each participant will wear a CGM.
    - 18 adults at Stanford will use the Dexcom G5 CGM as the input to the iLet and as the CGM during usual care. 18 adults at MGH will use the Senseonics Eversense CGM as the input to the iLet and as the CGM during usual care. All 36 adults will participate in the same three arms, regardless of CGM.

- Pediatric RCT Period: (i) the iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, the Dexcom G5 CGM, and the insulin analog that they use for their usual care (either Humalog or Novolog), and (ii) the participant's own usual care (UC), where each participant will wear a Dexcom G5 CGM.

The participant's randomization group assignment is determined by entering the Randomization Visit data on the study website. The Jaeb Center will construct a Master Randomization List using a block design.

4.4. Senseonics Eversense CGM sensor insertion Visit (MGH Senseonics Eversense Test Run and RCT Period only)

- The Senseonics Eversense sensor insertion will take place after participants have been confirmed as eligible to participate but before they start their first study period. In order to test the performance of the full life of the sensor, the study team will endeavor to schedule these visits so subjects have the sensor placed in a roughly even distribution over the six weeks prior to the Initial Startup Visit, averaging 3 sensor insertions per week.
- A urine pregnancy test will be performed in female volunteers prior to the sensor insertion. If the test is positive, the volunteer will be informed of the result, the visit will be ended and the sensor will not be inserted.
- The temperature of the subject will be documented. Study staff will ask about any recent fever or vomiting, in addition to other adverse events or changes to medications. If the subject has a temperature greater than 100.4 degrees F, or has had one in the previous 24 hours, the visit will be ended and the sensor will not be inserted.
- The subject's skin will be numbed using a local anesthetic (i.e. lidocaine without epinephrine). The study physician will make a small incision in the skin between the shoulder and the elbow using the Insertion Templates provided by Senseonics to mark in the incision site.
- Senseonics will provide sterile, one-time use tools for placing the sensor. The Blunt Dissector is used to create the subcutaneous pocket for insertion of the sensor, and has guide marks to assist in determining the correct pocket length. The Insertion Tool is used in combination with the Sensor Holder to transfer the sensor, and has guide marks on the cannula to assist in proper placement in the subcutaneous pocket. See the Investigator Brochure for details on sensor insertion.
- The sensor will be inserted at least three inches away from any infusion or injection sites.
- Once the sensor is inserted, the incision will be closed using surgical tapes or a suture and a bandage. Blood loss during the procedure is expected to be minimal (less than 3 ml)
- Subjects will be instructed to leave the bandage on for approximately 24 hours. They will be instructed to monitor for any discharge, excessive bleeding, redness, warmth, or swelling at the insertion site and to contact study staff if this occurs.
- A study physician will follow up with a phone call within 48 hours of insertion to assess appropriate healing and query for any adverse events.
- During this visit, subjects will be trained on how to use the Senseonics Eversense transmitter and mobile app, as well as the study glucose meter. Subjects will be instructed to put their transmitter on approximately 24 hours after sensor insertion to begin the Initial Calibration phase. Subjects will be instructed to then calibrate twice daily and continue to wear the transmitter in the weeks before their start of the RCT Period.
- Subjects will be told that their sensor must be removed within 90 days of the insertion date at the insertion visit. Study staff will add all insertion visits to a log, for tracking removal

visit dates and deadlines.

- The procedures for this visit will be the same, regardless of if the subject is participating in the Senseonics Eversense Test Run, the RCT Period or both.

4.5. Initial Startup Visit

The same procedures for the initial startup visit will be followed in the Test Run, Transitional Study Session, the Senseonics Eversense Test Run and the Adult and Pediatric RCT Period.

Participants may be trained on the operation of the all study devices in a group setting or may be trained one-on-one. Both the participant and the study staff must be satisfied that the participant is comfortable with the operation of all study devices before he/she begins the study. Additional training sessions may be arranged as needed.

- Participants will complete their baseline psychosocial questionnaires
    - Senseonics Eversense Test Run has no questionnaires
- Their body weight 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 participants will be given additional Dexcom G5 CGM sensors where applicable, an Ascensia Contour Next One SMBG meter with test strips, a ketone meter and ketone test strips, insulin, and a glucagon emergency kit.
- Participants at Nemours, Colorado and Stanford will be trained on the insertion and use of the Dexcom G5 CGM. Participants will insert their own CGM sensor and study staff will confirm they are doing it correctly. Study staff will remind participants to only use FDA approved insertion sites (abdomen only for > 17 years old, abdomen or upper buttocks for ages 6-17 years old) for their CGM sensor.
- Study staff will review all study procedures and policies (including the use of the Dexcom G5 or Senseonics Eversense, the Contour Next One, the blood ketone meter and the iLet BP) and the upcoming visit schedule.
- MGH site only: For the adult subjects at the MGH site, the Senseonics Eversense CGM sensor will serve as the input to the iLet. This sensor may be placed any time after the participant has screened into the study before the start of their first study period. It must be placed in advance to allow for the 24 hour warm up period of the sensor prior to the startup visit. Instructions will be given for calibration and use of the sensor. The Senseonics Eversense sensor will only be in place for up to 90 days. It will be removed by a study provider after the completion of the study, or before the 90th day.
- The Dexcom G5 or Senseonics Eversense CGM will be calibrated by the participant using the Ascensia Contour Next One SMBG glucometer, and study staff will confirm they are doing it properly.

Usual Care period (RCT period and Pediatric Transitional Study Session only)

- Participants will be instructed to follow their usual diabetes management (see section 5.1).

Bionic Pancreas periods (all study phases)

- The control algorithm will be initialized with the participant's current weight
- The participant will remove his/her own insulin infusion pump (if used) and the participant will set up and start the BP under the supervision of study staff. Participants will be instructed to not take any further insulin outside of the BP throughout the study. A study provider will specifically address the transition of participants off of their MDI therapy as needed.
- The staff will confirm that the BP is functioning properly prior to discharging the participant.

- Study staff will provide the following additional supplies: the iLet BP, iLet ready-to-fill insulin cartridges along with iLet pigtail adapters or Fiasp in PumpCart along with iLet pigtail adapters and Contact Detach infusion sets.
- Due to the adaptive nature of the BP, patients on multiple daily injections will be started on the BP without a need for active management of the transition period by study staff, but the new equilibrium will not be reached until all of the insulin glargine (the most common insulin used by this group of patients) has completely cleared their system, which may take approximately 48 hours. Participants will be trained to expect escalating dosing by the BP during this period.

4.6. Subsequent Startup Visits

The Test Run, Senseonics Eversense Test Run and the Transitional Study Session each only have one startup visit.

The Adult RCT Period will have two subsequent startup visits after the initial visit. The procedures at this visit will be as follows:

- The participants body weight 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 last study visit.
- All participants will be given additional supplies as needed.
- Participants at Stanford will insert their own Dexcom G5 CGM sensor and study staff will confirm they are doing it correctly. Study staff will remind participants to only use FDA approved insertion sites (abdomen only for > 17 years old, abdomen or upper buttocks for ages 6-17 years old) for their CGM sensor.
- Study staff will review all study procedures and policies (including the use of the CGM, the Contour Next One, the blood ketone meter and the iLet BP) and the upcoming visit schedule.
- Study staff will assess the site of the Senseonics Eversense CGM sensor for any signs of infection or other adverse signs. (MGH site only)
- The Dexcom G5 or Senseonics Eversense CGM will be calibrated by the participant using the Ascensia Contour Next One SMBG glucometer, and study staff will confirm they are doing it properly.

Usual Care period

- Participants will be instructed to follow their usual diabetes management (see section 5.1).

Bionic Pancreas periods

- The control algorithm will be initialized with the participant's current weight
- The participant will remove his/her own insulin infusion pump (if used) and the participant will set up and start the BP under the supervision of study staff. Participants will be instructed to not take any further insulin outside of the BP throughout the study. A study provider will specifically address the transition of participants off of their MDI therapy as needed.
- The staff will confirm that the BP is functioning properly prior to discharging the participant.
- Study staff will provide the following additional supplies: the iLet BP, iLet ready-to-fill insulin cartridges along with iLet pigtail adapters or Fiasp in PumpCart along with iLet pigtail adapters and Contact Detach infusion sets.
- Due the adaptive nature of the BP, patients on multiple daily injections will be started on the BP without a need for active management of the transition period by study staff, but the new equilibrium will not be reached until all of the insulin glargine (the most common

insulin used by this group of patients) has completely cleared their system, which may take approximately 48 hours. Participants will be trained to expect escalating dosing by the BP during this period.

The Pediatric RCT Period will have one subsequent startup visit after the initial visit. The procedures for this visit will be as follows:

- The participants body weight 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 last study visit.
- All participants will be given additional supplies as needed.
- Participants will insert their own CGM sensor and study staff will confirm they are doing it correctly. Study staff will remind participants to only use FDA approved insertion sites (abdomen only for > 17 years old, abdomen or upper buttocks for ages 6-17 years old) for their CGM sensor.
- Study staff will review all study procedures and policies (including the use of the Dexcom G5, the Contour Next One, the blood ketone meter and the iLet BP) and the upcoming visit schedule.
- The Dexcom G5 will be calibrated by the participant using the Ascensia Contour Next One SMBG glucometer, and study staff will confirm they are doing it properly.

Usual Care period

- Participants will be instructed to follow their usual diabetes management (see section 5.1).

Bionic Pancreas period

- The control algorithm will be initialized with the participant's current weight
- The participant will remove his/her own insulin infusion pump (if used) and the participant will start the BP. Participants will be instructed to not take any further insulin outside of the BP throughout the study.
    - Due the adaptive nature of the BP, patients on multiple daily injections will be started on the BP without a need for active management of the transition period by study staff, but the new equilibrium will not be reached until all of the insulin glargine (the most common insulin used by this group of patients) has completely cleared their system, which may take approximately 48 hours. Participants will be trained to expect escalating dosing by the BP during this period.
- The staff will confirm that the BP is functioning properly prior to discharging the participant.
- Study staff will provide the following additional supplies: the iLet BP, iLet ready-to-fill insulin cartridges along with iLet pigtail adapters and Contact Detach infusion sets.

CHAPTER 5: PROTOCOLS FOR ADULT TEST-RUN PERIOD, PEDIATRIC TRANSITIONAL STUDY SESSION, AND RCT PERIOD IN ADULTS AND PEDIATRIC PARTICIPANTS

5.1. Introduction

The Test-Run Period will include 8 adult participants who use the BP who will follow the protocol as described in this chapter for the BP period in the RCT Period. Any exceptions will be noted.

The Transitional Study Session will include 20 adolescent and pre-adolescent participants who use the BP and who follow the protocol as described in this chapter for the BP period in the RCT period. Any exceptions will be noted.

The Test-Run Period will be completed before the Adult RCT Period starts. If any events described in the study stopping criteria (section 8.7) occur during the Test-Run Period, the data for the Test-Run Period will be reviewed by the DSMB to determine if the RCT Period will commence. If there are no events for DSMB review during the Test-Run Period, the RCT Period will proceed prior to review of the data by the DSMB. A similar approach will be applied between the Transitional Study Session and the RCT Period in pediatric subjects, and between the Senseonics Eversense Test Run and the Adult RCT Period at MGH.

5.2. Home Procedures and Study Policies for both UC and BP

- The protocol outlined below is the same for all study participants in all study periods.
- Study participants will use the Contour Next One glucometer for all glucose measurements in the study.
    - Study participants will keep the study glucometer easily accessible at all times in case a calibration is needed. They will keep fast-acting carbohydrates and a glucagon emergency kit easily accessible in case they are needed.
    - Participants 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 driving, before exercise and at intervals during exercise, and for any symptoms of hypoglycemia or hyperglycemia.
    - Participants will use the study provided blood ketone meter for all ketone measurements in the study.
- The participants will calibrate the Dexcom G5 or Senseonics Eversense CGM before breakfast and supper (approximately every 12 hours) daily using the study glucometer.
    - Participants may perform additional calibrations if the Dexcom G5 (or Senseonics Eversense CGM) is inaccurate relative to a BG measurement.
    - Participants will be reminded not to perform a calibration if they have eaten carbohydrates within the last 30 minutes, or there is a steep rise or fall in their glucose.
- Participants in the Pediatric Transitional Study Session will be required to check a fingerstick BG between 2:00 and 3:00 AM on the first two nights of each study arm. Participants and their overnight companions will be instructed to contact study staff if they have any concerns with the result of this fingerstick BG. The same remote monitoring protocols will be in place for hypoglycemia and hyperglycemia on these two nights.
- Participants may not take acetaminophen during all study periods due to potential interference with CGM sensing.
- Participants will not be allowed to travel by airplane throughout the study, due to our inability to remotely monitor for hypoglycemia and hyperglycemia.
- Participants will complete a brief daily e-mailed survey during all study periods including

questions about hypoglycemia, carbohydrate interventions, and any other adverse events. They will be reminded that a portion of their reimbursement is dependent on completing at least 90% of these surveys.

- Participants will not tamper with or alter the iLet BP device in any way, including changing their weight in the iLet. Participants will be instructed not to change their weight in the iLet during a study period, even if their weight changes. They will not edit any of the alarm settings of the CGM.
- Participants will be asked to change their insulin reservoir and infusion set every 2 days in both the BP and UC periods (for CSII users).
- Participants will be asked to replace the batteries in the iLet every 2 days to ensure optimal performance of the device.
- A new Dexcom G5 CGM sensor will be placed every 7 days if no replacement was required before this time. The Dexcom G5 app will generate an alarm when replacement is required. Participants will be reminded to only use FDA approved insertion sites for the G5 CGM sensor.
- Alarms will sound and a visual alert will appear at the lowest threshold allowed for each CGM system: on the G5 mobile app when the CGM glucose is ≤ 55 mg/dl, or on the Senseonics Eversense app for CGM glucose ≤ 60 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 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 CGM app (Dexcom or Senseonics Eversense) if CGM glucose is > 300 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:
            - CSII or BP users 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.
            - MDI participants on UC will be asked to review their previous insulin doses, and consider correction insulin per their home regimen.
            - 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 ≥0.6 mmol/L are present:
        - CSII participants on UC will be advised to change their pump infusion set and take correction insulin per their home regimen.
        - MDI participants on UC will be advised to take correction insulin per their home regimen.
        - BP users 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.
- There are no restrictions of any kind on diet, exercise, or other activities. Participants will be asked to keep their diet and activity as similar as possible throughout the study.
- The BP is not water resistant and therefore must be removed for showering and swimming and must be kept dry during exercise. Participants are urged to take appropriate precautions when they are disconnected from the BP, including frequent BG checks and having carbohydrate readily available. They are urged to limit the amount of time they are disconnected from the iLet to ensure optimal glucose control.
- Any medical advice needed by the participants during their participation that is not directly related to the study protocol should be obtained by them in the usual manner with their own physician.
    - If a participant develops an illness during the study he/she can seek medical care as usual. As long as the participant is not hospitalized, the study can be continued. If the participant 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 to use the BP. BP use may be temporarily discontinued if study staff believes this is warranted.

5.3. Home Procedures specific to the UC Group

- The protocol outlined below is the same for the entire RCT period. The only modifications for the Transitional Study Session are as follows:
    - Participants will spend the daytime hours under the supervision of study staff participating in group activities and meals
    - Participants will wear an activity monitor
    - Participants will be required to use CSII as their usual care
- The Test-Run Period and Senseonics Eversense Test Run have no usual care group.
- The UC group will continue its pre-study diabetes management, including their approach to insulin delivery and monitoring. The study will provide the CGM supplies and glucometer for use by this group. Diabetes management will be handled by the participant's diabetes

health care provider. If participants use a continuous glucose monitor as a part of usual care they are specifically encouraged to continue use of the CGM during the study period.

5.4. Home Procedures specific to the Insulin-Only BP Group

- The protocol outlined below are the same protocol for the Test-Run Period, and the entire RCT Period.
    - The only modification for the Transitional Study Session are as follows:
        - Participants will spend the daytime hours under the supervision of study staff participating in group activities and meals
        - Participants will wear an activity monitor
    - The only modifications for the Senseonics Eversense Test Run are as follows:
        - Participants will spend the daytime hours under the supervision of clinically licensed study staff, in a limited area surrounding MGH.
- All functionality of the BP will remain the same regardless of which CGM system is driving the iLet.
- The BP will alarm if the CGM glucose is ≤ 50 mg/dl. Participants will follow the same hypoglycemia protocol outlined above.
- If there is a technical fault with the BP, the participant will call the technical support line immediately. If necessary, a staff member will meet the participant to assist with troubleshooting. This meeting may be delayed until morning if the problem occurs overnight - in this case, the participant will use their own pump or use injectable insulin until a meeting is possible. A member of the study staff (within their scope of practice and under the supervision of the site principal investigator) may advise them on how to manage their diabetes in the interim. If necessary, the BP device may be replaced.
    - If there is a complete failure of BP operation and it is anticipated that restarting it will take more than an hour, participants may revert to usual care using their own insulin pump or with insulin injections until the BP can be brought back online with the help of study staff. Every effort should be made to correct the problem as soon as possible, which should almost always be possible within 12 hours.
- If the CGM sensor fails during the course of an experiment, the system will provide automated basal insulin based on past requirements, and will allow announcement of meals (with 75% of predicted insulin delivered based on past requirements), and entry of fingerstick BG measurements (which will be treated as CGM data and may result in administration of insulin or temporary suspension of basal insulin). The system will alarm and request a BG measurement every 120 minutes when the CGM signal is not available, but the system will remain in closed-loop mode even if CGM data are not available. Participants will be encouraged to enter a fingerstick BG measurement into the BP as frequently as they wish to achieve optimal control during CGM downtime. The CGM sensor will be replaced as soon as possible and normal (online) BP control will resume when the new sensor is calibrated.
- Participants will be encouraged to announce the three major meals of the day to the BP. The meal announcement will consist of choosing the timing of the meal relative to one's regular sleep period (first of the day, middle of the day, end of the day, or during what would be regular sleep hours if one occasionally happens to be up) and the size of the meal relative to typical meals for that participant (snack, smaller than typical, typical, larger than typical). Participants will be trained not to announce snacks that occur between major meals.
- The iLet ready-to-fill insulin cartridge or Fiasp in PumpCart, insulin cartridge connectors, and tubing will be replaced as needed, but at least every 2 days.
- Once the BP is initialized on day 0, participants who use MDI therapy will stop taking insulin by injection. If they take their long-acting insulin in the evening, then they will take their last

dose of long-acting insulin in the evening of day -1. If they take their long-acting insulin in the morning before the scheduled time of the day 0 visit, then they will take their last dose on the morning of day 0. The bionic pancreas will ramp up insulin dosing automatically as needed as the levels of long-acting insulin fall.

5.5. Remote Monitoring

- All remote monitoring protocols will be the same for the Test-Run Period, the Transitional Study Session, the Senseonics Eversense Test Run and the RCT Period. They will also be the same regardless of if the participant is using the BP or is under usual care. They will also be the same regardless of which CGM system is serving as the input to the iLet.
- Real-time remote telemetric monitoring for biochemically severe hypoglycemia or persistent hyperglycemia will be performed by the study staff 24 hours a day. There will be at least one provider (MD, NP, or PA) and at least one additional study staff member on call in addition to the staff member monitoring for alarms. A staff member will make contact with participants as necessary and help them troubleshoot any issues that may arise.
- When an alert comes in, a study staff member will call the participant. Depending on the circumstances, they may call locations the participant is known to frequent (e.g. usual work location) or they may be dispatched to make contact with the participant (if the location is nearby and reaching the location would be no risk to the safety of staff member or violate employment rules).
- Remote monitoring is only possible when the participant has Verizon network coverage and data can be transmitted to the cloud service. There may be times when a participant enters an area where Verizon coverage is not available. We may provide participants with WiFi boosters for their homes or WiFi hot spots to carry with them in order to improve data throughput. We may also encourage participants to connect to public but secure wireless networks if they are having trouble connecting to cellular service.
- An alert will be generated if remote monitoring indicates that a participant is offline. We will call the participant every 2 hours to check on safety and device function until remote monitoring is restored. 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. The same rules will be used for checking in when the participant in in the UC and BP periods.
- Participants in the Adult Test Run and Senseonics Eversense Test Run will have designated contacts who will serve as an emergency contact person in the event the study staff is unable to get in touch with the participant in response to such an alarm. These designated contacts should have access to where the participant may be sleeping if necessary.
- Participants in the Pediatric Transitional Study Session will be supervised by study staff during the day, and discharged to a parent or guardian at the end of the day until they return to the study site the following morning. This parent or guardian must be at home when the participant is home and/or sleeping and will serve as the contact for overnight alarms.
- Participants in the Senseonics Eversense Test Run will be supervised by study staff during the day, and discharged to home at night. Remote monitoring will be continuous regardless of if the subject is with the staff or at home.

5.5.1. Remote Monitoring for Hypoglycemia

- The remote monitoring system will generate an alarm if the CGM glucose is < 50 mg/dl for 15 minutes.
- 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, 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 applied in the Test-Run Period, the Transitional Study Session, the Senseonics Eversense Test Run, and the RCT Period. Monitoring will be identical if participants are on the BP or UC.

5.5.2. Remote Monitoring for Hyperglycemia

- 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 applied in the Test-Run Period, the Transitional Study Session, the Senseonics Eversense Test Run, and the RCT Period. Monitoring will be identical if the participants are on the BP or UC.

5.6. Resources for Participants

- Questions relating to study protocol will be dealt with by a study staff member on call. Participants will be referred to their own medical providers for issues not directly related to the study and to local Emergency Medical Services for medical emergencies.
- A central technical support line for the BP will be staffed 24 hours a day. An engineer will be on call to deal with non-routine matters.
- If there is a technical problem with the BP that cannot be resolved over the phone, the participant may be asked to come to the local study site or the study staff may meet them at another location. If this is not possible or would be too disruptive (i.e. in the middle of the night) the participant will be asked to take over his/her own glycemic control using his/her insulin pump (if on CSII) or by giving subcutaneous insulin injections (if on MDI) 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.

5.7. Daily At-Home Questionnaire

Participants in all study periods will complete a web-based questionnaire daily. Participants will be asked to report certain events occurring during the prior day such as hypoglycemia, other medical conditions, alcohol use, exercise, and use of a personal CGM as a part of usual care. In addition, events during the prior 24 hours including nausea and/or vomiting will be solicited.

Participants will complete this questionnaire during all study periods (with the assistance of a parent/guardian as needed in the Pediatric periods).

5.8. Follow-Up Phone Contacts

The schedule for follow-up visits and phone contacts is the same for both BP and UC. In all groups, study staff will ask participants about any adverse events

- Test-Run Period: Phone contacts will occur on days 3 or 4 out of the 7-day period.

- Transitional Study Session: there will be no phone contact, as the participants are with the study staff daily
- Senseonics Eversense Test Run: there will be no phone contact, as the participants are with the study staff daily
- Pediatric RCT Period: Phone contacts will occur on days 3 or 4 out of the 7-day period.
- Adult RCT Period: Phone contacts will occur on days 3 or 4 out of the 7-day period.

5.9. Shutdown Visits

The protocol below describes visit shut down procedures for the Test-Run Period, the Transitional Study Session, the Senseonics Eversense Test Run, and the RCT Period. The Test Run, the Transitional Study Session, and the Senseonics Eversense Test Run each only have one shutdown visit. The Adult RCT Period will have three shutdown visits. The Pediatric RCT Period will have two shutdown visits. Shutdown visits occur at the end of each study period.

The following procedures will be performed during each shutdown visit:

- The body weight of the participant will be documented.
- All study devices, including the iLet BP, the CGM system, the ketone meter and the study glucometer will be downloaded. The subject's personal insulin pump will be downloaded as needed. The Dexcom G5 transmitter will be cleaned and disinfected per the validated protocol provided by the manufacturer.
- Any changes to medications or medical history will be documented.
- The participant will be queried regarding the occurrence of any adverse events
- Participants will complete psychosocial questionnaires at the end of each period. The Bionic Pancreas User Opinion Survey (BPUOS) will be completed after each BP study period. See chapter 7 for more details.
    - The Senseonics Eversense Test Run will not include questionnaires.
- A study provider will review the last few hours of glucose trend data and insulin on board from the BP, and assist the participants in resuming their usual diabetes management if they are transitioning off of the BP to their usual care.

5.10. Final Shutdown Visit

The Final shutdown visit will occur at the end of the last study period. The following procedures will be performed at the Final Shutdown Visit:

- The body weight of the participant will be documented.
- All study devices, including the iLet BP, the CGM system, the ketone meter and the study glucometer will be downloaded. The subject's personal insulin pump will be downloaded as needed. The Dexcom G5 transmitter will be cleaned and disinfected per the validated protocol provided by the manufacturer.
- Any changes to medications or medical history will be documented.
- The participant will be queried regarding the occurrence of any adverse events
- Participants will complete psychosocial questionnaires. The Bionic Pancreas User Opinion Survey (BPUOS) will be completed after each BP study period. See chapter 7 for more details.
- A study provider will review the last few hours of glucose trend data and insulin on board from the BP, and assist the participants in resuming their usual diabetes management if they are transitioning off of the BP to their usual care.

5.10.1. Post-study Transition Period

- Adult and pediatric participants randomized to a BP period for their final study period will be discharged to a usual care regimen following the dosing recommendations calculated by the iLet for 48 hours.

- The iLet will recommend doses to be used as basal, for meals, and for corrections. This is intended to provide future consumers of the iLet with a regimen to follow in the event their iLet breaks and it will take a few days to get a replacement.
- All participants will use either Humalog or Novolog. They will use whichever insulin they used during the BP period.
    - Adult participants will only follow the iLet recommendations based on their iLet BP period using either Humalog or Novolog. If the completed the Fiasp BP period as their last period, they will still be discharged to the Post-Study Transition Period, but will be following the recommendations from the previous period where they used Humalog or Novolog in the iLet.
- During this time, participants will continue to wear the CGM used during the RCT Period. They will be monitored remotely for severe hypoglycemia and prolonged hyperglycemia according to the same protocol during the study. They will be required to follow all of the same study policies and procedures, including completion of the daily e-mail survey.
- At the end of this 48-hour period, participants will return to the research clinic for an additional study visit. The CGM data and their insulin pump data where applicable will be collected and analyzed for safety and efficacy of the iLet's recommendations.
- Participants will then return to their usual CSII or MDI diabetes regimen.

5.11. Senseonics Eversense CGM sensor removal

- Senseonics Eversense CGM sensor removals will be scheduled for immediately after the RCT Period (or Post-Study Transition Period where appropriate) is finished. This may be on the same day as the Final Shutdown Visit, or in the next few days after as schedules allow, on the condition that no sensor remains in place for 90 days or more.
- This procedure is similar to the sensor insertion. The skin near the sensor is numbed using a local anesthetic, a small incision is made in the skin using the Removal Template provided by the sponsor, and the sensor is removed. The incision will be closed using surgical tape or a suture, and covered with a bandage.
- Subjects will be instructed to leave the bandage on for approximately 24 hours. They will be instructed to monitor for any discharge, excessive bleeding, redness, warmth or swelling at the removal site and to contact study staff if this occurs.
- A study physician will follow up with a phone call within 48 hours of removal to assess appropriate healing and query for any adverse events.

CHAPTER 6: STUDY DRUGS AND DEVICES

6.1. Study Drugs

The study involves subcutaneous administration of insulin lispro (Humalog, Eli Lilly), insulin aspart (Novolog, Novo Nordisk), or faster-acting insulin aspart (Fiasp, Novo Nordisk). Humalog and Novolog are commercially available by prescription and are indicated for patients with type 1 diabetes, but not for use in a BP. Fiasp is approved for use in an MDI regimen, but not in PumpCart or for use in a BP. The current version of the package insert for Fiasp will be used for this protocol. Participants will use their usual rapid-acting insulin analog during the UC period of the study and during the Humalog/Novolog BP period. Adults in the Fiasp BP period will use Fiasp as pre-specified.

The control system can administer bolus doses of each drug up to every five minutes. A single autonomous bolus of insulin will not exceed 3 units per 5-minute dose [30 µl] (except when it is in response to an isolated BG entry, where the dose will not exceed 12 units [120 µl]) and a single meal-priming dose, which is triggered by the user but automatically determined by the control system, will not exceed 18 units [180 µl]. The dual pump can administer as little as 0.10 µl (0.01 units of U-100 insulin) in single programmable bolus doses. Insulin exposure is expected to be comparable to that of participants when not participating in the study.

6.2. Devices

6.2.1. Infusion Sets

Participants will be provided with infusion sets (Contact Detach infusion sets, Unomedical) for the Test-Run Period, Transitional Study Period and BP periods of the RCT Period. These infusion sets utilize a 6 mm 29 G steel cannula and 23 inch tubing with a leur-lock connection. Participants will be instructed to replace their infusion set every 2 days at least. If the infusion set fails for any reason during the experiment it will be replaced promptly.

6.2.2. Continuous Glucose Monitors

6.2.3. Dexcom G5 CGM

One transcutaneous glucose sensor for the Dexcom G5 will be inserted in the subcutaneous tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the BP. If the Dexcom G5 CGM sensor fails for any reason during the experiment it will be replaced promptly.

All participants in the Test-Run Period, the Transitional Study Session and the Stanford site of the RCT Period will wear a Dexcom G5 CGM sensor. In these cohorts, the Dexcom G5 CGM will serve as the input to the iLet.

6.2.4. Senseonics Eversense CGM

One subcutaneous glucose sensor for the Senseonics Eversense Continuous Glucose Monitor System will be inserted in the subcutaneous tissue of the upper arm. The insertion is an office procedure that takes approximately 5 minutes. The insertion requires local anesthesia and a sterile field. After up to 90 days, the sensor is removed in a brief office procedure under local anesthesia. The sensor is approximately 3.3 mm in diameter and 15.7 mm long. It contains a ring that elutes the steroid dexamethasone and core electronics that are potted in epoxy within a poly-methylmethacrylate (PMMA) encasement. The glucose indicating copolymer, which is grafted onto the PMMA surface, is fluorescent and changes in intensity in response to changes in glucose concentrations. That intensity data is transmitted to a battery-powered transmitter that is worn on

the upper arm over the insertion site of the sensor. The transmitter is a reusable device that powers the sensor and collects information about glucose levels. It is secured over the sensor insertion site with a transmitter strap or adhesive patch. The transmitter communicates via Bluetooth Low Energy (BTLE) to a Mobile Medical Application (MMA) installed on a smartphone or other handheld device. This MMA displays glucose information and allows for calibration of the sensor.

Only participants at the MGH site of the Senseonics Eversense Test Run and adult RCT Period will wear a Senseonics Eversense CGM. The Senseonics Eversense CGM will act as the input to the iLet in this cohort.

6.2.5. BP Control Unit

The iLet bionic pancreas is compatible with both the Dexcom G5 CGM and the Senseonics Eversense CGM. It 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. Participants will be instructed to announce meals in the same way when using the BP with Humalog or Novolog, or with Fiasp.

The default “usual” glucose target level for the bionic pancreas in the insulin-only mode is 120 mg/dl. This default will be the same when using Humalog or Novolog, or Fiasp. 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. Participants will be allowed to modify the target of the BP according to the same protocol in the Humalog or Novolog periods and the Fiasp period.

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.

CHAPTER 7: QUESTIONNAIRES

7.1. Introduction

Questionnaires are completed by all participants at the Initial Startup Visit and each Shutdown Visit. Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual. Age appropriate versions of each questionnaire will be administered wherever possible. Parents/guardians of pediatric subjects and designated contacts in the Adult Test Run may complete parent or partner versions of these questionnaires where applicable. Questionnaires will not be administered in the Adult Senseonics Eversense Test Run.

7.2. Brief Description of Questionnaires

7.2.1. Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs)

The DTSQs measures patient satisfaction with diabetes treatment. It consists of a 6 item scale for assessing treatment satisfaction and two additional items assessing perceived frequency of hyperglycemia and hypoglycemia. The DTSQs is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for BP studies for our use, along with a version for younger children. It is administered at the Initial Startup Visit. The DTSQs is valid and reliable. Administration time is less than 5 minutes.

7.2.2. Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)

Although the DTSQ is responsive to treatment changes, ceiling effects are often seen with this instrument, where maximum or close-to-maximum scores at baseline provide little opportunity for registering improvement. The DTSQc contains the same items as the DTSQs version but asks patients to consider their satisfaction with their current treatment compared with their previous treatment. The DTSQc is meant for adults and older children. Dr. Clare Bradley has produced a version that is appropriate for BP studies for our use, along with a version for younger children. It is administered at each Shutdown Visit. The DTSQc is valid and reliable. Administration time is less than 5 minutes.

7.2.3. Diabetes Distress Scale (DDS)

There are two versions of the DDS which we will be using; Adult and Partners of Adults. The DDS is a 28-item survey that assesses seven sources of diabetes distress for type 1 adults. It captures feelings of powerlessness; management distress; hypoglycemia distress; negative social perceptions by others; eating distress; physician (health care) distress; and friend/family distress. Items are scored on a 6-point scale from not a problem to a very serious problem. It is administered at the Initial Startup Visit and each Shutdown Visit. The scale is valid and reliable, and has been shown to be sensitive to change over time. Administration time is 5 minutes.

7.2.4. Problem Areas in Diabetes Survey (PAID)

There are four versions of the PAID which we will be using; Teen (PAID-T), Parents of Children (PAID-C), Parents of Teens (PAID-T) and Child (PAID-C) versions. This measure of diabetes-specific emotional distress in youth with diabetes and their parents is 26 items. A total score is generated. It is administered at the Initial Startup Visit and each Shutdown Visit. The PAID-T and PAID-P are valid and reliable. Psychometric analysis of the PAID-C is in progress. Administration time is 5 minutes.

7.2.5. Hypoglycemia Fear Survey (HFS)

There are three versions of the HFS, Adult (HFS), Youth (HFS-Y) and Parent (HFS-P). The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. It consists of 23 items and produces two sub-scale scores; a Behavior sub-scale that measures behaviors involved in avoidance and/or over-treatment of hypoglycemia and a Worry sub-scale that

measures anxiety and fear surrounding hypoglycemia. The HFS-Y consists of 25 items and the HFS-P consists of 26 items; both produce sub-scale scores similar to the Adult HFS. It is administered at the Initial Startup Visit and each Shutdown Visit. All versions of the HFS are valid and reliable. Administration time is 5-10 minutes.

7.2.6. Hypoglycemia Confidence Scale (HCS)

The HCS (20) is a 9-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and insulin-using type 2 diabetes. It is administered at the Initial Startup Visit and each Shutdown Visit. Administration time is approximately 5 minutes.

7.2.7. INSPIRE Survey

There are five versions of the INSPIRE; Adolescent, Adult, Child, Parent and Partner. The INSPIRE (Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations) survey was developed to assess various aspects of a user's experience regarding automated insulin delivery for both patients and family members. The surveys include various topics important to patients with type 1 diabetes and their family members based upon >200 hours of qualitative interviews and focus groups. The adult survey includes 31 items; the adolescent survey includes 28 items; and the parent survey includes 30 items. Response options for all surveys include a 5-point Likert scale from strongly agree to strongly disagree, along with an N/A option. It is administered at the Initial Startup Visit and each Shutdown Visit. Administration time is approximately 5 minutes.

7.2.8. Bionic Pancreas User Opinion Survey (BPUOS)

The BPUOS is a 38 item measure that assesses both the benefits from, and difficulties with, use of the BPA total score is generated. It is administered at the end of each BP intervention only. Administration time is 10 minutes.

CHAPTER 8: ADVERSE EVENTS, DEVICE ISSUES, AND STOPPING RULES

8.1. Adverse Events

8.1.1. Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered/using a Product and which does not necessarily have a causal relationship with this treatment. An Adverse Event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a Product, whether or not considered related to the Product. For clarity, an adverse event can occur any time during the course of the study from the time of screening through the final study visit, irrespective of whether a study device or drug is being used at the time of the untoward medical occurrence.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).
- Suspicion of transmission of an infectious agent will also be considered an SAE

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint.

Device Malfunction: Any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3)

8.1.2. Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1) Non-serious adverse events
2) A serious adverse event
3) An Adverse Device Effect as defined in section 8.1.1, unless excluded from reporting in section 8.2
4) An Adverse Event occurring in association with a study procedure
5) Hypoglycemia meeting the definition of severe hypoglycemia as defined below
6) Diabetic ketoacidosis (DKA) as defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Pregnancy occurring during the study will be recorded.

Reporting to Novo Nordisk
For NovoLog: Copies of reports submitted to the FDA.
For Fiasp PumpCart:

- Copies of reports submitted to the FDA.
- All non-serious adverse events
- All Serious adverse events
- All events of pregnancy
- All technical issues with the product alone, all technical issues with the combined system (pump and PumpCart®) and all issues with the packaging material and labelling"

8.1.2.1 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: 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.

8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following criteria is met: (1) the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or (2) 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

All reportable Adverse Events—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

8.1.3. Relationship of Adverse Event to Study Device and/or Study Drug

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 device and/or study drug.

Relationship between an AE/SAE and the relevant trial product*(s*) should be assessed as:

Unrelated: The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.

Unlikely Related: The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.

Possibly Related: The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.

Probably Related: The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.

Definitely Related: The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Not Assessable: Causality of an adverse event cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Alternative etiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the *investigator's brochure* for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.

The investigator may change his/her opinion of causality in light of follow-up information and updated causality assessment on the electronic CRF completed for the AE/SAE.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.1.4. Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.

SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

8.1.5. Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

8.1.6. Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.

RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.

FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.

UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

ONGOING – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.

An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.

The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

8.2. Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- Dexcom G5 CGM sensors lasting fewer than 7 days
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that don't meet criteria for AE reporting

8.3. Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported on an AE Form.

8.4. Timing of Event Reporting

Serious or unexpected device-related or drug-related adverse events must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events and device malfunctions (with or without an adverse event) will be reported within 3 days of the investigator becoming aware of the event by completion of an electronic case report form.

Device complaints not associated with device malfunction or an adverse event must be reported within 7 days of the investigator becoming aware of the event.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

Device malfunctions will be handled by the Sponsor or designee as described below. In the case of a CGM transmitter or sensor device malfunction, information will be forwarded to Dexcom by the site personnel, to be handled by their complaint management system.

Beta Bionics will notify the Investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP. In addition, the Investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Beta Bionics will inform the regulatory authorities of trial product-related SUSARs. In addition, Beta Bionics will inform the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of trial product-related SUSARs in accordance with local requirement and GCP, unless locally this is an obligation of the Investigator.

Prompt notification to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial product under clinical investigation are met. Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institution review board (IRB), independent ethics committee (IEC), and investigators.

Drug related UADEs will also be reported to Novo Nordisk within 15 days of the investigator's first knowledge of the event. At a minimum, the following should be reported: Study name, Patient identification (e.g. subject number, initials, sex, age), Event (Preferably diagnosis), Trial drug, Reporter, Causality, and Outcome.

8.5. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. Details regarding review will be documented in standalone DSMB procedural documentation.

8.6. Potential Risks and Side Effects

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia is always a risk in participants with type 1 diabetes and participants will be closely monitored for this.

Hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be closely monitored for this.

8.6.1. Venipuncture Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

8.6.2. Fingerstick Risks

About 1 drop of blood will be removed by finger stick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as finger pokes are part of the usual care for people with diabetes.

8.6.3. Subcutaneous Continuous Glucose Sensor and Subcutaneous Catheter Risks

Participants using the Dexcom continuous glucose sensor will be at low risk for developing a local skin infection at the site of the sensor needle placement. On rare occasions, the Dexcom continuous glucose sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The participant should be further instructed to notify the study coordinator immediately if this occurs.

There are additional risks associated with the Senseonics Eversense CGM sensor insertion, removal, and/or use of the CGM system. The risks are greater than in the lives of people with diabetes outside this trial, as the Senseonics Eversense system is not approved for consumer use in the United States. In studies using the Senseonics Eversense CGM system to date, no device related serious adverse events have been reported, and only a few device related averse events have been reported. Of those, most were predominately expected local skin reactions to the insertion and/or the local anesthesia provided during this procedure, which all recovered without residual damage after short time periods. In our own experience with the Senseonics Eversense sensor, 27 sensors were implanted and removed without any unexpected or serious adverse events. Study staff will examine the insertion site at each study visit and make appropriate notes that will be relayed back to the sponsor. Subjects will be instructed to contact study staff immediately upon any sign of extreme irritation or discomfort.

If a subcutaneous infusion set catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk). When wearing sensors and insulin infusion sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site. Infections occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used.

8.6.4. Risk of Hypoglycemia

Hypoglycemia could occur if the system delivers an inappropriate amount of insulin given the participant's underlying glycemic state. This could occur if, for example, a sensor is functioning poorly and significantly over-reading glucose values. Over-delivery may be minimized if the sensor's trend data remains accurate despite inaccurate level values, or by the safety constraints of the closed loop system. However, there is a risk of having a low blood sugar (hypoglycemia) that may exceed the risk present as part of normal daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as with normal daily living, there is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of low blood

sugar.

8.6.5. Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A sensor which was functioning poorly and significantly under-reading glucose values could lead to inappropriate reduction of insulin delivery.

8.6.6. Psychosocial Questionnaires

As part of the study, participants will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

8.6.7. Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, the activity monitor, or the insulin infusion sets. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Data downloaded from the BP, the SMBG meter, and the ketone meter, and the activity monitor will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

8.7. Study Stopping Criteria

In general, once a participant is randomized, he/she will remain in the study through Shutdown Visit unless the investigator believes it is not safe for the participant to continue. However, the criteria below will be used to determine whether use of the BP should be discontinued for a participant.

8.7.1. Criteria for Individual Participants

Rules for discontinuing study device are described below.

1. The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety.
2. The participant requests that the treatment be stopped
3. Developing >1.0 mmol/L ketones on more than 3 days total due to prolonged periods of inadequate insulin delivery recommendation.
4. Participant Pregnancy
5. One episode of DKA (as defined in section 8.1.2.2), unrelated to infusion site failure, related to automated attenuation of insulin delivery
6. One severe hypoglycemia event (as defined in section 8.1.2.1) related to automated insulin delivery

If BP use is stopped according to the above criteria, but the participant is willing, he/she will remain in the trial and will continue to make all of the scheduled visits and participate in all monitoring. The primary analysis will be intention to treat. Since participants in the UC period are following their normal diabetes care regimen, there will be no change in their participation in the trial if they experience one of the events that would trigger stopping in the BP period.

Study participation is voluntary, and participants may withdraw at any time.

8.7.2. Criteria for Suspending/Stopping Overall Study

The DSMB will have the responsibility of determining if the overall study should be stopped. If there are no events for DSMB review during the pilot study for the first 8 participants in the Test Run, then the Adult RCT crossover study will be initiated prior to review of the data from the pilot study. Similarly for the pediatric population, if there are no events for DSMB review during the pilot study for the first 20 participants in the Transitional Study Session, then the Pediatric RCT crossover study will be initiated prior to review of the data from the pilot study.

In case of a recurring system malfunction or participant safety issue observed with multiple participants, the overall study will be suspended while the problem is diagnosed. The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

An instance of severe hypoglycemia or hyperglycemia as defined in section 8.1 in the BP group will result in temporarily stopping additional enrollment of participants until DSMB review of the data to determine whether the event was triggered by the system or not and whether it is safe to proceed. The currently-enrolled participants will continue use of the system during this time unless the DSMB determines it is unsafe for them to do so.

CHAPTER 9: MISCELLANEOUS CONSIDERATIONS

9.1. Benefits

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. This research is one step on the path towards development of a fully closed-loop system. The individual participant may not benefit from study participation.

9.2. Participant Compensation

Participants will be compensated $50 for each pre-specified clinic visit during the study and $50 for completing at least 90% of the daily questionnaires.

9.3. Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The investigator may withdraw a participant who is not complying with the protocol. Withdrawal of a participant will be considered for the reasons listed in section 8.7. For participants who withdraw, their data will be used up until the time of withdrawal.

For participants using the BP who withdraw, a study provider will help them transition to their own CSII or MDI therapy safely.

9.4. Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

CHAPTER 10: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the start of the study.

10.1. Sample sizes

Eight adult participants are expected to complete the Test-Run Period, 4 adults are expected to complete the Senseonics Eversense Test Run, and 36 adult participants will be enrolled in the RCT Period. 20 pediatric participants are expected to complete the Transitional Study Session and 20 pediatric participants will be enrolled in the Pediatric RCT Period. These are convenience samples not based on statistical principles.

10.2. Test-Run Period

10.2.1. Summary

Eight adult participants (age ≥18 years) will use the iLet in the insulin-only configuration with Humalog or Novolog (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) for 7 days at a single site. The uncontrolled Test-Run Period will be completed and data reviewed to verify safety before proceeding with Transitional Study and with Adult RCT Period.

10.2.2. Outcomes

No formal statistical comparisons will be done for Test-Run Period. This period has no control period and is primarily intended to verify that the iLet is operating as expected (based on its design and on bench testing) in the outpatient setting.

Since the main aim for Test-Run Period is to verify safety and feasibility, plus some trends in efficacy, the following outcomes will be considered:

- Safety:
  - Episodes of severe hypoglycemia as defined in section 8.1.2.1
  - Episodes of diabetic ketoacidosis (DKA) as defined in section 8.1.2.2
  - Other serious adverse events
- Questionnaires (treatment satisfaction):
  - For each questionnaire completed at 0 and 7 days, mean (standard deviation [SD]) values or medians (interquartile range [IQR]) appropriate to the distribution will be given for the total score and where indicated for each subscale
- Sensor:
  - Hypoglycemia:
    - time <70, 60, and 54 mg/dl
    - low blood glucose index (LBGI)
    - hypoglycemic events per 24 hours - defined as ≥15 consecutive minutes with a sensor glucose <50 mg/dL
  - Overall Control:
    - mean glucose
    - time in the target ranges of 70-180 and 70-120 mg/dl
    - glucose variability measured with coefficient of variation (CV)
  - Hyperglycemia:
    - time >180 and 250mg/dl
    - High blood glucose index (HBGI)
    - hyperglycemic events per 24 hours - defined as ≥90 consecutive minutes with a

sensor glucose >300 mg/dL

- Sensor accuracy:
  - The following will be calculated using the Ascensia Contour Next One point-of care glucose meter:
    - MARD for the Dexcom G5 overall and in the following SMBG ranges: < 70, 70–180, > 180, > 250

- System and remote monitoring:
  - percentage of time IOBP was in use
  - number and rates of different errors or malfunctions
- Daily at-home questionnaire:
  - symptomatic hypoglycemia
  - hypoglycemia requiring carbohydrate intervention
  - alcohol use
  - exercise
  - nausea and/or vomiting
  - use of a personal CGM as a part of usual care

Sensor metrics will be calculated using data from days 3-7. The Test Run will be completed and the data will be reviewed to verify safety prior to beginning the Adult RCT Period.

10.3. Senseonics Eversense Test Run Period

10.3.1. Summary

Four adult participants (age ≥18 years) will use the iLet in the insulin-only configuration with Humalog or Novolog (using the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Senseonics Eversense CGM) for 3 days at a single site. This uncontrolled study period will be completed and data reviewed to verify safety before proceeding with the Adult RCT Period at MGH using the Senseonics Eversense CGM as the input to the iLet.

10.3.2. Outcomes

No formal statistical comparisons will be done for Senseonics Eversense test run period. This period has no control period and is primarily intended to verify that the iLet is operating as expected (based on its design and on bench testing) in the outpatient setting using this alternative CGM that has not been tested with the iLet before.

Since the main aim for this period is to verify safety and feasibility, plus some trends in efficacy, the following outcomes will be considered:

- Safety:
  - Episodes of severe hypoglycemia as defined in section 8.1.2.1
  - Episodes of diabetic ketoacidosis (DKA) as defined in section 8.1.2.2
  - Other serious adverse events
  - distribution will be given for the total score and where indicated for each subscale
- Sensor:
  - Hypoglycemia:
    - time <70, 60, and 54 mg/dl
    - low blood glucose index (LBGI)
    - hypoglycemic events per 24 hours - defined as ≥15 consecutive minutes with a sensor glucose <50 mg/dL
  - Overall Control:
    - mean glucose

        - time in the target ranges of 70-180 and 70-120 mg/dl
        - glucose variability measured with coefficient of variation (CV)
    - Hyperglycemia:
        - time >180 and 250mg/dl
        - High blood glucose index (HBGI)
        - hyperglycemic events per 24 hours - defined as ≥90 consecutive minutes with a sensor glucose >300 mg/dL
- Sensor accuracy:
    - The following will be calculated using the Ascensia Contour Next One point-of care glucose meter:
        - MARD for the Senseonics Eversense CGM overall and in the following SMBG ranges: < 70, 70–180, > 180, > 250
- System and remote monitoring:
    - percentage of time IOBP was in use
    - number and rates of different errors or malfunctions
- Daily at-home questionnaire:
    - symptomatic hypoglycemia
    - hypoglycemia requiring carbohydrate intervention
    - alcohol use
    - exercise
    - nausea and/or vomiting
    - use of a personal CGM as a part of usual care

Sensor metrics will be calculated using data from days 2-3. The Senseonics Eversense Test Run will be completed and the data will be reviewed to verify safety prior to beginning the Adult RCT Period with the Senseonics Eversense CGM as the input to the iLet.

10.4. Pediatric Transitional Study Session

10.4.1. Summary

20 pediatric participants (~ 6 participants age 6–11 years at Nemours, ~ 6 participants age 12–17 years at Colorado, and ~ 8 participants age 6–17 years at Stanford) will be randomly assigned to the following study periods: (1) use of iLet in the insulin-only configuration with the iLet pigtail adapter and the iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, the Dexcom G5 CGM, and the insulin analog that they use for their usual care (either Humalog or Novolog), and (2) participant's own usual care (UC) where each participant will wear a Dexcom G5 CGM. The two experimental periods will each span approximately 5 days with a washout period of ~ 3 days in between. The Pediatric Transitional Study Sessions will be completed and the data will be reviewed to verify safety prior to beginning the Pediatric RCT Period.

10.4.2. Outcomes

- The outcomes and analyses will parallel the ones mentioned above for Test-Run Period (i.e, Section 10.2.2) with the exceptions:
    - Sensor metrics will be calculated using data from days 2–5 from each experimental period.
    - The results will be presented by both experimental periods without any formal statistical comparison. Summary statistics appropriate to the distribution will be given separately for the two experimental periods.
    - Questionnaires will be completed at baseline and day 5 of each experimental period.

10.5. Adult RCT Period

10.5.1. Summary

Forty adult participants (age ≥18 years) will be enrolled at two sites and will be randomly assigned to the following study periods: (1) the iLet in the insulin-only configuration (with the iLet pigtail adapter, the iLet ready-to-fill insulin cartridge, and the Contact Detach infusion set) using insulin analog that they use for their usual care (either Humalog or Novolog), (2) the iLet in the insulin-only configuration (with the iLet pigtail adapter, and the Contact Detach infusion set) using faster insulin aspart (Fiasp), where the pharmacokinetic (PK) parameter for t_{max} used by the insulin-dosing algorithm will be set to the same value as is used for Humalog and Novolog (65 minutes), and (3) UC (with CGM). Each treatment period will last 7 days and there will be approximately 7 days of wash-out in between them.

10.5.2. Outcomes

10.5.2.1 Main Efficacy Outcomes

All pre-specified main efficacy outcomes in adult subjects will be calculated by pooling data from subjects enrolled at the MGH and Stanford sites (and therefore using the Senseonics Eversense and Dexcom G5 CGMs, respectively). All reference to CGM data below refers to the CGM system that is serving as the input to the iLet.

There are two primary outcome metrics (mean glucose and time <54 mg/dl) and three treatment group comparisons [(2) BP with rapid insulin vs. (3) UC, (1) BP with analog insulin vs. (3) UC, and (2) BP with rapid insulin vs. (1) BP with analog insulin], for a total of six statistical comparisons.

To preserve the overall type 1 error, a hierarchical gatekeeping testing procedure will be used. If a comparison results in a statistically significant result ($p < 0.05$), then testing will proceed to the next one on the list in the following order:

1. Mean glucose for (2) BP with rapid insulin vs. (3) UC
2. Time <54 mg/dl for (2) BP with rapid insulin vs. (3) UC
3. Mean glucose for (1) BP with analog insulin vs. (3) UC
4. Time <54 mg/dl for (1) BP with analog insulin vs. (3) UC
5. Mean glucose for (2) BP with rapid vs. (1) BP with analog insulin
6. Time <54 mg/dl for (2) BP with rapid vs. (1) BP with analog insulin

This process continues iteratively moving to the next combination down on the list until a non-significant result ($p \geq 0.05$) is observed, or all six tests are performed.

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment period for each metric.

Time <54 mg/dl and mean glucose will be computed from all available CGM data during days 3-7 for each one of the three treatment periods in the Adult RCT Period. The performance in the iLet periods and the difference between the iLet periods and the usual care periods can be compared with historical data from previous bionic pancreas trials using previous generations of hardware. If the performance of the iLet in this study is comparable to our previous data from trials using the iPhone-based bionic pancreas that will support the hypothesis that the iLet is an effective and safe implementation of the bionic pancreas. All participants with at least 24 hours of CGM data during days 3-7 of any two of the three treatments periods will be included in these analyses. Summary statistics appropriate to the distribution for time <54 mg/dl and mean glucose will be reported for all periods; while a linear model that accounts for correlated data from the same subject will be used to compare the treatment periods for the Adult RCT Period as described above. From prior experience, the values for time <54 mg/dl will

have a skewed distribution and for mean glucose a bell-shaped distribution, but the paired differences may follow an approximate bell-shaped curve. Residual values for the paired differences will be examined for an approximate normal distribution. If values are highly skewed then a rank test will be used instead. Additional models will be run to test for any carry-over effects, by adding a treatment by order interaction term.

Scatter plots for time <54 mg/dl and for mean glucose by the three randomized treatment periods in the Adult RCT Period will be generated. Additionally, boxplots for all three periods will be generated for both outcomes.

Assuming an effective SD of 1.0% for the pair differences between any one of the three pairwise comparisons for time <54 mg/dl, the half width of the associated 95% confidence interval are approximately ±0.4% for N=36 and ±0.6% for N=18. Similarly, assuming an effective SD of 25 mg/dl for mean glucose, the half width of the associated 95% confidence interval are approximately ±10 mg/dl for N=36 and ±15 mg/dl for N=18. Results from the Medtronic 670G Pivotal Trial were used to estimate SD for time <54 mg/dl and data from the control period of the JDRF CGM RCT were used to estimate SD for mean glucose in the proposed study.

All other analyses discussed below will be considered exploratory and the overall type I error will not be controlled. The models for these exploratory outcomes will parallel the above primary models (including residuals diagnostics and alternative non-parametric models).

10.5.2.2 Secondary Efficacy Outcomes

The following CGM outcomes will be analyzed for the 24-hour period, daytime (6am-12mn) and overnight (12mn-6am):

Hypoglycemia

time <60 and <70 mg/dl

- low blood glucose index (LBGI)
- hypoglycemic events per 24 hours - defined as ≥15 consecutive minutes with a sensor glucose <50 mg/dl

Overall Control

- time in the target ranges of 70-180 and 70-120 mg/dl
- glucose variability measured with coefficient of variation (CV) and with mean of daily difference (MODD)

Hyperglycemia

- Time >180 and >250 mg/dl
- High blood glucose index (HBGI)
- hyperglycemic events per 24 hours - defined as ≥90 consecutive minutes with a sensor glucose >300 mg/dL

For all secondary analyses (including subgroup analyses), the false discovery rate (FDR) will be controlled using the adaptive Benjamini-Hochberg procedure.

10.5.2.3 Other Secondary Outcomes

The following additional outcomes will be included in secondary analyses:

- Total daily dose of insulin
- Sensor accuracy:

- The following will be calculated using the Ascensia Contour Next One point-of care glucose meter:
    - MARD for the Dexcom G5 and Senseonics Eversense overall and in the following SMBG ranges: < 70, 70–180, > 180, > 250

- Daily at-home questionnaire:
    - symptomatic hypoglycemia
    - hypoglycemia requiring carbohydrate intervention
    - alcohol use
    - exercise
    - nausea and/or vomiting
    - use of a personal CGM as a part of usual care
- All glycemic CGM outcomes will be calculated for the first 24 hour period separately as a secondary analysis of the BP as participants transition off of an MDI regimen onto closed loop control.

10.5.2.4 Safety Outcomes

All adverse events will be tabulated. Additionally, the following outcomes will be tabulated by treatment period:

- Episodes of severe hypoglycemia per participant
- Episodes of diabetic ketoacidosis (DKA) per participant
- Other serious adverse events per participant

Due to the relatively short follow-up duration for this study, it is unlikely there will be enough such events for a formal statistical comparison. However, if there are enough events, a Poisson regression that accounts for correlated data from the same subject will be used to compare the number of events between the three treatment periods. The amount of follow up will be included as an offset covariate to compare the rates. Influence diagnostics will be reviewed and if outliers are present then the model will be run without them and the results compared.

10.5.2.5 Questionnaires

For each questionnaire completed at screening and the end of each one of the three 7-day treatment periods, mean (SD) values or median (IQR) appropriate to the distribution will be given for the total score and where indicated for each subscale.

10.5.3 Subgroup Analyses

Subgroup analyses/assessments of effect modification (interaction) will be conducted for each of the two main outcomes (time <54 mg/dl and mean glucose). These analyses will include, but will not be limited to, evaluating potential differences between sites, including differences between the RCT Period at the MGH site using the Senseonics Eversense as the input to the iLet and the RCT Period at the Stanford site using the Dexcom G5 CGM as the input to the iLet. The general approach for these analyses will be to add an interaction term for the subgroup factor by treatment into the models used for the primary analyses. Moreover, the continuous variables will be used in the models, while for presentation purposes, a binary variable will be created.

Summary statistics appropriate to the distribution will be tabulates in each subgroup by treatment period. The study is not expected to have sufficient statistical power for definitive conclusions in subgroups and statistical power will be low to formally assess for the presence of interaction. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. In the absence of such an overall difference and if performed, subgroup analyses will be interpreted with caution and used to suggest hypotheses for further investigation in future studies.

The following baseline factors will be assessed:

- Age
- Baseline HbA1c
- Study center
- Insulin method: pump versus injection (participants will be recruited with a 1:1 ratio)
- T1D duration

10.5.4 Analyses for the Two BP Treatment Periods Only

The amount of time the system is active and CGM data available to the system, and the frequencies of different system errors during the two BP treatment periods only will be reported.

10.5.5 Additional Tabulations and Plots

The following tabulations will be performed:

- Baseline demographics and clinical characteristics
- Flowchart accounting for all subjects and both phases
- Visits and phone contacts as scheduled
  Number and reasons for unscheduled visits and phone contacts
- Protocol deviations
- Twenty-four hour plots with median line and IQR bands for % CGM <54 mg/dl, >180 mg/dl, mean, 70-180 mg/dl, and coefficient of variation by the three periods.

10.6. Pediatric RCT Period

10.6.1. Summary

Twenty pediatric participants (age 6–17 years) will be enrolled at two sites and will be randomly assigned to the following study periods: (1) the iLet in the insulin-only configuration (with the iLet pigtail adapter and iLet ready-to-fill insulin cartridge, the Contact Detach infusion set, and the Dexcom G5 CGM) using insulin analog that they use for their usual care (either Humalog or Novolog)and (2) UC (with Dexcom G5 CGM).

10.6.2. Outcomes

All the above Adult RCT Period outcomes and analyses will be replicated here with the exceptions that, since there are only 2 treatment periods here (instead of 3 above). For the primary outcomes, a similar hierarchical gatekeeping procedure as the one described above for Adult RCT Period will be used; the list will include only two outcomes in this order:

1. Mean glucose for (1) BP with analog insulin vs. (2) UC
2. Time <54 mg/dl for (1) BP with analog insulin vs. (2) UC

10.7. Post-Study Transition to Usual Diabetes Management

10.7.1. Summary

All adult and pediatric participants randomized to complete a BP period as their final study period in the RCT period will participate in this post-study transition period. For 48 hours immediately after the RCT period, they will be discharged to their usual care using the iLet's dosing recommendations. They will be monitored remotely and continue to follow all study procedures.

10.7.2. Outcomes

No formal statistical comparisons will be done for the Post-Study Transition Period.

Since the main aim of the Post-Study Transition Period is to verify safety and feasibility, plus some trends in efficacy; the following outcomes will be considered:

- Safety:
  - Episodes of severe hypoglycemia as defined in section 8.1.2.1
  - Episodes of diabetic ketoacidosis (DKA) as defined in section 8.1.2.2

    - Other serious adverse events
- Hypoglycemia: time < 54 mg/dl
- Mean CGM glucose
- Daily at-home questionnaire:
    - symptomatic hypoglycemia
    - hypoglycemia requiring carbohydrate intervention
    - alcohol use
    - exercise
    - nausea and/or vomiting

CHAPTER 11: DATA COLLECTION AND MONITORING

11.1. Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device datafiles obtained from the study software and individual hardware components (BP, CGM, SMBG meter, and blood ketone meter). These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

11.2. Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study. The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.