CONFIDENTIAL

The Insulin-Only Bionic Pancreas Pivotal Trial: Testing the iLet in Adults and Children with Type 1 Diabetes

Version 10.0

25 April 2021

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SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: The Insulin-Only Bionic Pancreas Pivotal Trial: Testing the iLet in Adults and Children with Type 1 Diabetes

Protocol Version/Date: Version 10.0/25 April 2021

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow): United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I 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), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, 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.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name: _____

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TABLE OF ACRONYMS

Acronym	Abbreviation For
ADA	American Diabetes Association
AP	Artificial Pancreas
BG	Blood Glucose
BP	Bionic Pancreas
BPMC	Bionic Pancreas Multicenter Study
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP1	Glucagon-Like Peptide 1
GUI	Graphical User Interface
HbA1c	Hemoglobin A1c
IDE	Investigational Device Exemption
MDI	Multiple Daily Injections
MGH	Massachusetts General Hospital
MPC	Model predictive controller
NIH	National Institutes of Health
NYHA	New York Heart Association
PD	Proportional derivative
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled/Clinical Trial
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SGLT2	Sodium Glucose Cotransporter 2
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose

Acronym	Abbreviation For
T1D	Type 1 Diabetes
TDD	Total Daily Dose
UADE	Unanticipated Adverse Device Effect
UI	User Interface

PROTOCOL SUMMARY

	Description
Title	The Insulin-Only Bionic Pancreas Pivotal Trial: Testing the iLet in Adults and Children with Type 1 Diabetes
Précis	This multi-center randomized control trial (RCT) will compare efficacy and safety endpoints using the insulin-only configuration of the iLet Bionic Pancreas (BP) System versus a control group using CGM during a 13-week study period. Participants may be enrolled initially into a screening protocol and then transfer into the RCT protocol, or they may enter directly into the RCT protocol. At the completion of use of the BP system (end of RCT for BP Group), participants will enter a 2–4 day Transition Phase and be randomly assigned to either transition back to their usual mode of therapy (MDI or pump therapy) based on therapeutic guidance from the iLet BP System or transition back to their usual mode of therapy based on what their own insulin regimens were prior to enrolling in the RCT.
Investigational Device	iLet Bionic Pancreas System, which consists of an integrated infusion pump, touchscreen display, Bluetooth radio, and insulin dosing algorithms, that automatically controls insulin delivery based on glucose values obtained by communicating with a Dexcom G6 sensor.
Objectives	Primary Objective • To compare the efficacy and safety of the insulin-only configuration of the iLet BP System using insulin lispro, insulin aspart, and Fiasp (adults only) in maintaining near-normal glycemia relative to usual care in a home-use study in adults and children with T1D. Secondary Objectives • To assess the impact of the insulin-only configuration of the iLet BP System on quality of life and treatment satisfaction.
Study Design	Randomized clinical trial followed by a Transition Phase for those using the iLet BP System
Number of Sites	~16
Endpoints for RCT	The primary analysis will include both the pediatric and adult participants in a single analysis. BP aspart/lispro Group and BP Fiasp Group will be compared separately with the Control Group. Superiority for HbA1c at 13 weeks will be considered the primary endpoint. Non-inferiority for time <54 mg/dL measured with CGM at intervals over the 13 weeks (pooled for analysis) will be considered a key secondary endpoint. To preserve the overall type 1 error, a hierarchical gatekeeping testing procedure will be used. If a comparison results in a statistically significant result ($p < 0.05$ for superiority testing and <0.025 for one-sided non-inferiority testing), then testing will proceed to the next one on the list. The order of testing will be as follows: 1. HbA1c at 13 weeks (superiority) 2. CGM time < 54 mg/dl (non-inferiority) Superiority for the following CGM metrics 3. Mean glucose 4. Time 70-180 mg/dL

	Description
	5. Time >180 mg/dL 6. Time >250 mg/dL 7. Standard deviation 8. Time <70 mg/dL 9. Time <54 mg/dL 10. Coefficient of variation **Key Safety Outcomes:** • severe hypoglycemia • diabetic ketoacidosis • other serious adverse events **Other Key Outcomes:** • quality of life questionnaires
Eligibility Criteria	Eligibility may be assessed initially in a separate screening protocol or at a screening visit in the RCT protocol. To be eligible for all phases of the study, a participant must meet all of the following inclusion criteria and none of the exclusion criteria: **Inclusion** 1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year 2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months prior to collection of CGM data (either from personal Dexcom G6 device or blinded G6 device) 3. Age ≥ 6 years old 4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available). 5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. 7. For participants ≥18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached. 8. Investigator believes that the participant can safely use the iLet and will follow the protocol • *The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility.* 9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used.

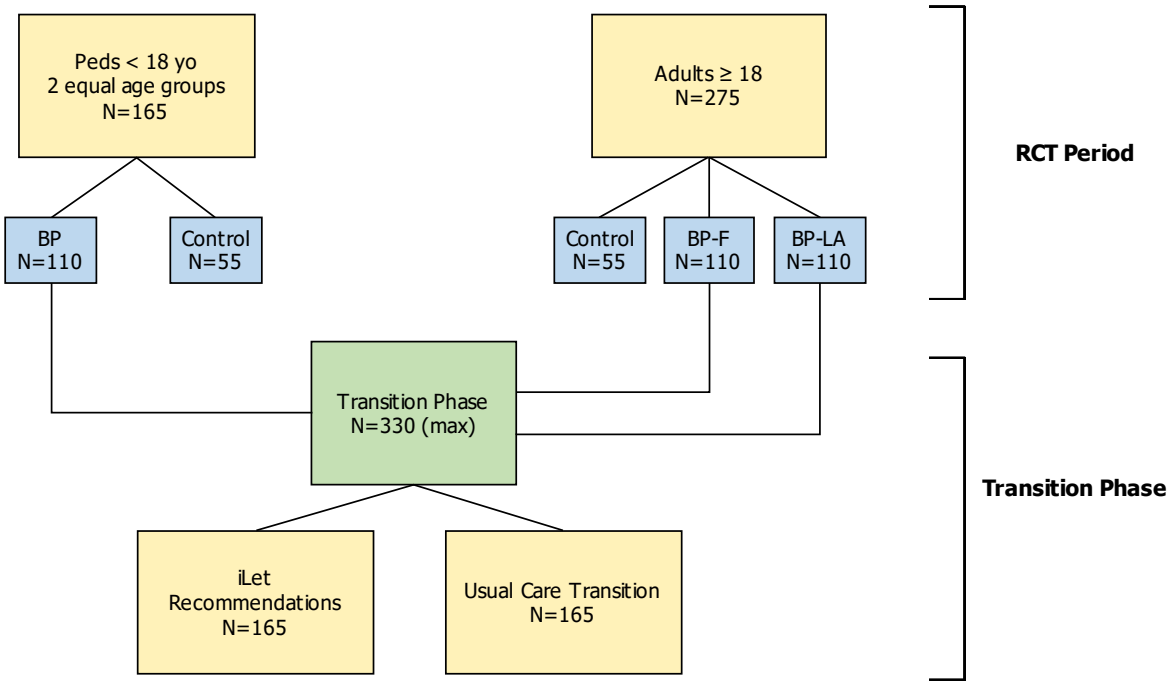
	Description
	Exclusion 1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English • *For pediatric participants, both caregivers and participants must be able to speak and read English* 4. Plan to change usual diabetes regimen in the next 3 months • This would include changing from MDI to pump. pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another. o *Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed.* 5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system 6. Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study 7. Known hemoglobinopathy (sickle cell trait is not an exclusion) 8. Current participation in another diabetes-related clinical trial 9. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy 10. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference 11. Established history of allergy or severe reaction to adhesive or tape that must be used in the study 12. Current use of SGLT2 inhibitors or a sulfonylurea drug (*use more than 3 months prior to enrollment is acceptable*) • *If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (and as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT).* 13. Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception • *If the visit is conducted virtually, a pregnancy test will be provided to the participant and verbal report of the result will be acceptable* 14. For adults $\geq$18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min; OR currently in renal failure on dialysis • *If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility* 15. Presence of a medical condition or use of a medication that, in the

	Description
	judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following: • Alcohol or drug abuse • Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study • Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) 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 • Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV • History of TIA or stroke in the last 12 months • Untreated or inadequately treated mental illness • History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight • History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment 16. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
Sample Size	**RCT Period:** ~ 440 participants (165 participants 6–<18 years and 275 participants ≥18 years) **Transition Phase for All Participants on Completion of BP Use:** up to ~440 participants (up to ~165 pediatric participants and ~275 adult participants)
Treatment Groups	**Pediatric (6-<18 years old) RCT Period:** Random assignment in a 2:1 ratio to the BP Group (with lispro or aspart) or the Control Group (~110 and ~55 participants, respectively) for a period of 13 weeks, such that a minimum of 100 in the BP Group will complete the 13-week RCT. **Adult (≥18 years) RCT Period:** Random assignment in a 2:2:1 ratio to the BP Group (with lispro or aspart), the BP Fiasp Group, or the Control Group (~110, 110, and 55 participants, respectively) for a period of 13 weeks such that a minimum of 100 in each BP Group complete the 13-week RCT. **Transition Phase** (all adult and pediatric participants at end of RCT [BP Group]**:** random assignment in a 1:1 ratio to transition back to either participant's usual therapy or the dosing recommendations from the iLet BP.
Participant Duration	~3 months

	Description
Protocol Overview/Synopsis	The study has two major parts: (1) the RCT Period, and (2) the Transition Phase. These parts are described below and detailed in the main part of the protocol. The 13-week, parallel-group, multi-center RCT Period is designed to compare the insulin-only iLet BP Group using insulin lispro, insulin aspart, or Fiasp (adults only); and a control group using CGM (Control Group). Upon completion of the RCT Period, the BP Group will enter the 2–4 day Transition Phase and eligible participants in the Control Group will be offered participation in a separate Extension Study. A 2–4 day Transition Phase will be conducted for all participants who complete BP use at the end of the RCT Period (BP Group). Participants will be randomly assigned (1:1) to either transition back to their usual mode of therapy (MDI or pump therapy) based on therapeutic guidance from the iLet BP system or transition back to their usual mode of therapy based on what their own insulin regimens were prior to enrolling in the RCT Period. For those randomized to using their pre-study regimens, the dosing can be adjusted by the investigator to mitigate safety issues but should follow pre-study regimen as closely as possible.
Protocol Overview/Synopsis (continued)	**RCT Period Visit and Phone Contact Schedule** • Screening Visit (which may be completed as part of a separate screening protocol) – Eligibility assessed, informed consent signed, point-of-care/local HbA1c, psychosocial questionnaires completed, baseline Dexcom G6 CGM data collection. o For baseline data collection, participants using a personal Dexcom G6 who have at least 85% of possible glucose data in last 14 days can skip the CGM data collection o Participants using a personal Dexcom G6 with <85% of data will use their personal Dexcom G6. o Participants using a personal Dexcom G5 will be provided with an unblinded Dexcom G6 for CGM data collection. o Participants who do not use a Dexcom G5 or G6 will be provided with a blinded Dexcom G6 for CGM data collection. o For participants who completed the separate screening protocol, eligibility will be reassessed. Participants will not need to repeat the point-of-care/local HbA1c, psychosocial questionnaires or CGM data collection. • If the separate screening protocol was completed or CGM data collection is not needed, randomization can proceed immediately. If CGM data collection was performed as part of this protocol, randomization visit will occur14-21 days after screening. • Prior to randomization, eligibility will be reassessed and blood collected for central lab HbA1c • BP study start/Control study start on day of Randomization Visit • Phone contacts after 1-2 days and 7 (±2) days • Visits at 2 weeks (±4 days), 6 weeks (±4 days), 10 weeks (±4 days), and ~13 weeks (91–98 days from randomization):

	Description
	○ Participants in the Control Group will be trained on use of the unblinded Dexcom G6 unless they are current users of the Dexcom G6 CGM. All participants in the Control Group will be provided with Dexcom G6 supplies to use the CGM unblinded for the duration of the RCT phase. ○ At the 6-week and 13-week visits, central lab HbA1c determination and psychosocial questionnaires **Transition Phase Visit Schedule** • Randomization and transition to usual care regimen at 13-week visit for BP Group, for a period of 2–4 days in duration. • Visit 2-4 days later for end of study

SCHEMATIC OF STUDY DESIGN



Numbers in cells are approximations and assume no dropouts and exact randomization distributions

SCHEDULE OF STUDY VISITS AND PROCEDURES

Table 1. Schedule of Study Visits[8] and Procedures During 13-Week RCT Period

	Screening	Randomization/ Study Start (0w)	1-2d (phone call)	1w (phone call)	2w	6w	10w	13w
Informed Consent	X							
Eligibility assessment	X	X						
Hypoglycemia Unawareness Assessment	X							X
HbA1c point of care/local lab[9]	X[7]							
HbA1c central lab		X				X		X
C-peptide and glucose central lab[9]		X						
Blood collection for storage[1, 9]		X						X
Urine pregnancy test[2]	X	X[6]			X	X	X	
Height/Weight	X	X[6]				X		X
Psychosocial questionnaires[3]	X[7]					X		X
Placement of CGM sensor	X[4]				X[4]	X[4]	X[4]	
Data download	X[5]				X	X	X	X
Adverse event querying		X	X	X	X	X	X	X

[1]Optional for participants
[2]Pregnancy test for post-menarche and pre-menopausal women with child-bearing potential
[3]Questionnaires (See Chapter 8)
[4]At screening, CGM wear can be skipped for the purpose of collection of baseline data by current users of Dexcom G6 sensor with at least 85% usage in last 14 days. Current users of a Dexcom G5 will be provided with an unblinded G6 device for baseline data collection. Participants who do not use a Dexcom G5 or G6 will be provided with a blinded Dexcom G6 device. During follow-up, a sensor will be placed for participants in the Control Group if they are not already wearing one. An unblinded sensor will be placed for those in the BP Group who have stopped using the iLet BP system and Dexcom G6 CGM and agree to wear a Dexcom G6 sensor.
[5]For participants who use a Dexcom G6 CGM
[6] If randomization date is different from screening date
[7] If not completed as part of separate screening protocol
[8] Study visits can occur in clinic or virtually
[9] Will be skipped if visit is conducted virtually

Table 2. Schedule of Study Visits[2] and Procedures During the Transition Phase

	Randomization/ Study Start (0d)		2-4d
Questionnaire[1]			X
Placement of CGM sensor (if not already wearing one)	X		
Data download			X
Adverse event querying			X

[1]Customized questionnaire (See Section 8.2.1)

[2]Study visits can occur in clinic or virtually

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. This allows the BP to ask less of the user (less need to respond to alarms, take carbohydrates to treat hypoglycemia) and allows the user to be more spontaneous (no need to announce exercise in advance).

The use of glucagon provides the BP with a powerful tool to automatically prevent and treat hypoglycemia, but it does present several challenges. First, exogenous glucagon must be shown to be safe when administered in micro-doses intermittently on a chronic basis. This means that clinical trials must be longer to allow adequate exposure to demonstrate safety. 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 were no stable glucagon formulations or glucagon analogs available. However, Zealand Pharma's development program for its glucagon analog (dasiglucagon) is now sufficiently advanced to meet our timeline for pivotal studies. 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. However, 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 and exceeded 400 pg/ml on only 4 occasions, all of which were transient. In the glucagonoma syndrome, clinically evident cases are associated with glucagon levels chronically in excess of 1,000 pg/ml. A review of case series suggests that glucagonomas and other neuroendocrine tumors producing chronic glucagon levels <400 pg/ml are usually discovered incidentally on imaging, suggesting that unless glucagon levels are chronically above this threshold, the tumors are asymptomatic. In previous studies, the doses of glucagon administered by the BP are vastly lower than levels that have been shown to be safe in pre-clinical studies. In our home use Bionic Pancreas Multi-Center Study (BPMC), mean glucagon usage on the BP was 7 mcg/kg/day. Doses of glucagon up to 9 mg/kg/day (1,286-fold higher) have been administered to rats, rabbits, cats, and dogs for 6 months without any toxic effects or weight loss. In rats and beagle dogs given up to 4 mg/kg/day and 0.2 mg/kg, respectively (571-fold and 29-fold higher than our BP doses, respectively), the only changes were increases in serum glucose and a small increase in liver weight without adverse histopathologic changes. Based on these results, we expect that the doses of glucagon used by the BP will be safe. Finally, there will inevitably be additional cost associated with use of a second drug, but this may be balanced by the advantages associated with the improvement in glycemic control that is possible with a bihormonal BP.

In consideration of the potential for automated glucagon delivery, we have developed a bionic pancreas system that can be used in either the bihormonal, insulin-only, and glucagon-only configurations.

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 suite of three mathematical dosing algorithms for insulin infusion, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control (MPC) 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 (PD) 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.

In the insulin-only configuration the BP keeps track of the glucagon that would have been given had it been in the bihormonal configuration. In both configurations, use of glucagon has the effect of reducing the aggressiveness of the insulin controller. In the insulin-only configuration glucagon doses cannot actually be given so the CGM glucose does not rise in response. Therefore, more virtual glucagon is given by the insulin-only configuration compared to the amount of actual glucagon that would have been given by the bihormonal configuration. This has the effect of reducing insulin dosing more in the insulin-only configuration than in the bihormonal configuration and leads to a higher average glucose achieved by the insulin-only configuration than the bihormonal configuration for the same glucose target.

The intended use for the insulin-only configuration of the BP system is to provide automated glucose control prior to commercial availability of a stable glucagon analog. It may also be used for people for whom goals for therapy can be achieved with minimal hypoglycemia and/or use of oral carbohydrates without the use of glucagon. This may include people with type 2 diabetes or cystic fibrosis-related diabetes.

1.3.1 iPhone-Based BP System

Our BP hardware platform began as a laptop-driven system, which we used in all of our inpatient studies (between 2008–2012) at MGH. In late 2012, we received FDA approval to conduct our first outpatient study using our new mobile wearable iPhone-Based BP System, which we used in all of our outpatient and home-use studies between 2013 and 2017. The system consisted of one or two (depending on the configuration of the system) t:slim infusion pumps (Tandem), a G4 Platinum AP CGM (Dexcom), and the BP insulin-dosing and glucagon-dosing control algorithms. The control algorithms were encoded in an app together with a simple graphical user interface (GUI) that ran on an iPhone 4S (Apple). The iPhone and the Dexcom CGM receiver were connected through their external communication ports with a custom hardware interface and were housed together in a custom enclosure. The iPhone, CGM, and enclosure together comprised our BP Control Unit. The BP app ran the insulin-dosing and glucagon-dosing control algorithms, managed connectivity between the iPhone and the Dexcom receiver, and controlled the Bluetooth radio, which effectuated communication between the iPhone and the t:slim pump. The GUI displayed the current CGM glucose, the CGM trend, and the insulin and glucagon doses. The BP app also provided the interface to input meal announcements. Meal announcements (1) specified a type of meal (as “breakfast,” “lunch,” or “dinner”) (2) designated the size of the meal (as “larger than typical,” “typical,” “smaller than typical,” or “just a bite”), and (3) triggered a partial meal-priming bolus, the size of which automatically adapts during the course of the trial to meet a target of 75% of the insulin required for that size and type of meal. The BP managed all insulin and glucagon dose calculations when the CGM was online and

offline. When the CGM was offline, the control algorithm administered correction boluses of insulin or glucagon as appropriate in response to any entered BG value, just as if they were CGM values. The GUI also displayed visual alarms associated with an audio signal if communication was dropped between the BP app and the t:slim pump, or if the CGM glucose was below a low threshold. The BP Control Unit communicated to a server that allowed the BP to support remote telemetry of CGM data.

Using our iPhone-based BP, we have conducted over 110 outpatient experiments of 5–11 days in duration in each participant with T1D (> 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 from the fact that the average total daily dose of insulin among these participants varied by over 13-fold (from 11 to 145 units/day) among children and adults with T1D.

Using the iPhone-based BP we have also performed a study with the bihormonal configuration in children and adolescents with congenital hyperinsulinism after subtotal pancreatectomy. We have performed studies using the glucagon-only configuration as an adjunct to patient-controlled insulin dosing in adults with T1D and a study using the glucagon-only configuration as an adjunct to usual therapy in adults with post-bariatric hypoglycemia. In addition, we have performed pilot studies with both the insulin-only and bihormonal configurations in adults with cystic fibrosis-related diabetes and adults with insulin-dependent type 2 diabetes with inadequate glycemic control despite multiple daily injections or use of an insulin pump.

Studies that have utilized the iPhone-based BP system are summarized in the table below and described in more detail in Appendix A.

Table 3. iPhone BP System Studies

	Year	Name of Study	Setting	N	Duration of Use	BP Configuration	Monitoring	Protocol Description
1	2013	Beacon Hill Study	Supervised hotel stay	20	5 days	Bihormonal	Direct supervision	Adults 21 and older, randomized crossover with usual care (at home)
2	2013	2013 Summer Camp Study	Supervised summer camp setting	32	5 days	Bihormonal	Remote telemetric monitoring	Adolescents aged 12 to 20, randomized crossover with usual care at camp
3	2014	2014 Summer Camp Study	Supervised summer camp setting	19	5 days	Bihormonal	Remote telemetric monitoring	Pre-adolescents aged 6 to 11, randomized crossover with usual care at camp
4	2014	BP Multi-center Study	Outpatient, unsupervised at home, 4 study centers	39	11 days	Bihormonal	Remote telemetric monitoring	Adults 18 and older, randomized crossover with usual care
5	2015-2016	BP Set Point Study	Outpatient, unsupervised at home	20	8 arms, 4 days each	Bihormonal and Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, randomized crossover with usual care and 8 different

	Year	Name of Study	Setting	N	Duration of Use	BP Configuration	Monitoring	Protocol Description
								BP configurations testing different glucose target set points in addition to insulin only for the first time
6	2015	Stanford Insulin-only Study	Outpatient, unsupervised at home	16	2 arms, 7 days each	Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, compared with usual care
7	2017	Monitoring Study	Outpatient, unsupervised at home	23	4 arms, 7 days each	Bihormonal and Insulin-only	Each arm repeated with and without remote telemetric monitoring	Adults aged 18 and older, compared with usual care with and without remote monitoring
8	2017	Zealand Feasibility Study	Supervised, in clinic	12	2 arms, 8 hours each	Bihormonal	N/A	Adults aged 18 and older, randomized crossover comparing Eli Lilly glucagon with dasiglucagon in structured clinic setting

1.3.2 Fully Integrated iLet® BP System (Beta Bionics)

The iLet® Bionic Pancreas System (iLet), developed by Beta Bionics, Inc., is a wearable device that autonomously manages glycemia in people with diabetes and other conditions of glycemic dysregulation. The iLet integrates CGM technology (choice of either Dexcom G6 or Senseonics Eversense) via its built-in Bluetooth radio. It includes two independent motor–drivetrain pumping mechanisms, which independently actuate the delivery of insulin and glucagon from cartridges that are separately loaded into the iLet. The iLet is capable of functioning in an insulin-only, glucagon-only, or bihormonal configuration. The iLet is compatible with three insulin analog formulations (insulin lispro, Lilly; insulin aspart and Fiasp, Novo Nordisk) and one glucagon analog (dasiglucagon, Zealand Pharma). The iLet also includes a touchscreen display that enables user interactions through a custom graphical user interface with smartphone simplicity. Finally, the iLet contains embedded software that includes adaptive control algorithms that autonomously and continually adapt to the ever-changing insulin requirements of each individual to enable lifelong adaptive learning. The control algorithms used by the iLet only require initialization with the user's body mass and are the very same algorithms that were developed for the Boston University iPhone-Based BP and were tested and refined in all of the clinical trials described above (i.e. the Beacon Hill Study, the 2013 and 2014 Summer Camp Studies, the Bionic Pancreas Multi-Center Study the Stanford Insulin-Only Study, the Bionic Pancreas Set-Point Study, and the Bionic Pancreas Monitoring Study). As such, the iLet requires only the patient's body weight for initialization. It does not require carbohydrate counting, nor does it require any information about the patient's total daily dose of insulin, basal or long-acting insulin requirements, carbohydrate-to-insulin ratios, or insulin correction factors for managing

hyperglycemia. It is a fully autonomous glycemic control system that requires very little management on the part of the patient or provider. Figure 1 illustrates the iLet's features and drug-delivery configurations and is shown together with its compatible CGM devices.

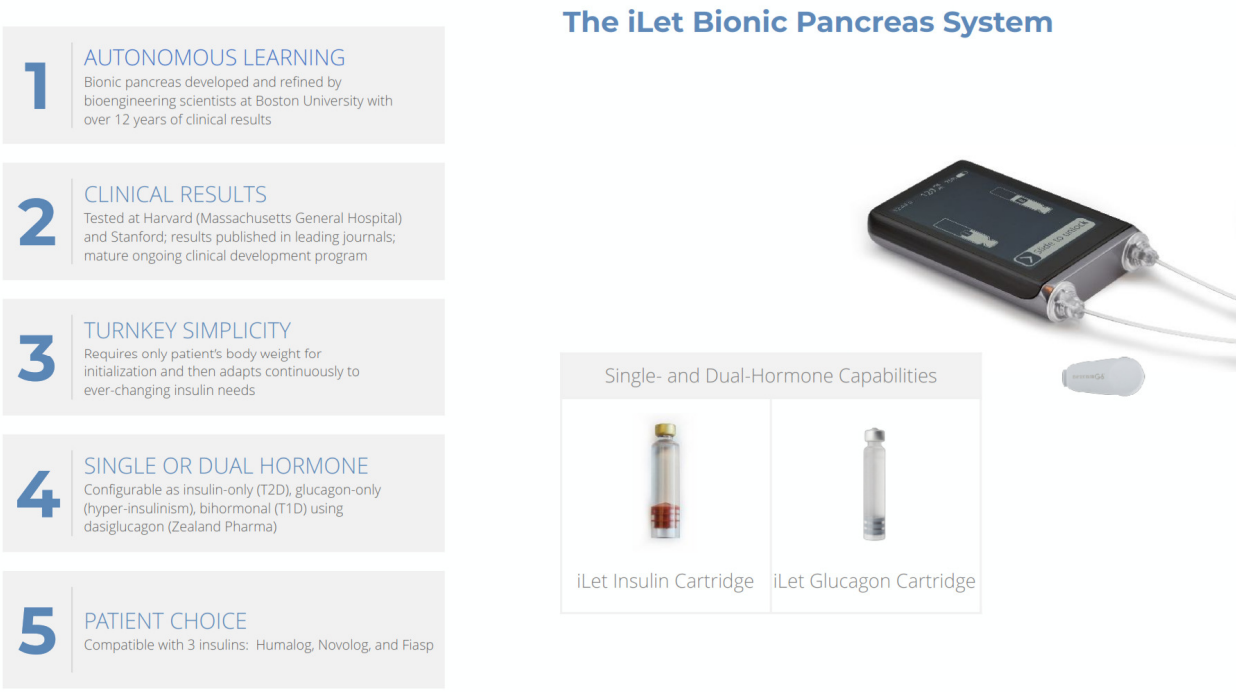


Figure 1 The commercial version of the iLet bionic pancreas system (Beta Bionics, Inc.) uses adaptive control algorithms that autonomously and continuously adapt to the patient's ever-changing insulin needs to enable lifelong adaptive learning. The control algorithms in the iLet only require initialization with the user's body mass, have been tested, refined, and improved through over 10 years of clinical research. The iLet can be configured in the insulin-only, glucagon-only, or bihormonal configurations. It is interoperable with one of two CGM devices and is compatible with three insulin analog formulations and one glucagon analog.

The iLet is set to either the insulin-only, bihormonal, or glucagon-only configuration by manually selecting the desired configuration in the user interface. When in the bihormonal configuration, the control algorithm may 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 an occlusion detected in the glucagon fluid path. Whenever the iLet is in an insulin-only mode, the minimum glucose target is 110 mg/dl. Whenever the iLet is in a bihormonal or glucagon-only mode, and the glucagon fluid path is patent and primed, the minimum glucose target is 100 mg/dl.

In addition to the iLet ready-to-fill glass insulin cartridge and the prefilled glass dasiglucagon cartridge, the iLet uses separate insulin and glucagon administration sets, which each have their own proprietary connectors to the insulin and glucagon cartridges in the iLet and to the infusion site on the patient.

The iLet BP will make recommendations for multiple daily injection (MDI) dosing (for those on MDI therapy) AND for continuous subcutaneous insulin infusion (CSII) dosing via an insulin pump (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 (TDD) of insulin used by the BP is consistent with usual care. The iLet 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 iLet provides a daily readout with updated estimates of daily basal insulin (in terms of a daily long-acting insulin dose for MDI users and a 24-hour, four-segment basal rate dose for CSII users), prandial insulin (for breakfast, lunch, and dinner) and correction doses. Thus, the iLet is designed to provide an up-to-date recommendation of these quantities for both MDI and CSII users if, for any reason, the iLet may be temporarily unavailable to the user.

Studies conducted using the iLet are summarized in the table below and described in Appendix A.

Table 4. iLet BP System Studies

	Year	Name of Study	Setting	N	Duration of use	BP Configuration	Monitoring	Protocol Description
1	2018	Adult Bridging Study	Outpatient, unsupervised at home, 2 centers	34	2 arms, 7 days each	Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, compared with usual care. One arm used insulin aspart/lispro, the other arm used Fiasp. MGH used Senseonics Eversense CGM, Stanford used Dexcom G5 CGM
2	2018	Day-Camp Transitional Study	Supervised day camp setting followed by unsupervised at home nightly, 2 centers	20	5 days	Insulin-only	Remote telemetric monitoring	Children aged 6-17, randomized crossover with usual care

	Year	Name of Study	Setting	N	Duration of use	BP Configuration	Monitoring	Protocol Description
3	2019	Fiasp Exploratory Study	48 hour supervised hotel stay, followed by 5 days unsupervised at home	24	2 arms, 7 days each	Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, randomized to compare default insulin PK settings with faster PK settings. Faster PK setting was escalated over three cohorts of 8 subjects
4	2019	Bihormonal Crossover Study	Outpatient, unsupervised at home	10	2 arms, 7 days each	Bihormonal and Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, randomized to compare insulin-only with bihormonal using dasiglucagon, testing bihormonal iLet for the first time
5	2019	MultiPK BP Study	Outpatient, unsupervised at home	Ongoing	3 arms, 7 days each	Insulin-only	Remote telemetric monitoring	Adults aged 18 and older, randomized to compare one week each on insulin lispro, insulin aspart and BioChaperone lispro

1.3.3 Fiasp (Novo Nordisk)

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 stabilizes 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 with the bionic pancreas in some individuals may provide improved glycemic control relative to lispro or aspart.

1.4 Potential Risks and Benefits of the Investigational Device and Study Participation

Risks and benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for this.

1.4.1 Known Potential Risks

1.4.1.1 Venipuncture Risks

A hollow needle/plastic tube may 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.

1.4.1.2 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick 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 fingersticks are part of the usual care for people with diabetes.

1.4.1.3 Subcutaneous Catheter Risks (CGM)

Participants using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a 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 causes a bruise (1 in 10 risk).

Study staff should verbally alert the participant that on rare occasions, the CGM 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.

1.4.1.4 Risk of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, 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 hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.4.1.5 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 CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

1.4.1.6 Questionnaires

As part of the study, participants will complete questionnaires, which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing 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.

1.4.1.7 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. 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.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore, participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, and the home glucose and ketone meter 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.

1.4.2 Known Potential Benefits

One purpose of this research is to reduce the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using an automated closed loop to control the glucose level and is intended to develop data to support a future PMA application for approval from the FDA to commercially distribute the iLet bionic pancreas in the United States. The individual participant may not benefit from study participation.

1.4.3 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of

the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

1.5 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 (GCP).

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

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

Chapter 2: Participation Enrollment and Study Initiation

2.1 Participant Recruitment

Study participants will be recruited from ~16 clinical centers in the United States. The recruitment target for the RCT is 440 (165 participants 6–<18 years and 275 participants ≥18 years) in the 13-week randomized trial such that a minimum of 100 in the pediatric BP group and at least 100 in each of the two adult BP groups will complete the 13-week RCT. Up to 600 may be screened to achieve the RCT recruitment targets.

The study is expected to be conducted at ~ 8 sites that will enroll pediatric participants and ~ 8 sites that will enroll adult participants in the United States, although there may be crossing over of the age groups of participants that sites enroll. It is anticipated that each pediatric site will randomize ~15-20 participants and each adult site will randomize ~ 30-35 participants. The maximum number of randomized participants at a pediatric site will be 40 and at an adult site will be 66; and the maximum number enrolled into screening at each site will be 60 and 80, respectively.

No individuals will be excluded on the basis of gender or race. An approximately equal gender distribution between males and females is anticipated. A study goal will be to include 15% of participants of minority race/ethnicity in the study overall. The percentage of minority race/ethnicity participants is expected to vary by site.

Individuals generally will be recruited from each site's existing patient population or from a pool of individuals who contact the site. Central and local IRB requirements regarding recruitment materials and policies will be adhered to. Study recruitment methods may consist of the following:

- Culling of pre-existing databases (held by one of the 16 clinical sites, Boston University, or Beta Bionics, Inc.) of patients who have expressed interest in the bionic pancreas or research participation. Those identified will be contacted via IRB-approved mailing sent through post, email blast, or via phone and will be provided information about how to complete the consent process and demographics survey;
- IRB-approved press release announcing study and study fact sheet;
- Support groups, patient education classes, and not-for-profit community support groups (e.g., Children with Diabetes, College Diabetes Network, etc.);
- IRB-approved paper and digital advertisements, brochures, postcards, flyers, and/or newsprint advertisements;
- IRB-approved digital advertisements posted on social media sites like LinkedIn, Twitter, YouTube, Instagram, Facebook, and other public forums managed by a clinical trial site or Beta Bionics, Inc.;
- In-person recruitment and telephone recruitment by individual clinical sites; and
- An IRB-approved website dedicated to clinical trial recruitment.

All recruitment methods and specific advertising materials will be approved by the Central and/or local IRB prior to their implementation.

Participants may be included who completed a separate screening protocol which determined eligibility for this protocol (with eligibility verified prior to randomization).

2.2 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination or as part of a separate IRB-approved screening protocol. Before completing any procedures or collecting any data that are not part of usual care, informed consent will be provided and the participant's electronic signatures will be obtained (and assent from minors as indicated).

For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study. If the study participant decides to participate their electronic signature will be obtained.

For potential participants under 18 years of age, a parent/legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Potential participants meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the minor will verbally provide their assent, and the parent/legal guardian's electronic signature will be obtained. A copy of the consent form will be provided to the participant and his/her parent and another copy will be added to the participant's study record.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when informed consent has been obtained.

The principal investigator at each site will be responsible for assuring that the informed consent process is properly followed and that each study participant is well informed about the study and the participant's responsibilities.

2.2.1 RCT Period

Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the randomization goal has been reached. Participants who turn 18 during the course of the study will need to review the adult Informed Consent Form and re-consent by providing their electronic signature. Participants who turn 7 during the course of the study will need to review the Child Assent Form and provide assent verbally that they still want to participate, the parent/LAR will need to re-consent by providing their electronic signature.

For the pediatric cohort, there will be a goal to have ~50% aged 6-<12 years and 50% aged 12-<18 years old. For the adult cohort, there will be a goal to have at least 33% of the cohort ≥ 50

years old. There also will be approximate goals within each of the 3 age strata (6–<12, 12–<18, and ≥18 years old) for the following:

Pump/multiple daily injection users: at least 33% of each

HbA1c: at least 33% < 8.0% and 33% ≥ 8.0%; and no more than 20% with HbA1c <7.0%

2.2.2 Transition Phase

All participants who complete BP use at the end of the RCT Period at 13 weeks (BP Group) will be randomly assigned (1:1) to either transition back to their usual mode of therapy (MDI or pump therapy) based on therapeutic guidance from the iLet BP system or transition back to their usual mode of therapy based on what their own insulin regimens were prior to enrolling in the RCT Period. For those randomized to using pre-study regimen, the dosing can be adjusted by the investigator to mitigate safety issues but should follow pre-study regimen as closely as possible.

2.3 Eligibility and Exclusion Criteria

2.3.1 Eligibility

To be eligible for the RCT, a participant must meet all of the following inclusion criteria and none of the exclusion criteria at the time of screening (which may occur as part of a separate screening protocol):

Inclusion

1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year
2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months prior to collection of CGM data (either from personal Dexcom G6 device or blinded G6 device)
3. Age ≥ 6 years old
4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available).
5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.
6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia.
7. For participants ≥18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached.
8. Investigator believes that the participant can safely use the iLet and will follow the protocol

The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility.

9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used.

Exclusion

1. Unable to provide informed consent (e.g. impaired cognition or judgment).
2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory)
3. Unable to speak and read English.
    - *For pediatric participants, both caregivers and participants must be able to speak and read English.*
4. Plan to change usual diabetes regimen in the next 3 months
    - This would include changing from MDI to pump, pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another.
        - *Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed.*
5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system.
6. Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study.
7. Known hemoglobinopathy (sickle cell trait is not an exclusion).
8. Current participation in another diabetes-related clinical trial.
9. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy.
10. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference.
11. Established history of allergy or severe reaction to adhesive or tape that must be used in the study.
12. Current use of SGLT2 inhibitors or a sulfonylurea drug (*use more than 3 months prior to enrollment is acceptable*).
    - *If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT).*

13. Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception.

    If the visit is conducted virtually, a pregnancy test will be provided to the participant and verbal report of the result will be acceptable.

14. For adults ≥18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min OR currently in renal failure on dialysis
    - *If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility*

15. Presence of a medical condition or use of a medication that, in the judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following:
    - Alcohol or drug abuse
    - Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study
    - Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) 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
    - Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV
    - History of TIA or stroke in the last 12 months
    - Untreated or inadequately treated mental illness
    - History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
    - History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment

16. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

2.4 Eligibility Assessment and Baseline Data Collection

Potential participants will be evaluated for study eligibility through the elicitation of a medical history and local laboratory testing as needed in the judgment of the investigator (as part of usual care).

In the event that in-person visits cannot be conducted due to institutional restrictions or the participant's unwillingness to attend an in-person clinic visit, visits may be conducted virtually using video conference. Study staff will discuss the feasibility of conducting video visits with each participant and provide support as needed to ensure adequate access.

2.5 Historical Information

A history will be elicited from the participant and/or parent/guardian where applicable and extracted from available medical records with respect to the participant's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies.

2.6 Screening Testing and Procedures

At the Screening Visit the following procedures will be performed:

Informed consent/assent process

Assessment of eligibility

HbA1c assessment via fingerstick or blood draw and measured at local laboratory or using DCA2000 or equivalent NGSP-certified point-of-care method or (value within 28 days prior to enrollment acceptable)

- *If the visit is conducted virtually, then verbal report of most recent HbA1c or most recent HbA1c in medical record will be acceptable.*
- *If the participant was part of the separate screening protocol, the local HbA1c will not be collected if the visit is conducted in clinic.*

Measurement of height/weight

- *If the visit is conducted virtually, a verbal report of the participant's weight and verbal report of height will be acceptable. A scale will be provided for participants who do not already have a scale at home.*

Urine pregnancy test for all post-menarche and premenopausal women who are not surgically sterile

- *If the visit is conducted virtually, a home pregnancy test will be provided and verbal report of the result will be acceptable.*

Completion of the Clarke Hypoglycemia Awareness Survey

Completion of baseline questionnaires (see chapter 8)

For participants who completed the separate screening protocol, eligibility will be reassessed at the randomization visit. Participants will not need to repeat the point of care/local HbA1c, psychosocial questionnaires or baseline CGM data collection.

2.7 Baseline CGM Data Collection

Participants using a Dexcom G6 sensor with at least 85% of sensor values in the prior 14 days can skip the baseline CGM data collection.

For all other participants, a period of CGM usage must be completed prior to randomization. Users of a personal Dexcom G6 can continue to use their personal sensor. Users of a personal Dexcom G5 will be provided with an unblinded Dexcom G6 for baseline data collection. All others will use a blinded Dexcom G6 sensor that will be placed by the participant (or parent/guardian) under the supervision of study staff. Participants will be instructed on use and care of the sensor and on placing a new sensor after 10 days (or sooner if necessary). The supplies may be shipped to the participant and a virtual visit completed to monitor sensor insertion and device startup along with training on use of the device.

2.8 Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion.

Chapter 3: RCT Randomization Visit and Start Up

3.1 Timing of Visit

The RCT randomization visit will be scheduled to occur 14–21 days after the screening visit for participants who must collect baseline CGM data and who did not participate in the separate screening protocol . Participants not in the separate screening protocol who meet criteria to skip the baseline CGM data collection can complete the randomization visit on the same day of the screening visit or any time within 21 days following the screening visit.

3.2 Testing and Procedures

The following will be done at the randomization visit:

Review CGM data to verify that there are a minimum of 14 days of CGM data and at least 85% of CGM values during 14 days of CGM wear (unless CGM run-in was skipped)

Review medical history since screening visit to verify that there have been no changes or events that affect participant eligibility, and any adverse events that may have occurred since their last study visit (if not on the same day as the screening visit)

Verify eligibility if randomization visit is not on the same day as the screening visit

Verify that participant understands the protocol and is willing to accept assignment to any treatment group

Measure height and body weight (if not within 7 days of screening visit).

- *If the visit is conducted virtually, a verbal report of the participant's weight and verbal report of height will be acceptable. A scale will be provided for participants who do not already have a scale at home.*

Perform urine pregnancy test for all post-menarche and premenopausal women who are not surgically sterile (can be skipped if Randomization Visit occurs within 7 days of the Screening Visit)

- *If the visit is conducted virtually, a pregnancy test will be provided to the participant and verbal report of the result will be acceptable.*

Collect blood sample for central lab measurement of HbA1c

- *If the visit is conducted virtually, a collection kit will be provided to the participant and will be shipped to the central laboratory by the participant.*

Collect blood sample for storage.

- *Blood drawn may include serum and plasma; participants will have the option of declining.*
- *If the participant consents to having blood samples stored, but the visit is conducted virtually, the samples may be collected at a later in-clinic visit for the study.*

3.3 Randomization

Pediatric participants (6–<18 years old) for whom eligibility has been verified will be randomly assigned in a 2:1 ratio to:

Insulin-only Bionic Pancreas (BP) Group with lispro or aspart

Control Group

Adult participants (≥18 years old) for whom eligibility has been verified will be randomly assigned in a 2:2:1 ratio to

Insulin-only Bionic Pancreas (BP) Group with lispro or aspart

Insulin-only Bionic Pancreas (BP) Group with Fiasp

Control Group

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

Note: randomization will not be stratified by age, HbA1c or other factors because of the small number per site that is possible and considering the 2:2:1 randomization in adults and 2:1 randomization in pediatrics. If an imbalance in age or baseline HbA1c exists among groups, an adjustment will be made in the analytic model.

3.4 Study Procedures for the Control Group

Participants in the Control Group will be instructed to follow their usual diabetes management as directed by their own diabetes care team (see section 4.2). For users of the Dexcom G6, they will continue to use their own system but will be provided with transmitters and sensors. Those who are not users of the Dexcom G6 will be trained on use of the Dexcom G6 system and will be provided with the necessary supplies for the duration of the RCT phase. All participants in the Control Group will be asked to use the Dexcom G6 daily throughout the RCT phase.

3.5 Study Procedures for the BP Group

Initiation of BP use for the BP Group will occur on the day of randomization. If the visit is conducted virtually, initiation of the BP may be delayed until the device and supplies are provided to the participant (via shipping or drop off/pickup) and training is provided. The training may be done in person or via a Zoom, Skype, or similar video conference.

The approach to training of the BP Group will depend on whether the participant is already a pump and/or CGM user. The training on use of the BP may occur completely at this visit or may be spread out over a few days in multiple visits. All participants in the BP Group will initiate therapy on the iLet BP by being guided through the procedures outlined in the set of screens under the Setup Screen onboard the iLet BP device.

Study staff will review the use of the study devices including the iLet BP, blood glucose meter, and ketone meter, and the study CGM system.

Participants will be trained to only use only fingersticks when measuring blood glucose levels with the blood glucose meter. Alternate site testing will not be used.

Participants will be trained on the use and maintenance of the Dexcom G6 CGM.

- Participants will be trained on sensor insertion and optional calibration procedures. They will insert their own sensor using an approved insertion site and study staff will confirm they are doing it properly.
- All participants will be trained on possible CGM errors and how to respond promptly to resume closed loop control by the BP.

The control algorithm will be initialized with the participant's current weight.

The initial glucose target will be set. This should be the default target in most cases, but may be set to the "high" target in participants on MDI and using long-acting insulin at baseline, in participants with very low insulin needs, or in participants who have a high A1c and may experience hypoglycemic symptoms in the normal plasma glucose range.

The iLet BP will be configured to recognize the Dexcom G6 CGM signal and will be paired with the participant's transmitter.

Study staff will supervise the participant preparing the insulin cartridge, loading the cartridge into the iLet and inserting the infusion set.

The participant will remove his/her own insulin infusion pump (if used) and the participant will start the bionic pancreas.

The staff will confirm that the iLet BP is functioning properly prior to discharging the participant.

Study staff will provide supplies for use with the study CGM, study glucose and ketone meters and the iLet.

Due the adaptive nature of the BP, participants on multiple daily injections may simply 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 long-acting insulin glargine has completely cleared their system, which may take 48 hours or more. In participants using a long-acting insulin pre-study, the glucose target may be set to the "high" setting for the 3 or more days before moving down to the default target. Participants will be trained that they may see escalating dosing by the BP during this period.

Chapter 4: RCT Outpatient Study Procedures

4.1 Outpatient Procedures for Both Groups

Participants will be advised not to use alcohol or other drugs in sufficient quantity to reduce sensitivity to symptoms of hypoglycemia or hinder appropriate decision-making.

Any medical advice needed by the participants during their participation that is not directly related to the study protocol should be obtained in the usual manner with their own physician.

There are no restrictions of any kind on diet, exercise, or other activities.

Participants will be asked to complete a once-weekly survey including questions about hypoglycemia and carbohydrate interventions that occurred in the prior 24 hours.

- With participant permission, text and/or email will be sent at the time when survey completion is needed.

4.1.1 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.

Participants will be instructed to contact the study staff for any issues that arise with the bionic pancreas system. The site staff will escalate the issue to Beta Bionics as needed.

4.1.2 Weekly At-Home Questionnaire

Participants in all RCT Groups will complete a questionnaire weekly.

Participants will be asked to report on hypoglycemia and treatment interventions during the prior 24 hours.

A link to the online survey will be sent via email or text message once a week. The day the survey is sent may be rotated systematically so that all days of the week are sampled approximately equally.

As part of the consent process, the participant will be asked to provide an email address or a phone number for texting for this purpose. A reminder will be sent on the scheduled day of the weekly questionnaire. For participants who do not have the ability to complete the questionnaires electronically, paper questionnaires may be provided. Participants will be reminded that their eligibility for the separate Extension Study (Control Group) is dependent on missing no more than 3 of these questionnaires during the 13-week RCT, collection of at least 80% of the expected CGM data during the 13-week RCT, and on completion of all study visits.

4.2 Outpatient Procedures for Control Group

The Control Group will continue its pre-study diabetes management, including approach to insulin delivery. Diabetes management will be handled by the participant's diabetes health care provider. *No adjustments to the diabetes care plan will be made by the study team.*

Participants using FDA-approved devices as part of their pre-study usual care, such as a CGM system, insulin pump, or closed-loop system can continue use of their personal devices during the study period. Use of devices that are not FDA-approved are prohibited.

Participants who were using a G5 at the time of enrollment who were provided with a G6 transmitter and sensors will continue to use the unblinded G6 for the duration of the 13-week RCT period. Sensors and transmitters will be provided to these participants as needed.

Participants not using a Dexcom G6 CGM also will be asked to use a Dexcom G6 CGM for the duration of the 13-week RCT period. Training and supplies for the Dexcom G6 supplies will be provided to these participants as needed.

- Participants will be trained on the insertion of the sensor at an approved sensor insertion site and use of the Dexcom G6 CGM. They will insert their own sensor and study staff will confirm they are doing it properly. Participants will be instructed to only use approved insertion sites (abdomen for adults and abdomen or upper buttocks for participants 6-<18), and to insert a new sensor every 10 days or sooner if the sensor comes off prior to day 10 of CGM wear.

4.3 Outpatient Procedures for BP Group

Participants using the iLet will not be allowed to travel outside the United States or its territories for the entire time the system is in use.

Participants may perform calibrations of the Dexcom G6 CGM if it is inaccurate relative to a BG measurement, per the device manufacturer's instructions.

Study participants will be instructed to keep fast-acting carbohydrates and a glucagon emergency kit easily accessible in case they are needed.

Following the initiation of use of the iLet, participants with hypoglycemia unawareness (Clarke Hypoglycemia Awareness Survey score >=4) will be asked to perform an overnight fingerstick blood glucose measurement (between 2-3AM) for 2-3 nights. They will be trained that if SMBG is <70 mg/dL they should treat with carbohydrate, with less carbohydrate (e.g. 5 g) as the initial treatment if the SMBG is >60 mg/dL or if the CGM trend is not sharply downward, and more carbohydrate indicated if the SMBG is lower or if the CGM trend is sharply downward (up to 15 g), recheck in 15 minutes to confirm the hypoglycemia is adequately treated, and notify the investigator or designee the next day for advice. Study staff will inquire about the fingersticks and reinforce the importance of these fingersticks at the 1-2 day phone call.

The iLet BP will have CGM glucose alarm settings available to the participants. Study staff will work with participants to configure the alarm settings in a way that will be most appropriate for each individual.

Study staff will recommend a low CGM glucose alarm be set for 70 mg/dl or lower and a high CGM glucose alarm be set for 250 mg/dl or higher.

If participants receive a high or low CGM glucose alarm, they will be trained to verify the CGM glucose with a fingerstick glucose value using the Contour Next One glucometer.

If the glucometer confirms hypoglycemia, the participant will be trained to treat hypoglycemia with rapid acting carbohydrates. This may be done according to their usual practice or with less carbohydrate than their usual practice since the BP system will typically have suspended insulin delivery prior to the occurrence of hypoglycemia. They will be trained to continue to monitor their glucose levels until they return to normoglycemia.

If the glucometer confirms hyperglycemia, participants will be trained to assess their infusion set and tubing for patency, the insulin reservoir for sufficient insulin supply, the iLet BP for sufficient battery power, proper functioning, and insulin delivery. If hyperglycemia > 300 mg/dl persists for more than 90 minutes they will be trained to check their blood ketone level using the Precision Xtra blood ketone meter.

- If ketones are ≥0.6 mmol/l, they will be trained to replace their infusion set and to inform study staff. They will be trained to continue to monitor their glucose and blood ketone levels until they return to normoglycemia and ketones are < 0.6 mmol/l.
- If ketones are <0.6 mmol/l, they will be advised to continue to monitor their glucose until it returns to normoglycemia and to repeat the ketone measurement in 90 minutes if necessary

If the glucometer reading is not consistent with the CGM glucose reading, participants will be trained to look for possible scenarios that could lead to an inaccurate CGM reading.

- They will be educated about the lag between interstitial and capillary glucose readings, and to delay a calibration in times of rapid changes in glucose. They will also be trained about the standard difference between CGM and capillary glucose readings, and to consider the CGM inaccurate if it is >20% different than their capillary glucose reading. If their CGM glucose is not changing rapidly and is >20% different from their capillary glucose reading, they will be instructed to calibrate their CGM if possible.
- A compression artifact at the site of the sensor may cause false hypoglycemic readings. This should resolve by removing the compression of the sensor.

If there is a technical fault with the iLet BP, the participant will be instructed to call the clinical site immediately.

All contacts from a study participant will be documented on an Unscheduled Contact form. The site will be responsible for all reporting of device issues and adverse events.

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 the iLet 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 iLet 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 within 12 hours.

- If the CGM sensor is not reading glucose levels, the system will provide basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated as 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 2 hours 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 trained in various ways to bring their study CGM sensor back online. This may involve replacement of the Dexcom G6 CGM sensor. Normal (online) BP control will resume automatically when the CGM sensor is reporting glucose values again.
- Study staff will contact Beta Bionics for additional troubleshooting as necessary.

Participants will be encouraged to announce up to three major meals a day to the iLet BP. The meal announcement will consist of choosing the size of the meal relative to typical meals for that participant (more, usual for me, less, much less). Participants will be trained not to announce snacks that occur between major meals.

Participants will be trained on the interface to change the glucose targets. They will be asked to consult with study staff before making any changes to the permanent target or to setting a daily/night recurring target alteration schedule.

Participants will be asked to change their infusion set every 3 days or sooner if there is a problem.

Participants will be instructed to change the insulin cartridges, cap connectors, and tubing whenever one of two conditions are met: (1) when there is <20 units remaining in the cartridge, or (2) the cartridge or tubing have been in place for the maximum number of days according to the labeling for the insulin being used.

A new Dexcom CGM sensor will be placed in an approved sensor insertion site every 10 days for Dexcom users if no replacement was required before this time. The iLet BP will generate an alarm when replacement is required.

Participants will be asked to charge their iLet BP routinely (preferably at least once daily, such as when they are bathing) and whenever they notice the battery level is low. The iLet BP will alarm at low battery thresholds.

Participants will not tamper with or alter the iLet BP device in any way.

The iLet BP is water resistant but participants will be instructed to remove it for showering and swimming and to keep it dry during exercise.

Participants will be trained to take appropriate precautions when they are disconnected from the iLet BP, including frequent BG checks using the study Contour Next One glucometer if they are not monitoring CGM glucose by another method (e.g. their phone) and to have carbohydrate readily available. They are urged to limit the amount of time they are disconnected from the iLet BP to ensure optimal glucose control.

If a participant develops an illness during the study, he/she can seek medical care as usual. If the participant is unable to eat for a period exceeding one day, he/she must notify study staff so that the medical staff can assess the safety of continuing to use the iLet BP. iLet BP use may be temporarily discontinued if study staff believe this is warranted. If a participant is hospitalized, instructions will be provided to contact the study staff as soon as possible and discontinue iLet BP System use.

If a participant discontinues use of the BP system either due to investigator judgment that it is not safe for the participant to continue to use the iLet in closed loop mode or the participant's choice, the participant will return to his/her prestudy insulin delivery and glucose monitoring method. If the participant is not using a personal G6 sensor, he/she will be asked to wear a blinded sensor for data collection at the scheduled time points as described in section 5.2.2.

Chapter 5: RCT Follow-up Study Visits

5.1 Timing of Visits

The schedule for follow-up visits and phone contacts is the same for all treatment groups.

Phone contacts will occur after 1-2 days and after 7 (± 2) days.

Clinic visits will occur after 2 weeks (± 4 days), and then at 6 weeks (± 4 days), and 10 weeks (± 4 days) prior to the 13-week primary outcome visit (window 91-98 days from randomization).

In the event that in-person visits cannot be conducted due to institutional restrictions or the participant's unwillingness to attend an in-person clinic visit, visits may be conducted virtually via a Zoom, Skype, or similar video conference mechanism.

5.2 Procedures at Phone Contacts and Follow-up Visits

5.2.1 Phone Contacts

Study staff will contact participants via phone twice in their first week of participation. Study staff will query the participant for any adverse events and assess the participant's ability to follow protocol and use the device at this time. Participants will be asked about their glucose control and study staff will educate as needed. The study staff may suggest a change to the permanent glucose target if indicated.

5.2.2 Clinic Visits

The following procedures will be performed at each in-clinic visit, unless otherwise specified:

The date of the last menstrual period will be documented for female participants.

A urine pregnancy test will be performed for all women who are post-menarche, premenopausal and have not been surgically sterilized through the 10-week visit.

- *If the visit is conducted virtually, a pregnancy test will be provided to the participant and verbal report of the result will be acceptable.*

Study staff will measure the participant's height and weight at 6 weeks and 13 weeks.

- *If the visit is conducted virtually, a verbal report of the participant's weight and height will be acceptable. A scale will be provided for participants who do not already have a scale at home.*
- *In the BP Group, if the weight has changed outside of ±15% of its current value, then the weight will be updated on the iLet GUI with the new value.*

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.

For the BP Group, recent CGM data (e.g. on the iLet's graph screen and/or in the summary statistics provided on the mobile app used by the study staff to download iLet data in the case of in-clinic study visits) will be reviewed and study staff may suggest a change to the permanent glucose target if indicated.

All study device data will be downloaded. In the BP Group, iLet data will be downloaded to the Mobile App on the study tablet during each in-clinic visit. For participants where in-clinic visits are not possible, iLet data may be downloaded at select mid-study visits (e.g. at the 6-week visit or more often as needed) by either (1) a study staff member visiting the participant or (2) shipping a study tablet to the participant and guiding the participant through the data download process remotely. For the final 13-week visit, participants who come to clinic will give back their iLet and participants who are unable to come to clinic will factory-reset their iLet (which will end their 13-week iLet treatment session but will not delete the data for the treatment session from the iLet) and ship the iLet back to the study site. In all cases, a final full data download will be performed.

At all scheduled visits prior to the 13-week visit, a CGM sensor will be placed for participants in the Control Group (unless the participant is already wearing one). A CGM sensor will be placed for anyone in BP Group who has stopped using the iLet BP system and discontinued CGM but is willing to wear a Dexcom G6 sensor.

Study staff will provide supplies as needed and will go over the study procedures reminders.

Completion of the Clarke Hypoglycemia Awareness Survey at 13 weeks.

At 6 weeks and 13 weeks, blood will be collected for central HbA1c.

- At 13 weeks participants may have blood collected for storage. Blood drawn may include serum and plasma. Participants will have the option of declining.

At 6 weeks and 13 weeks, participants will complete questionnaires. Parents/guardians where applicable also may complete questionnaires.

5.3 Evaluation of Control Group for Extension Study

For participants in the Control Group, an assessment will be made as to whether the participant has completed all study visits, at least 10 out of 13 of the weekly questionnaires, and collected at least 80% of the expected CGM data. If yes, the participant will be offered participation in an optional Extension Study in which the participant will use the iLet BP system for 13 weeks.

5.4 Transition Phase

All users of the iLet BP System who are using the BP system at the end of the RCT (BP Group) will enter the Transition Phase and be randomly assigned (1:1) either to transition back to their usual therapy based on therapeutic guidance from the iLet BP or to transition back to their usual therapy based on their own insulin regimens prior to enrolling in the RCT. See chapter 6 for details about the Transition Phase procedures and visit schedule.

Note: randomization will be stratified by site but not by age, HbA1c or other factors because of the small number per site. If an imbalance in age or baseline HbA1c exists among groups, an adjustment will be made in the analytic model used to analyze the Transition Study outcomes.

Chapter 6: Transition Phase

6.1 Participants

All participants who are using BP in the RCT will enter the Transition Phase at the time that BP use ends (assuming BP use does not stop prematurely before the intended end of use - in such cases, therapeutic guidance will be provided by the investigator for the transition back to the participant's pre-study management).

6.2 Randomization

Participants in the Transition Phase will be randomly assigned (1:1) to either transition back to their usual therapy based on therapeutic guidance from the iLet BP or transition back to their usual therapy based on their own insulin regimens prior to enrolling in the RCT. For those randomized to using their pre-study regimen, the dosing can be adjusted by the investigator to mitigate safety issues but should follow the pre-study regimen as closely as possible.

6.3 iLet BP Guidance

For those participants who use CSII therapy for their usual care, the iLet BP will recommend the basal insulin regimen, the average prandial insulin bolus for typical meals for the start, middle, end, and sleeping periods of the day, and a correction factor and/or sliding scale of insulin for hyperglycemia.

For those participants who use MDI therapy for their usual care, the iLet BP will recommend the daily dose of long acting insulin, the average prandial insulin dose (e.g. insulin lispro or insulin aspart) for typical meals for the start, middle, and end periods of the day, and a sliding-scale correction dose of insulin (e.g. insulin lispro or insulin aspart) for hyperglycemia.

6.4 Visits

The Transition Phase will have one follow-up visit after 2-4 days. The visit may be conducted virtually. A daily survey will be completed about hypoglycemia events, treatment and deviations from recommended dosing.

Chapter 7: Study Drugs and Devices

7.1 Study Drugs

The study involves subcutaneous administration of insulin lispro (Humalog, Eli Lilly), insulin aspart (Novolog, Novo Nordisk), or Fiasp (Novo Nordisk), the latter for adults only. Lispro, aspart and Fiasp are commercially available by prescription and are indicated for use in people with diabetes who are on a pump or MDI regimen, but not on a BP.

Participants randomized to the Control Group will follow their standard diabetes regimen with the insulin prescribed by their healthcare provider. Pediatric subjects randomized to the BP Group will fill the iLet ready-to-fill insulin cartridge with either lispro or aspart. Adult subjects randomized to the BP Aspart/lispro Group will fill the iLet ready-to-fill insulin cartridge with either lispro or aspart. If a participant was using Fiasp, he/she will need to switch to either lispro or aspart for the study. Adult subjects randomized to the BP Fiasp Group will be provided with Fiasp in PumpCart ® cartridges size 1.6 mL. Fiasp will be called "Faster Aspart" on the cartridge label. However, it will be clarified to the participants in the study informed consent form as well as verbally and with a handout when Fiasp is dispensed, that this does not imply that Fiasp is faster than insulin aspart in the iLet device.

The control system can administer bolus doses of insulin up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 µl] (or 6 units [60 µl] if it is in response to isolated BG entries when the CGM is offline) and a single meal priming dose, which is triggered by the user, will not exceed 24 units [240 µl]. The dual pump can administer as little as 0.50 µl (0.05 units of U-100 insulin) in a single bolus dose. Insulin exposure is expected to be comparable to that of participants when not participating in the study.

7.2 Study Devices

7.2.1 iLet Infusion Sets

Participants in the BP Groups will be provided with iLet infusion sets for the system. Study staff will work with the participants to ensure they are properly inserting the infusion set and will help them troubleshoot if problems related to the infusion set arise. Participants will be instructed to replace their infusion set as needed when it fails (or is suspected of failing) or falls out, or every 2–3 days.

7.2.2 iLet Ready-to-Fill Insulin Cartridges

Participants in the BP Groups will be provided with iLet ready-to-fill insulin cartridges for the system (these are packaged with a drug-transfer hub and plunger rod, which are used in the process of transferring insulin from a vial to the ready-to-fill insulin cartridge). Study staff will work with the participants to ensure they are comfortable with the fill process and are able to remove most of the air from the cartridge. Participants will be instructed to replace their ready-to-fill insulin cartridge as needed (when it is nearly empty), when it fails (or is suspected of failing), or every 3 days.

7.2.3 Continuous Glucose Monitors

Participants using the iLet BP in all phases will use a Dexcom G6 sensor.

7.2.3.1 Dexcom G6 CGM

A transcutaneous glucose sensor for the Dexcom G6 CGM will be inserted in the subcutaneous tissue and will provide input to the controller. Only approved insertion sites will be used (abdomen for adults and abdomen or upper buttocks for participants 6-<18). The sensor is powered by the battery within the transmitter that clips to the sensor and the whole assembly is held to the skin with an adhesive patch and communicates wirelessly with the bionic pancreas. If the CGM sensor providing data to the iLet fails for any reason, it will be replaced promptly.

The Dexcom G6 blinded CGM can record data for up to 10 days and will be used prior to randomization for participants who are not current users of a Dexcom G5 or G6 CGM. The unblinded Dexcom G6 CGM also can record data for up to 10 days and will be used post-randomization for all participants randomized to the Control Group.

7.2.4 iLet Bionic Pancreas

The iLet BP has an integrated graphical user interface (GUI) and touchscreen display that displays the current CGM glucose from the Dexom G6 sensor, 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 qualitatively the meal carb content as “More”, “Usual for Me”, “Less”, or “Much Less”. This will trigger a partial meal-priming bolus, the size of which will adapt during the course of the trial in accordance with the insulin needs for that size and mealtime (e.g. a portion of the mealtime insulin need).

The target BG for the BP is 120 mg/dl by default (“Usual”), but the user may designate a lower default target (of 110 mg/dl, “Lower”) or a higher default target (of 130 mg/dl, “Higher”). A higher or lower default target can be set indefinitely, or for a limited time with automatic expiration, or for a recurring limited time with automatic renewal and expiration. When a temporary target is set, upon expiration the target will revert to the previously chosen default target. Although previous studies showed that the BP decreased hypoglycemia and the need for carbohydrate interventions relative to usual care, this will allow participants to raise the BG target for additional safety during periods when hypoglycemia would be particularly 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 average 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.

The default glucose target setting will be the same in all study periods regardless of participant age or insulin they are using. Participants transitioning to the BP from an MDI regimen or those who have a very low insulin TDD at baseline may be set to start the study period at the higher glucose target at the discretion of the site investigator. Participants who have a high HbA1c at screening and who may have symptoms of hypoglycemia in the normoglycemic range may be set to start the study period at a higher target at the discretion of the site investigator. Participants will be able to edit their glucose target in all BP Groups. They will be instructed to contact study staff to discuss changing their default target.

The GUI can also be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times the control algorithm will determine and direct the

administration of insulin basal rates 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 controller also will administer insulin or decrease basal insulin as appropriate, in response to any entered BG values, just 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 iLet.

The iLet can deliver insulin from pre-filled cartridges or sterile ready-to-fill cartridges.

The iLet may be reused among participants. Before this occurs, the pump will be wiped with Cavicide, consistent with standardized disinfecting procedures.

7.2.5 Contour Next Glucometer

The Contour Next One glucometer is an FDA approved glucose meter that is commercially available. We have tested the accuracy of this meter and found it to be highly accurate and reliable BG measurements will be obtained via fingerstick with this meter in the BP Groups.

7.2.6 Precision Xtra Blood Ketone Meter

The Precision Xtra blood ketone meter is an FDA approved ketone meter that is commercially available. Blood ketone measurements during episodes of hyperglycemia will be obtained via fingerstick with this meter in the BP Groups.

7.3 Participant Access to Study Device at Study Closure

Participants will be permitted to keep the blood glucometer and blood ketone meter at the end of the study, but will need to return all other devices.

Chapter 8: Laboratory Testing, Questionnaires and Focus Group

8.1 Laboratory Testing

HbA1c:

Performed locally at the Screening visit. This may be skipped if the visit is conducted virtually.

Collected for central lab analysis on a schedule as indicated in the visit grids for each phase.

C-peptide and Glucose:

- Collected for central lab analysis at the RCT randomization visit.
  - *If the visit is conducted virtually, this will not be completed.*

Urine Pregnancy:

Performed locally for females of child-bearing potential on a schedule as indicated in the visit grids for each phase. This also can be done anytime pregnancy is suspected. For visits conducted virtually, a home pregnancy test will be provided and a verbal report of the result will be acceptable.

8.2 Questionnaires

8.2.1 Introduction

Questionnaires are completed by all participants within 60 days of the screening visit. During the RCT, questionnaires will be completed at the 6-week and 13-week visit (or within 1 week leading up to each timepoint). In addition, there will be a customized questionnaire completed at the end of the Transition Phase that will query the participant about how they handled the transition and satisfaction with the iLet recommendations.

Each questionnaire is described briefly below. The procedures for administration will be described in the study procedures manual. Age-appropriate versions of each questionnaire will be administered wherever possible. Parents/guardians of pediatric participants may complete parent versions of these questionnaires where applicable. It is estimated that questionnaires will take less than 1 hour to complete for participants and parents of participants <18 years of age.

8.2.2 Brief Description of Questionnaires

Table 5. Psychosocial Questionnaires for the Person With Diabetes (PWD)

Measure	Construct Measured / Relevant Points	Who Completes/Age Range	Timing of Administration in RCT
Diabetes-Specific Emotional Distress . DDS for Adults . PAID-C for 8-12 yrs . PAID-T for 13-<18 yrs	Gold standard measures for understanding distress symptoms related to diabetes. .DDS = 28 items .PAID-C = 11 items	• DDS: ≥18 • PAID-C: 8-12 • PAID-T: 13-<18	Baseline, 6 weeks and 13 weeks

	.PAID-T = 14 items		
Hypoglycemia Confidence	Includes 8 different common situations where hypoglycemia occurs (e.g., physical activity, driving) and evaluates level of confidence in those situations (9 items)	≥18 through adults	Baseline, 6 weeks and 13 weeks
Diabetes Technology Attitudes	Subjective questions about attitudes related to diabetes technologies and devices (5 items)	≥18 through adults	Baseline, 6 weeks and 13 weeks
INSPIRE Surveys • Adult Pre/Post • Youth Pre/Post	Measures psychological expectations and response to closed loop treatment. **Adult** survey has 22 items **Youth** version 17 items.	Adult: ≥18 Youth: 8- <18	All receive the Pre-Inspire survey at baseline. ONLY those on the BP Group receive the POST-Inspire survey. Those post surveys will occur at 13 weeks
Fear of Hypoglycemia Scale • Adult Scale • Youth Scale	The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. • **Adults:** Worry (18 items) and behavior (15 items) • **Youth:** Worry (15 items) and behavior (10 items)	Adult: ≥18 Youth: 8- <18	Baseline, 6 weeks and 13 weeks
Diabetes Treatment Satisfaction Questionnaire • . Baseline version (s) • .Change version (c)	The DTSQ measures patient satisfaction with diabetes treatment and perceived frequency of hyperglycemia and hypoglycemia. Adult version (s and c) 8 items Teen version (s and c) 12 items	Adult: ≥18 Youth (Teens): 13-17	Baseline (s) version at the baseline and at 13 weeks for all Change (c)version at 13 weeks for all
EQ5D (5L and Y versions)	NICE approved QOL measure that translates into economics 5 items	Y version: 5L Version: ≥18 Y Version: 8- <18	Baseline, 6 weeks and 13 weeks
WHO-5	5 items	≥8 through adults	Baseline, 6 weeks and 13 weeks
Bionic Pancreas User Opinion Survey	35 items	≥8 through adults	ONLY administered at 6 and 13 weeks, and ONLY to those who are using the BP. NOT to the Control Group
Past Experience with Artificial Pancreas Systems	9 items	≥8 through adults	ONLY administered at 13 weeks, and ONLY to those who are using the BP. NOT to the Control Group

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Table 6. Psychosocial Questionnaires for Parents of Children Ages 6- <18 Years Old

Measure	Construct Measured / Relevant Points	Age Range	Timing of Administration in RCT
Diabetes-Specific Emotional Distress . P-PAID-C for 8-12 yrs . P-PAID-T for 13-<18 yrs	Gold standard measures for understanding distress symptoms related to diabetes. .P-PAID-C = 16 items .P-PAID-T = 15 items	P-PAID-C: Parents of those ages 6-12 P-PAID-T: Parents of those ages 13-<18	Baseline, 6 weeks and 13 weeks
INSPIRE Surveys Parent Pre/Post	Measures psychological expectations and response to closed loop treatment. Parent pre and post measures 21 items	Parents of youth ages 6-<18	All Parents receive the Pre-Inspire survey at baseline. ONLY those on the BP Group receive the POST-Inspire survey at 13 weeks
Fear of Hypoglycemia Scale • Parent report scale	The HFS measures several dimensions of fear of hypoglycemia among parents of youth with type 1 diabetes. . Parent: Worry (15 items) and behavior (11 items)	Parents of youth ages 6-<18	Baseline, 6 weeks and 13 weeks
Diabetes Treatment Satisfaction Questionnaire • Baseline version • Change version	The DTSQ measures patient satisfaction with diabetes treatment and perceived frequency of hyperglycemia and hypoglycemia. Parent version (s and c) **14** items	Parents of youth ages 6-<18	Baseline (s) version at the baseline and at 13 weeks for all Change (c)version at 13 weeks for all
Bionic Pancreas User Opinion Survey	35 items	Parents of youth ages 6-<18	ONLY administered at 6 and 13 weeks, and ONLY to those who are using the BP. NOT to the Control Group
Past Experience with Artificial Pancreas Systems	9 items	Parents of youth ages 6-<18	ONLY administered at 13 weeks, and ONLY to those who are using the BP. NOT to the Control Group

8.3 Focus Groups

Focus Groups

Focus groups will be completed for participants assigned to the BP Group who agree to participate. Focus groups (or individual interviews, depending on participants' schedules) will occur within 1-3 weeks after they have completed the BP Group (this is 14-16 weeks post study start). Virtual focus groups will be conducted using HIPAA-approved software supported by Northwestern University and run by researchers at Lurie Children's Hospital, Department of Pediatrics of Northwestern University's Feinberg School of Medicine. Focus groups will be run with 3-6 participants who are in the same developmental age group (e.g. children, adolescents,

young adults, adults, parents) and a script of open-ended questions will be used to gather feedback and reactions to the psychosocial impact of wearing the iLet BP system. There will also be time for discussion of content raised by participants. Use of a moderator with advanced training will help ensure consistency across groups. Trained study coordinators will observe the focus groups and take field notes. The study coordinator will keep time and manage group logistics. Sessions will be audio- and video-taped and transcribed by a professional transcription service.

Chapter 9: Unanticipated Problems, Adverse Events, and Device Issue Reporting

9.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Problems meeting IRB reporting requirements will be reported to the IRB within 7 calendar days of the site becoming aware of the problem. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems meeting reporting requirements, within 7 calendar days of becoming aware of the problem, that are not directly involving a specific site, such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as the central laboratory.

9.2 Adverse Events

9.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation.

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).

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 study 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 a study 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, unless excluded from reporting as defined in section 9.2). *An event that occurs solely due to participant (i.e., user) error in which the device functions properly generally will not be considered an ADE unless it is determined that the instructions on the screen of the device or user manual (or similar training materials) may have contributed to the event (note: the event may still meet criteria for reporting as an adverse event).*

Device Complaints and Malfunctions: 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. A device malfunction is 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). *Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.*

9.2.2 Reportable Adverse Events

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

- An SAE
- An ADE as defined in section 9.2.1, unless excluded from reporting in section 9.3
- An AE as defined in 9.2.1 occurring in association with a study procedure
- An AE as defined in 9.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
- An AE as defined in 9.2.1 for which a visit is made to a hospital emergency department
- Hypoglycemia meeting the definition of severe hypoglycemia as defined below
- Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, hyperglycemia or ketosis event meeting the criteria 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.

All reportable AEs—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 AE form online. Each AE form is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

9.2.3 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 loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. 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.

When a hypoglycemic event meets the above reporting requirements, a Hypoglycemia Form should be completed in addition to the Adverse Event Form. Severe hypoglycemia events are considered to be serious adverse events with respect to reporting requirements.

9.2.4 Hyperglycemic/Ketotic Events

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- Blood ketone level ≥1.0 mmol/L, even if there was no communication with a health care provider *(may not be identified until ketone meter data are uploaded)*

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.

When a hyperglycemia/ketotic event meets the above reporting requirements, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA criteria are considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in section 9.2.1 is met.

9.2.5 Relationship of Adverse Event to Study Device

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.

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

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

9.2.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. 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, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.

SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

9.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with known risk information.

9.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the clinical investigator will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). 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 as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

9.2.9 Outcome of Adverse Events

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

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

RECOVERED/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.

NOT RECOVERED/NOT RESOLVED (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.

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).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified UADEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. *Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.*

9.3 Reportable Device Issues

All UADEs and ADEs as defined in section 9.1.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment. As noted in section 9.1.1, events that occur due to participant (user) error generally will not require completion of a device issue form. Such 'errors' could include improper use of an insulin pump or using a pump infusion set or CGM sensor for a period of time longer than its labeling.

Device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue Form assuming criteria for a UADE or ADE have not been met:

CGM sensor lasting fewer days than expected per manufacturer

CGM tape adherence issues

Battery lifespan deficiency due to inadequate charging or extensive wireless communication

Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual

Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

9.4 Timing of Event Reporting

SAEs possibly related to a study device or study participation and UADEs must be reported to the Coordinating Center within 24 hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the online serious adverse event form and device issue form if applicable. If the form is not initially completed, it should be competed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion on the on line form within 7 days of the site 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.

9.5 Reporting to Novo Nordisk

For NovoLog: Copies of reports submitted to the FDA.
For Fiasp:

- 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 Fiasp) and all issues with the packaging material and labelling

Prompt notification to Novo Nordisk of a SAE by the Coordinating Center will occur so that Novo Nordisk's legal obligations and ethical responsibilities towards the safety of participants 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 by the Coordinating Center within 15 days of the Coordinating Center's first knowledge of the event. At a minimum, the following should be reported: Study name, Patient identification (e.g. subject number, sex, age), Event (Preferably diagnosis), Trial drug, Reporter, Causality, and Outcome.

9.6 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within 24 hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB).

The Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA and the Medical Monitor's assessment of relationship to the study device; and informed of all reported device issues.

A Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will be informed of all cases of severe hypoglycemia and diabetic ketoacidosis irrespective of device relationship, all device-related SAEs, and all UADEs at the time that they occur during the study and will review compiled safety data at periodic intervals. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding the DSMB's role will be documented in a separate DSMB document.

9.7 Stopping Criteria

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA event (or a malfunction that could have led to severe hypoglycemia or DKA), use of the BP system will be suspended while the problem is diagnosed. The UADE will be reported to the IRB, DSMB, and FDA. After assessment of the problem and any correction, use of the system will not be restarted until approval is received from the IRB, DSMB, and FDA.

In the absence of a device malfunction, use of the BP system by a participant will be discontinued if any of the following occur:

- 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*
- The participant requests that the treatment be stopped

Participant pregnancy

Two distinct episodes of DKA as defined in 9.2.4

Two distinct severe hypoglycemia events as defined in section 9.2.3

One episode of DKA as defined in 9.2.4 and one severe hypoglycemia event as defined in section 9.2.3

Each DKA or severe hypoglycemia event will be reviewed by the Medical Monitor and by the DSMB with respect to determination of cause and whether the occurrence of the event can be attributed to use of the BP system.

An additional requirement for continued system use following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor and DSMB concur. If either the Medical Monitor or DSMB determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the BP system, use will be discontinued.

9.7.1 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in 9.7, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities 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.

The Medical Monitor or the DSMB may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

Chapter 10: Miscellaneous Considerations

10.1 Collection of Medical Conditions and Medications

Pre-Existing Conditions: Collection of pre-existing conditions will include any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medical Conditions during the study: The following medical conditions that do not qualify for reporting on an Adverse Event Form should be reported on the Medical Conditions Form: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment) and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment. Transient conditions that do not affect the participant's ability to carry out the protocol or study data related to any study outcome do not need to be reported.

Medications: All medications that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. This will include the treatment of chronic pre-existing conditions, medical conditions that occur during the study (both reportable and not-reportable medical conditions), and/or adverse events. Medications only taken as needed either can be recorded when prescribed or only recorded if used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

10.2 Prohibited Medications, Devices, Treatments and Procedures

Participants are not permitted to initiate use of a blood glucose lowering medication that was not in use and met eligibility criteria at the time of screening. This includes but is not limited to SGLT2 inhibitor, sulfonylurea, GLP1, pramlintide, or metformin drugs.

Participants are not permitted to use diabetes management devices that are not FDA approved (such as do-it-yourself closed-loop systems).

10.3 Rescue Medications

All participants will be required to have a commercially available glucagon (or glucagon analog) preparation for treatment as needed of severe hypoglycemia.

10.4 Pregnancy Reporting

If pregnancy occurs, the study intervention will be discontinued while continuing safety follow-up. The occurrence of pregnancy will be reported to the Coordinating Center and to the JCHR IRB on the Unanticipated Problem form within 7 calendar days of becoming aware of the pregnancy.

10.5 Participant Compensation

Participant compensation will be described in the informed consent form.

10.6 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. 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.

10.7 Confidentiality

For security and confidentiality purposes, participants will be assigned identifiers that will be used instead of their names. 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 11: Statistical Considerations

11.1 Statistical and Analytical Plans

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.

11.2 Statistical Hypotheses

The primary outcome is:

- Superiority in HbA1c at 13 weeks

A key secondary outcome is

- Non-inferiority in CGM-measured time <54 mg/dL calculated over 13 weeks

Only superiority in HbA1c at 13 weeks needs to be met to declare efficacy. Primary outcome analyses will combine pediatric and adult participants into a single analysis. The study hypotheses can be stated as follows:

HbA1c Outcome:

- *Null Hypothesis*: There is no difference in the mean HbA1c at 13 weeks between BP aspart/lispro and Control Group
- *Alternative Hypothesis*: There is a nonzero difference in the mean HbA1c at 13 weeks between BP aspart/lispro and Control Group

Time <54 mg/dL Outcome:

- *Null Hypothesis*: There is a mean difference of at least 1% in the percentage of time spent with a sensor glucose level below 54 mg/dL between the BP aspart/lispro and Control Group over the 13 weeks
- *Alternative Hypothesis*: There is a mean difference of less than 1% in the percentage of time spent with a sensor glucose level below 54 mg/dL between the BP aspart/lispro and Control Group over the 13 weeks

The primary analyses will include only the BP aspart/lispro Groups compared with the Control Group. Separate analyses will be performed comparing BP Fiasp and Control Groups as described in Section 11.12, but no multiplicity adjustment will be applied as these can be considered two separate studies for purpose of analysis.

11.3 Sample Size

The sample size of 440 for the RCT was selected to provide sufficient exposure to the iLet BP system for regulatory purposes, with respect to different age groups and to use of both insulin aspart/lispro and Fiasp. RCT completion is expected for 200 participants randomized to BP aspart/lispro Group, 100 to the BP Fiasp Group, and 100 to the Control Group.

The primary analysis for BP aspart/lispro vs. Control Group will include both the pediatric and adult participants in a single analysis. Superiority for HbA1c at 13 weeks and non-inferiority for time <54 mg/dL measured with CGM at intervals over the 13 weeks are considered primary endpoints. Statistical power for each endpoint was computed assuming the following:

HbA1c: Statistical power is >99%, assuming true mean HbA1c difference of 0.4% between BP aspart/lispro and Control Group, standard deviation of 13-week HbA1c of 0.8%, correlation between baseline and 13-week HbA1c of 0.40, two-sided type 1 error of 5%

Time <54 mg/dL: Statistical power is 99%, assuming no true difference in mean time <54 mg/dL between BP aspart/lispro and Control Group, a non-inferiority margin of 1%, standard deviation of percent time <54 mg/dL of 2.0%, correlation between baseline and follow-up of 0.40, and one-sided type 1 error of 0.025%

Power calculations comparing BP Fiasp and Control Group are described in Section 11.12.

11.4 Efficacy Outcome Measures

11.4.1 Primary and Key Secondary Efficacy Endpoints

HbA1c at 13 weeks (superiority)

CGM time < 54 mg/dL (non-inferiority)

To preserve the overall type 1 error, a hierarchical gatekeeping testing procedure will be used with HbA1c at 13 weeks tested first. If the HbA1c analysis results in a statistically significant result ($p < 0.05$), then testing will proceed to the CGM time <54 mg/dL analysis.

11.4.2 Additional Secondary Efficacy Endpoints

11.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis

Assuming the primary and key secondary endpoints meet statistical significance as described above, the following CGM-measured secondary endpoints will be tested for superiority in a hierarchical fashion as described in Section 11.6.4.

Mean glucose

Time 70-180 mg/dL

Time >180 mg/dL

Time >250 mg/dL

Standard deviation

Time <70 mg/dL

Time <54 mg/dL

Coefficient of variation

11.4.2.2 Other Secondary Efficacy Endpoints

The following endpoints are considered exploratory. Type 1 error for these endpoints will be controlled using the false discovery rate (FDR). The Fiasp and aspart/lispro groups will be pooled for analyses of the secondary efficacy endpoints listed in this section if there are not statistically significant differences comparing the Fiasp and aspart/lispro groups for the primary and key secondary outcomes, as described in section 11.14.

HbA1c:

HbA1c <7.0% at 13 weeks

HbA1c <7.0% at 13 weeks in participants with baseline HbA1c >7.5%

HbA1c <7.5% at 13 weeks

HbA1c <8.0% at 13 weeks

HbA1c >9.0% at 13 weeks

HbA1c improvement from baseline to 13 weeks >0.5%

HbA1c improvement from baseline to 13 weeks >1.0%

HbA1c relative improvement from baseline to 13 weeks >10%

HbA1c improvement from baseline to 13 weeks >1.0% or HbA1c <7.0% at 13 weeks

CGM-Measured:

Time in range 70-140 mg/dL

Time in range 70-120 mg/dL

Time <60 mg/dL

Area over the curve (70 mg/dL)

Low blood glucose index

CGM-measured hypoglycemic events (≥15 minutes with glucose concentration <54 mg/dL)

CGM-measured hyperglycemic events (≥15 minutes with glucose concentration >300 mg/dL)

Time >300 mg/dL

Area under the curve (180 mg/L)

High blood glucose index

Time in range 70-180 mg/dL >70%

Time in range 70-180 mg/dL improvement from baseline to 13 weeks ≥5%

Time in range 70-180 mg/dL improvement from baseline to 13 weeks ≥10%

Mean of daily difference (MODD)

Time <70 mg/dL <4%

Time <54 mg/dL <1%

Combined Secondary Outcomes:

Improvement in HbA1c > 0.5% without an increase in time < 54 mg/dl by > 0.5% OR improvement in time < 54 mg/dl by > 0.5% without an increase in HbA1c by > 0.5%

Improvement in time 70–180 mg/dl by >10% without an increase in time < 54 mg/dl by > 0.5% OR improvement in time < 54 mg/dl by > 0.5% without a decrease in time 70–180 mg/dl by > 10%

BGRI = LBGI + HBGI

Mean glucose <154 mg/dL and time <54 mg/dL <1%

Time in range 70-180 mg/dL >70% and time <54 mg/dL <1%

Other Secondary Outcomes:

Questionnaires scores on each questionnaire that is administered (see chapter 8)

Insulin

- Total daily insulin (units/kg)
- Percentage change in the TDD of insulin over the first two-week period relative to the TDD of insulin in last two-week period (iLet Group only)

Weight and Body Mass Index (BMI)

From the weekly questionnaires, number of hypoglycemic events requiring carbohydrate treatment per 24 hours

From the weekly questionnaires, grams of carbohydrate taken specifically to treat hypoglycemic events per 24 hours

11.5 CGM Metrics Calculations

Baseline values for each CGM metric will be computed from either the participant's personal Dexcom G6 data or from the G6 wear prior to randomization. The most recent two weeks of CGM data prior to randomization will be included in the calculation of baseline CGM metrics.

During the RCT, CGM metrics will be calculated from the CGM data collected from the Control Group for comparison with the CGM data from the BP Group. Percentage of CGM values that fall within a specified range will be calculated by dividing the number of CGM values that fall within the range by the total number of CGM readings.

11.6 Analysis of the Primary and Secondary Efficacy Endpoints

The primary analysis will include both the pediatric and adult participants in a single analysis. All analyses comparing the BP aspart/lispro with the Control Group will follow the intention-to-treat (ITT) principle with the data from each participant analyzed according to the treatment assigned by randomization.

A per-protocol analysis that includes participants adhering to the protocol will be performed and detailed in the SAP. Sensitivity analyses on the primary and key secondary outcomes also will be described in the SAP.

11.6.1 HbA1c Analyses (Superiority)

HbA1c at 13 weeks will be compared between the BP aspart/lispro and Control Groups using a linear mixed effects regression model adjusting for baseline HbA1c, age, and clinical center

(random factor). HbA1c is expected to be normally distributed, but regression diagnostics will be performed to check the residuals and an appropriate alternative transformation or a nonparametric analysis based on ranks will be performed if the residuals have a skewed distribution. In the event that some HbA1c values are not available at 13 weeks, then the linear mixed effect regression model will use the method of direct likelihood to incorporate information from baseline measurements to calculate the maximum likelihood at 13 weeks. Only central lab HbA1c measurements will be used in the analyses.

Other secondary HbA1c outcomes will be tested and described in the SAP.

11.6.2 Time <54 mg/dL (Noninferiority)

Time below 54 mg/dL will be calculated over 13 weeks for each subject as described in Section11.5. A two-sided 95% confidence interval on the mean difference in % time <54 mg/dL between BP aspart/lispro and Control Group will be performed based on a linear mixed effects regression model adjusting for baseline % time <54 mg/dL, age, and clinical center (random factor). Noninferiority will be assessed by comparing the upper bound of this confidence interval to a noninferiority limit of 1%. Missing data will be handled by the method of direct likelihood. Residuals values will be examined for an approximate normal distribution. If the values are highly skewed, then a transformation or nonparametric method will be used instead. A two-sided p-value will be reported, and a 5% significance level will be used to declare significance.

Since noninferiority is typically framed in terms of a one-sided test, it is worth noting that the left half of a two-sided test at alpha = 0.05 gives the same rejection region as a one-sided test at alpha = 0.025. Therefore, reporting a two-sided 95% confidence interval will provide flexibility to test for inferiority if noninferiority cannot be declared while maintaining the overall type 1 error rate of 5%.

11.6.3 Secondary CGM Metrics (Superiority)

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured metrics at baseline and during follow up as well as for differences from baseline by treatment group.

Secondary CGM metrics will be calculated as described in Section 11.5. CGM metric differences between BP and Control Groups will be compared using a linear mixed effects regression model adjusting for the baseline value of the metric, age, and clinical center (random effect). Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. Missing data will be handled using direct likelihood.

11.6.4 Hierarchical Analyses

To preserve the overall type 1 error for the primary endpoint and key secondary endpoint as defined in section 11.4.1 and selected secondary endpoints listed in section 11.4.2.1, a hierarchical testing procedure will be used. If the primary analysis for HbA1c results in a statistically significant result ($p < 0.05$), then testing at the 0.05 level will proceed to the next outcome metric. This process continues iteratively moving to the next variable down on the list until a non-significant result is observed, or all 10 variables have been tested. If a non-

significant result is encountered, then formal statistical hypothesis testing is terminated and any variables lower on the list will not be formally tested.

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment group for each hierarchical outcome. A 95% confidence interval for the treatment group difference also will be calculated for all hierarchical outcomes listed above. However, a confidence interval that excludes zero will not be considered a statistically significant result if an outcome variable higher on the hierarchical list failed to reach statistical significance.

11.6.5 Questionnaires and Other Outcomes Analyses

For questionnaires administered to both randomization groups, comparisons will be made using similar linear models as described above for the primary and key secondary outcomes. If questionnaires include a total score, separate models will be run for the total score and any subscales listed in section 8.2.2.

Similarly, for insulin, weight and BMI metrics comparisons will be made using similar linear models as described above for the primary HbA1c analysis.

Details of the questionnaire scoring and other outcome assessment will be detailed in the SAP.

11.7 Safety Analyses

All randomized participants will be included in the safety analyses and all of their post-randomization safety events will be reported. Separately, any adverse events occurring between screening and randomization will be reported.

All reportable adverse events will be tabulated by treatment group (aspart/lispro and Fiasp groups will be reported separately). Details will be provided in a listing of each event, including Medical Dictionary for Regulatory Activities (MedDRA) term and MedDRA System Organ Class. Safety analyses for the RCT will include events occurring on or after randomization until and including the 13-week visit or Day 98 from randomization, whichever occurs first.

Formal statistical testing only will be performed for selected safety endpoints. For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group and formal statistical comparisons will be performed if there are enough events (at least 5 events combined between the BP aspart/lispro and Control Group):

- Number of SH events and SH event rate per 100 person-years
- Number of DKA events and DKA event rate per 100 person-years
- Other serious adverse events
- Worsening of HbA1c from baseline to 13 weeks by >0.5%

If enough events occur for the severe hypoglycemia and DKA outcomes and other serious adverse events, the numbers of events will be compared between the two treatment groups during the RCT using a robust Poisson regression as detailed in the SAP.

Since the Control Group is not provided with a study blood glucose meter or blood ketone meter, no treatment group comparisons of meter data will be performed. Additionally, no formal statistical comparison will be made of all reported adverse events combined since there are

specific requirements in the protocol for reporting certain events in real-time for the BP Group but not the Control Group, and adverse device effects are only reported for the BP Group.

11.7.1 Safety Tabulations Specific to the BP Group

For the BP Group, all of the following will be tabulated separately for the BP aspart/lispro Group and the Fiasp Group:

- Adverse device effects (ADE)
- Serious adverse device events (SADE)
- Unanticipated adverse device effects (UADE)

11.8 Additional Tabulations and Analyses

The following tabulations will be performed according to treatment group:

- Baseline demographics and clinical characteristics
- A flow chart accounting for all participants for all visits
- Visit completion rates for each follow-up visit
- Protocol deviations
- Modifications in diabetes management class in the Control Group (e.g. change between MDI/CSII) during the study
- Number and reasons for unscheduled visits and phone calls

11.8.1 Tabulations Specific to the BP Group

- Number of participants who stopped BP use and reasons
- % time in closed loop
- Occlusion events that occur while using the iLet BP system
- Device malfunctions requiring study team contact and other reported device issues

11.9 Planned Interim Analyses

No formal interim efficacy analyses are planned as study recruitment is expected to be rapid and the duration of follow up short. The DSMB will review safety data at intervals, with no formal stopping rules other than the guidelines provided in the participant-level and study-level stopping criteria (as defined in Section 9.6 of the protocol).

Upon completion of the RCT, the efficacy and safety analyses will be performed in preparation for PMA submission.

11.10 Subgroup Analyses

In exploratory analyses, the primary and key secondary outcomes plus time in range 70-180 mg/dL and mean glucose will be assessed separately for interaction with certain baseline variables, including baseline HbA1c, prior pump/CGM use, and other baseline characteristics as

described in the SAP. The Fiasp and aspart/lispro Groups will be pooled if there are not statistically significant differences comparing the Fiasp and aspart/lispro Groups for the primary endpoints as described in section 11.14, with the exception of subgroup analyses by age, in which only the BP aspart/lispro group will be compared with the Control Group. All primary and key secondary variables will be evaluated in the predefined age groups (≥18 years old and <18 years old, and further subdivided as 6-<13, 13-<18, 18-<26, 26-<50, ≥50 years old).Interpretation of the subgroup analyses will be made with caution, particularly if the primary analysis is not significant.

11.11 Multiple Comparison/Multiplicity

Hierarchical Analyses

The hierarchical testing procedure described above in Section 11.6.1 will be used to control the overall type 1 error for the primary endpoint and key secondary endpoints plus eight additional secondary outcomes identified above.

All Other Secondary Analyses

For the other secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

11.12 Additional Exploratory Analyses

Additional analyses comparing treatment groups will include:

- Comparison of aspart/lispro BP Group versus Control Group in adults ≥18 years old for the efficacy and safety outcomes described for the main RCT analyses
- Separate CGM analyses for daytime and nighttime
- Total daily dose of insulin at 13 weeks and at 2 weeks according to baseline HbA1c
- Intersubject variability of HbA1c

11.13 BP Fiasp Versus Control Group

All of the above analyses with the exception of subgroup analyses by age group will be replicated comparing the BP Fiasp and Control Groups. This analysis will be treated as a separate study, so the multiple hypothesis testing in the BP aspart/lispro vs Control comparison will not be adjusted for the BP Fiasp vs. Control Group comparison. However, the same hierarchical testing procedure will be performed for the BP Fiasp versus Control comparison for primary and secondary endpoints and the false discovery rate will be controlled for the other secondary endpoints as described in Section 11.11.

This analysis will include approximately 100 participants in BP Fiasp and 50 participants in Control Group. Statistical power for each primary endpoint was computed assuming the following:

HbA1c: Statistical power is 91%, assuming true mean HbA1c difference of 0.4% between BP Fiasp and Control Group, standard deviation of 13-week HbA1c of 0.8%, correlation between baseline and 13-week HbA1c of 0.40, two-sided type 1 error of 5%

Time <54 mg/dL: Statistical power is 86%, assuming no true difference in mean time <54 mg/dL between BP Fiasp and Control Group, a non-inferiority margin of 1%, standard deviation of percent time <54 mg/dL of 2.0%, correlation between baseline and follow-up of 0.40, and one-sided type 1 error of 0.025%

11.14 Comparison of Aspart/Lispro Group and Fiasp Group

For the primary and key secondary endpoints, the BP aspart/lispro Group and the BP Fiasp Group will be compared. If neither analysis has a p value >0.05 for superiority, then these groups will be pooled for the exploratory secondary and subgroup analyses that are not part of the hierarchy analyses.

11.15 Transition Phase

In the 2-4-day Transition Phase, participants are randomly assigned to transition back to their usual therapy based on therapeutic guidance from the bionic pancreas or transition back to their usual therapy based on their own insulin regimens prior to enrolling in the RCT.

Analyses will be considered exploratory. The primary analyses will be for safety, tabulating events. Exploratory analyses will include mean CGM glucose level and time of CGM measured time < 54 mg/dL.

Chapter 12: Data Collection and Monitoring

12.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation will be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

HbA1c measurements will be made by the central laboratory and the data will be transmitted to the Coordinating Center.

12.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 3 years after the final NIH grant reporting. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12.3 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, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. 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, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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
- Agent/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

Coordinating Center 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. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 13: Ethics/Protection of Human Participants

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant and if applicable, parent/guardian will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent/assent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant's electronic consent signature will be obtained prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Coordinating Center. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Coordinating Center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.3.3 Future Use of Data

Data collected for this study will be analyzed and stored at the Coordinating Center. After the study is completed, the de-identified, archived data will be archived at the Jaeb Center. A publicly-accessible, de-identified dataset will be made available on the Jaeb Center website and/or the NIDDK data repository.

13.3.4 Future Use of Biologic Samples

With the participant's approval and as approved by local IRBs, de-identified biological samples will be shipped to the central laboratory for temporary storage and later batch shipped for long-term storage at Massachusetts General Hospital. These samples could be used for diabetes-related research, including its treatment (including insulin assays), its causes, its complications and other conditions for which individuals with diabetes are at increased risk, and to improve treatment. The Massachusetts General Hospital will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

Chapter 14: Ancillary Study to Test the iLet with Inputted Blood Glucose Measurements

14.1 Objective

This Ancillary Study will assess the safety of utilizing blood glucose measurements instead of CGM measurements as input into the iLet for ~48-60 hours. The Study is intended to mirror a real-world situation where CGM may not be available for an extended period of time (eg, user runs out of sensors and is awaiting new shipment).

14.2 Sample Size

Participation in the Ancillary Study will be offered to participants who are using the iLet at the time of the 13-week randomized trial visit. The goal for sample size is to have234 complete the Ancillary Study, with a goal of 71 pediatric participants and 163 adults (with a goal to have approximately half of the adults using Fiasp and half using lispro/aspart). The maximum number in the Ancillary Study will be 260 and the final number will be dependent on the number who are willing to participate.

14.3 Eligibility Criteria

Participants must be currently using the iLet and be completing the 13-week visit of RCT on the day of enrollment into the Ancillary Study.

Inclusion in the Ancillary Study requires investigator judgment that it is safe for the individual to participate.

Participants < 18 years old must be living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. Participants ≥18 years old who live alone must have a companion with them during the 2 overnights of the study.

14.4 Study Protocol

On the day of the 13-week RCT visit, informed consent (and assent where indicated) will be obtained from interested participants, and eligibility will be verified. The iLet used in the preceding RCT will be continued, using the same insulin as used in the RCT. The first day of the Study will be referred to as Day 1 and the final day as Day 3.

At the clinic visit on Day 1 (13-week visit of the RCT), participants will be trained on the study protocol. Outpatient procedures described in Chapter 4 will be continued, with the exception of references to CGM. A new instruction sheet will be provided to participants with respect to the identification and management of hypoglycemia and hyperglycemia. The real-time CGM sensor will be removed and a blinded G6 Pro sensor will be placed.

For the next ~48-60 hours, the participant will use the study blood glucose meter to enter glucose measurements into the iLet at least every 2 hours during waking hours and at least once during each overnight. Participants will be instructed to measure and input blood glucose before and 2 hours after every meal plus prior to bedtime. The iLet will alarm to request the blood glucose

entry every 2 hours; however, during the overnight period, only one blood glucose measurement will be required.

Phone/video contact will be made on Day 2 for a safety check.

On Day 3, phone/video contact will be made and the participant will be instructed to stop the iLet session and to remove the iLet and to insert an unblinded G6 sensor. The participant will then continue to the Transition Phase as described in chapter 6. The iLet, blood glucose meter, ketone meter, and blinded CGM transmitter will be returned to the site at the end of the Transition Phase. A clinic visit can be substituted for the Day 3 contact.

14.5 Outcomes and Analysis Plan

A separate statistical analysis plan will be written for the Ancillary Study.

Outcomes will include the following:

Key Safety Outcomes:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Other serious adverse events
- Time <54 mg/dL
- Time >300 mg/dL
- CGM-measured hypoglycemic events
- CGM-measured hyperglycemic events

Other Outcomes

- Mean glucose
- Time 70-180 mg/dL
- Time >180 mg/dL
- Time >250 mg/dL
- Standard deviation
- Time <70 mg/dL
- Coefficient of variation

For each participant, the number of inputted blood glucose meter measurements each day will be tabulated and summarized across participants. Adverse events will be listed. CGM metrics will be computed overall and separately for daytime and nighttime.

14.6 Safety Monitoring

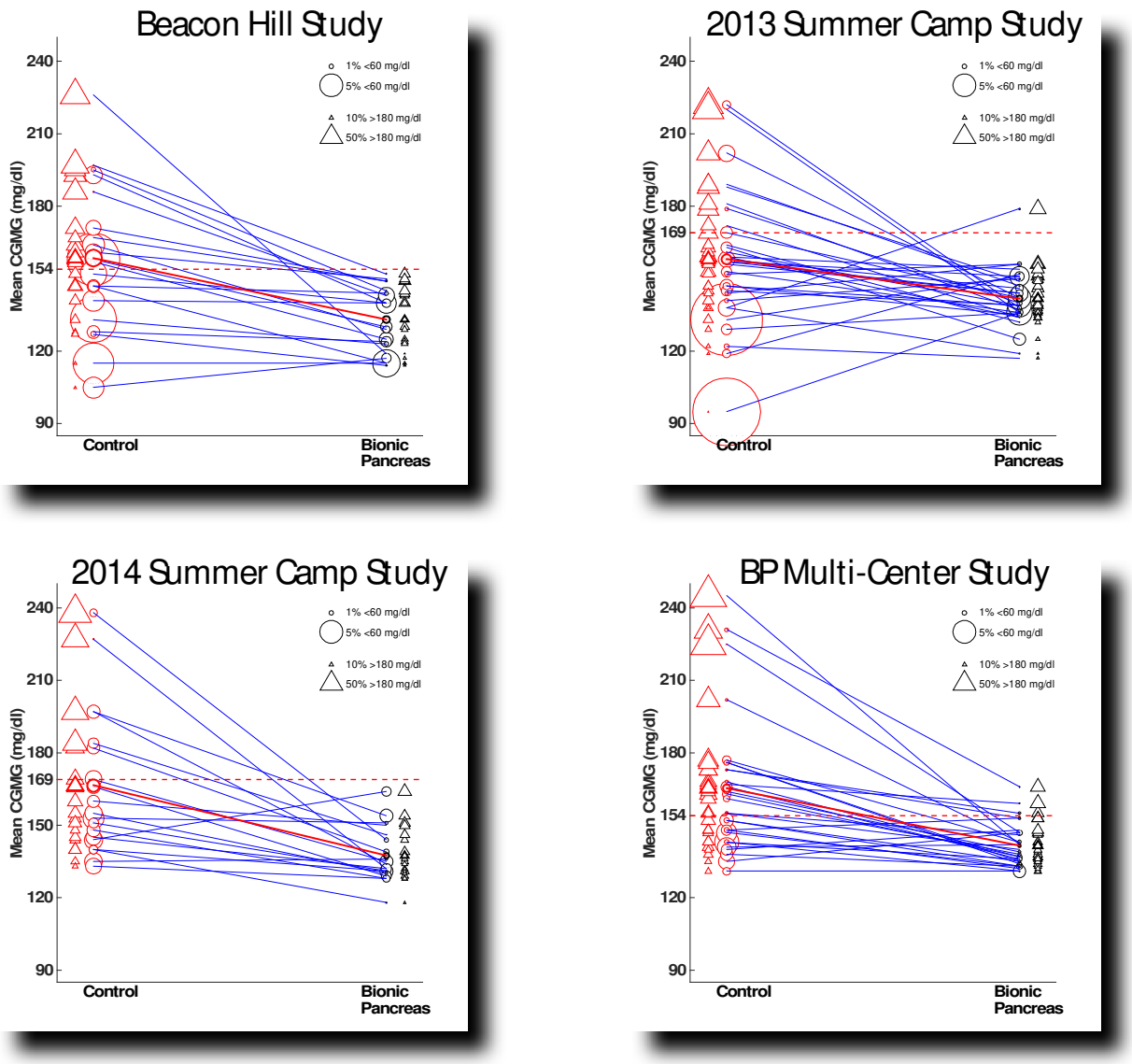
Safety oversight will be the same as for the RCT, as described in section 9.6. Additionally, an initial analysis of the safety outcomes listed in section 14.5 will be performed after data are available from 20 participants.

Appendix A: Prior Studies Conducted Using the Bionic Pancreas System

A.1 Studies Conducted with the iPhone-Based BP System

A.1.1 The Beacon Hill Study, the 2013 and 2014 Summer Camp Studies, and the Bionic Pancreas Multi-Center Study

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) set the stage for the outpatient and home-use 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 arm 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 arm, 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 2.



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 2. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the bihormonal BP and control arms from the Beacon Hill Study, 2013 and 2014 Summer Camp Studies, and the Bionic Pancreas Multi-Center Study. 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 with T1D ≥ 18 years old and 169 mg/dl (HbA1c < 7.5%) for children with T1D < 18 years old. 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 arm. In the control arm 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 study arms 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 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 2.

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 2.

In April 2014, we obtained FDA approval to conduct our first multi-center study, which was also our first home-use study, to test our BP in adults 18 years or older with T1D. This study, which we referred to as the 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 2.

A.1.2 The Bionic Pancreas Set Point Study

In July 2015 we obtained FDA approval to perform our first study testing the BP at different static glucose targets ("set-points") 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 study arms, each lasting 3 days. In all of our previous studies, the target glucose for the bihormonal BP was set to 100 mg/dl. Since this was the first study to test the BP in a configuration without glucagon, the insulin-only study arms initially used significantly elevated glucose targets of 130 mg/dl and 145 mg/dl (not shown). We subsequently obtained approval from the FDA to test glucose targets of 120 mg/dl and 110 mg/dl in December 2015. Results from the insulin-only BP arms and the usual-care arm are summarized in Figure 3. Results from the bihormonal BP arms and the usual-care arm are summarized in Figure 4.

Based on results from this study, we determined that, in terms of striking an optimal balance between minimizing mean glucose and hypoglycemia and maximizing patient satisfaction, the insulin-only configuration of the BP performed best with a glucose target of 120 mg/dl and the bihormonal configuration of the BP performed best with a glucose target of 110 mg/dl.

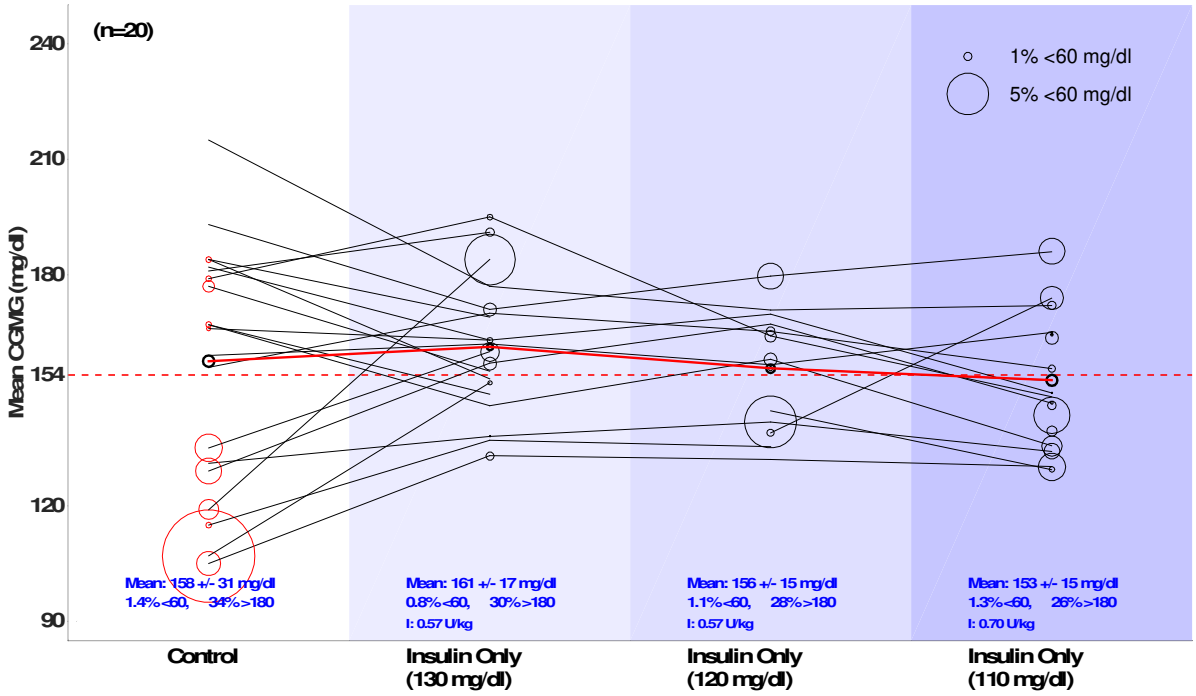


Figure 3. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP arms (with set-points 130, 120, and 110 mg/dl) and usual-care arm (control) from the Bionic Pancreas Set-Point Study. Mean CGM glucose levels for each participant in each study arm (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 with T1D ≥ 18 years old.

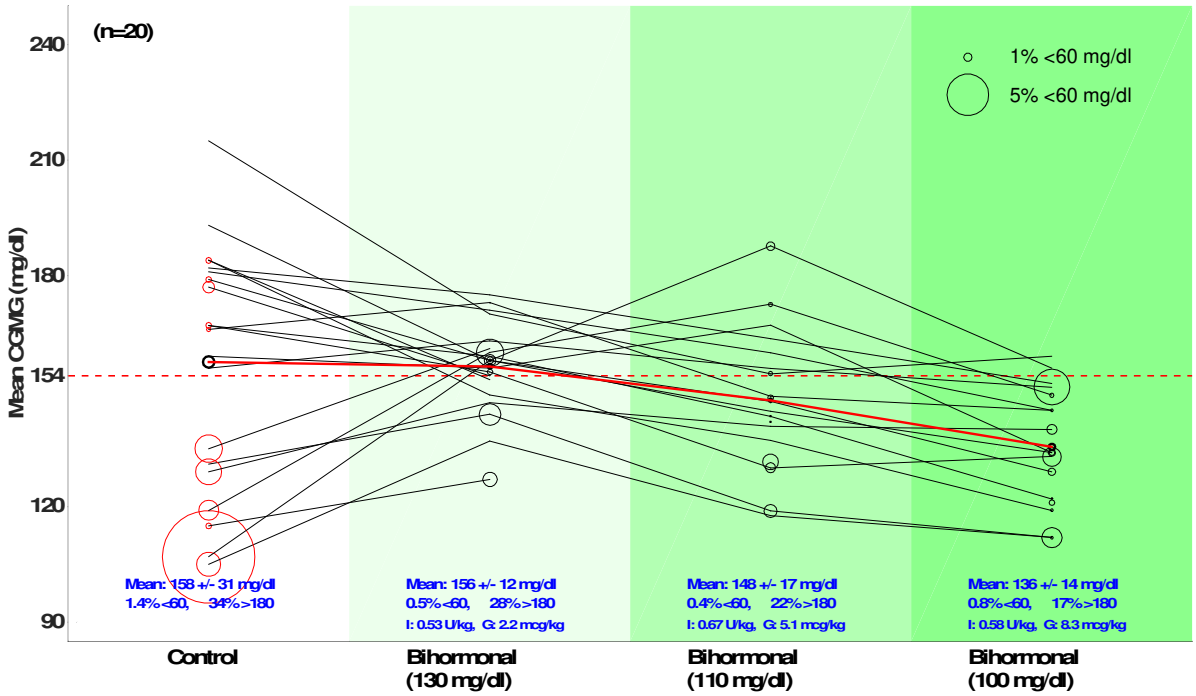


Figure 4. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the bihormonal BP arms (with set-points of 130, 110, and 100 mg/dl) and usual-care arm (control) from the Bionic Pancreas Set-Point Study. Mean CGM glucose levels for each participant in each study arm (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 with T1D ≥ 18 years old.

A.1.3 The Stanford Insulin-Only Study

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 called the Stanford Insulin-Only Study, 16 adults participated in a week of usual care followed by another week on the insulinonly BP. Participants were monitored remotely according to identical criteria in both study arms 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 arm 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. Results of the study are summarized in Figure 5. 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 obtained during the insulin-only BP arm was 159 ± 8 mg/dl (which was similar to the mean CGM glucose of 161 ± 17 mg/dl obtained during the insulin-only BP arm of the Bionic Pancreas Set-Point Study when the glucose target

was set to 130 mg/dl). Although the mean glucose was statistically significantly higher (p=0.001) during the insulin-only BP arm than during the usual-care arm (145 ± 20 mg/dl) in the very well controlled cohort of the Stanford Insulin-Only Study, there was a significant decrease in the time spent <60 mg/dL during the insulin-only BP arm relative to the usual-care arm (mean of 0.84 ± 0.91 versus mean 2.3 ± 2.1%, p = 0.04).

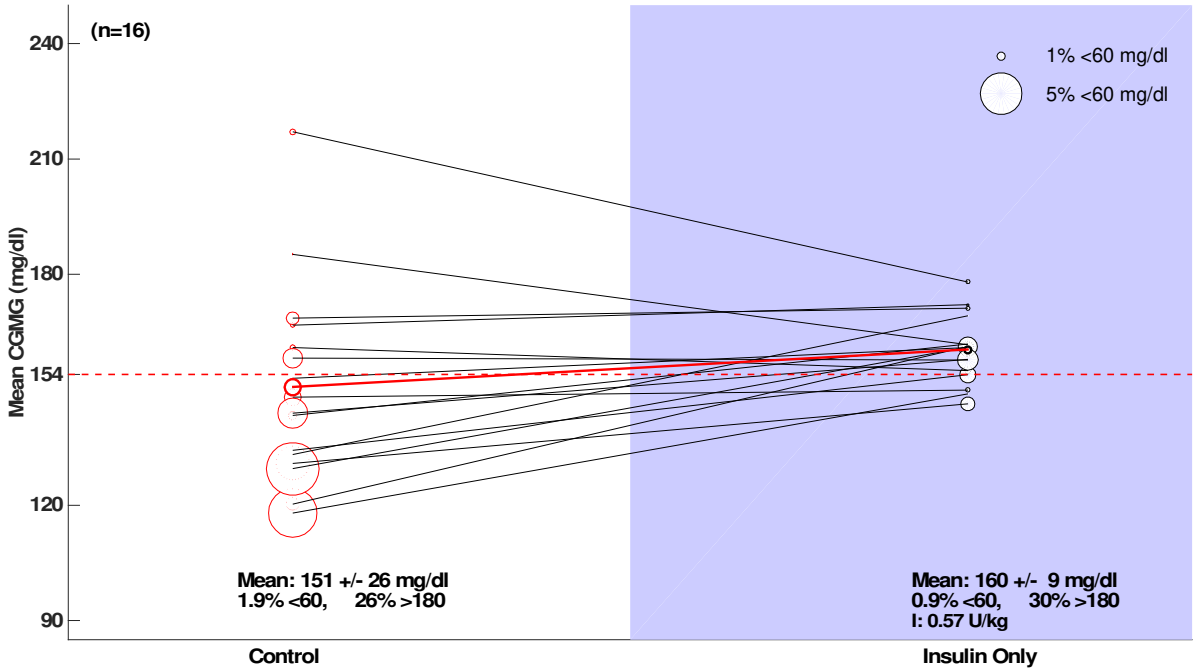


Figure 5. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Stanford Insulin-Only Study. Mean CGM glucose levels for each participant under usual care (shown as a red circle on the left) is connected with the participant's 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 with T1D ≥ 18 years old.

A.1.4 The Bionic Pancreas Monitoring Study

In April 2016, we obtained FDA approval to perform our first study removing remote telemetric monitoring for severe biochemical hypoglycemia from an outpatient study comparing the bihormonal bionic pancreas, the insulin-only bionic pancreas and the subject's own usual care. In the Monitoring Study6 each arm was repeated with and without remote monitoring to allow for a direct comparison of glycemic control and hypoglycemia. Each BP hormonal configuration used the lowest glucose target previously tested: 100 mg/dl for the bihormonal BP and 110 mg/dl for the insulin-only BP. The results are summarized in Figure 6. There was more hypoglycemia without monitoring relative to with monitoring in the two usual-care arms (1.95 versus 1.32%, p=0.02). However, there was no difference in hypoglycemia without monitoring relative to with

monitoring in the two bihormonal BP arms (0.99 versus 1.05%, p=0.82) and two insulin-only BP arms (1.66 versus 1.55%, p=0.74) arms. Without monitoring, hypoglycemia was reduced in the bihormonal BP arm relative to the usual-care arm (0.99 versus 1.95%, p=0.02) and was comparable on the insulin-only BP relative to usual care (1.66 versus 1.95%, p=0.47). The mean CGMG was significantly lower in all BP arms relative to the usual-care arms. There were no mean CGMG differences between the two bihormonal, two insulin-only, and two usual-care arms. We concluded that remote telemetric monitoring had no effect on hypoglycemia with the BP and could be safely omitted from future studies even at the most aggressive glucose set points. As a result of this study and the Bionic Pancreas Set-Point Study, we concluded that the default glucose set points should be set in future studies to 110 mg/dl for the bihormonal configuration and 120 mg/dl for insulin-only configuration. We further concluded that users could be allowed to lower each set point (to a minimum of 100 mg/dl for the bihormonal configuration and 110 mg/dl for insulin-only configuration) should they so desire without sacrificing their safety.

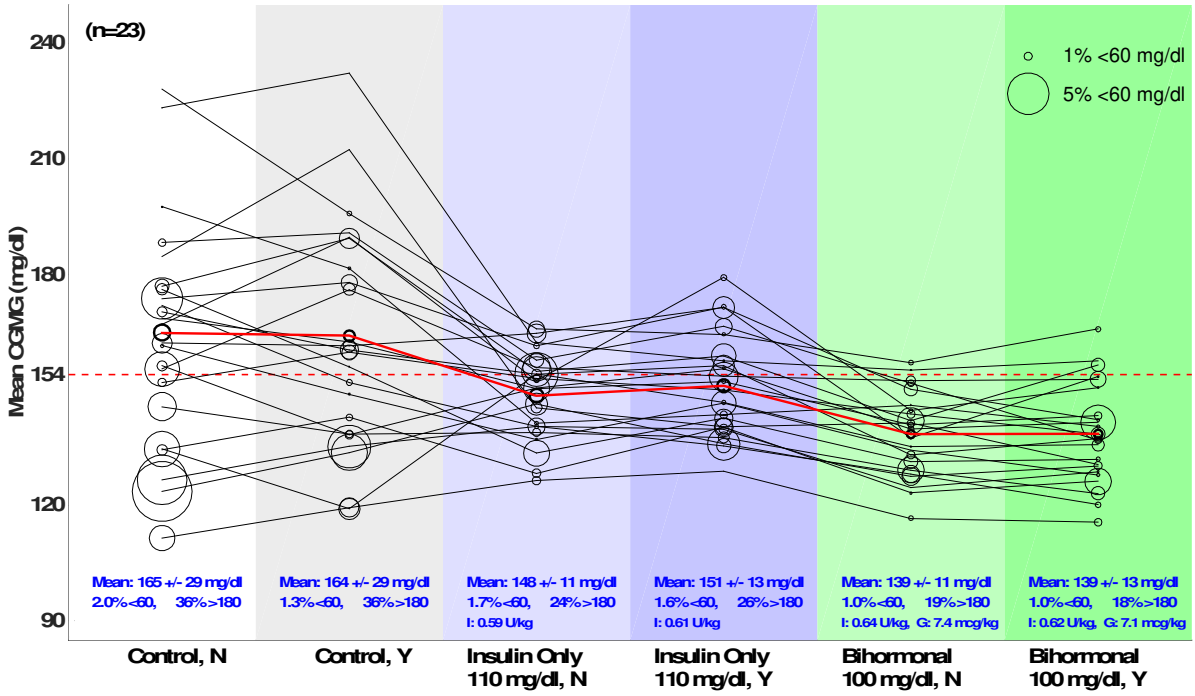


Figure 6. Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Bionic Pancreas Monitoring Study. Mean CGM glucose levels for each participant under usual care (shown as a red circle on the left) is connected with 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 with T1D ≥ 18 years old.

A.2 Studies Conducted with the Gen 3 iLet Bionic Pancreas System

All of the studies described below used the Gen 3 iLet BP System, rather than the commercial Gen 4 iLet system, and all used either the G5 Dexcom CGM or Senseonics Eversense CGM, rather than the G6 Dexcom CGM. The Insulin-Only Bionic Pancreas Pivotal Trial will use the Gen 4 iLet BP System with the G6 Dexcom CGM.

A.2.1 The iLet Insulin-Only Bionic Pancreas Bridging Study

The Insulin-Only Bionic Pancreas Bridging Study was conducted between July and October 2018 at MGH and Stanford University in adult subjects ≥ 18 years old with type 1 diabetes. The study was designed as a random-order, cross-over, home-use trial that compared the insulin-only configuration of the iLet using lispro or aspart to the insulin-only configuration of the iLet using Fiasp to each subject's own usual care (UC) for 7 days each. The study enrolled 12 subjects who used multiple daily injection therapy and 22 subjects who used insulin-pump therapy for their UC. Participants enrolled at MGH (n = 17) used the Senseonics Eversense CGM while those at Stanford (n = 17) used the G5 Dexcom CGM as the input CGM signal for the iLet. Results from the Insulin-Only Bionic Pancreas Bridging Study are summarized in Figure 7.

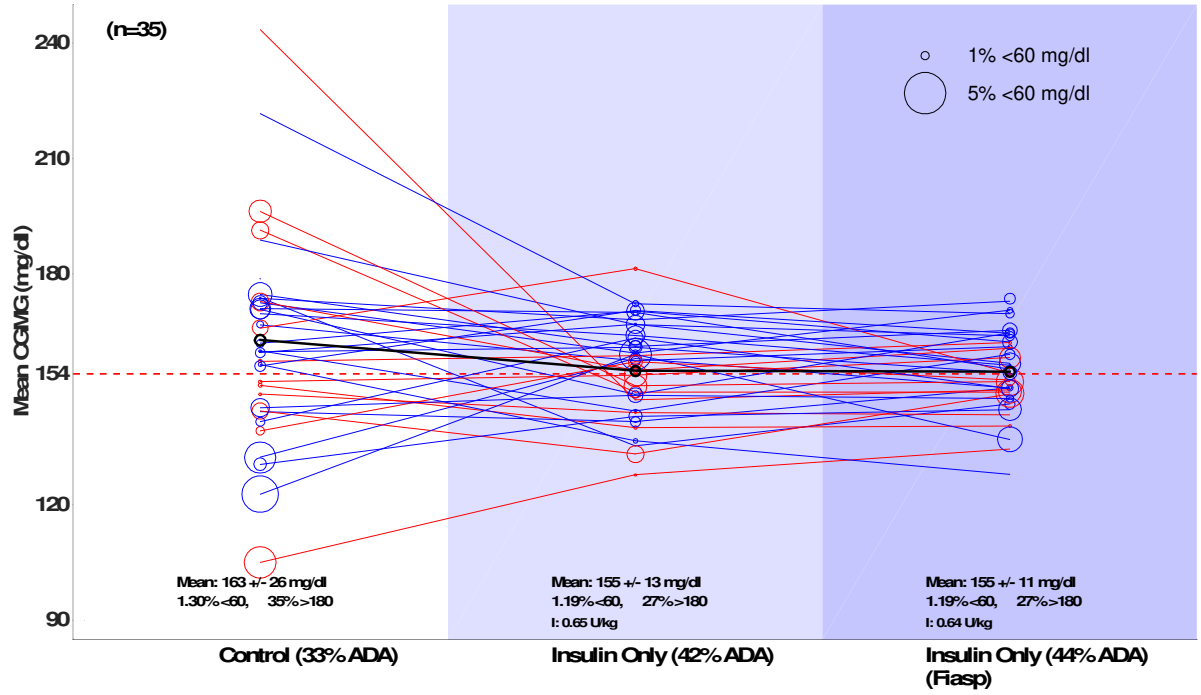


Figure 7. Distribution of mean glucose and hypoglycemia in the Insulin-Only Bionic Pancreas Bridging Study. Mean CGM glucose level for each subject is shown over Days 3–7 under usual care, (left panel), on the iLet in the insulin-only configuration using lispro or aspart (middle panel), and on the iLet in the insulin-only configuration using Fiasp (right panel). The diameter of each circle is proportional to the percentage time spent < 60 mg/dl for each subject under each study arm over Days 3–7. The mean CGM glucose was 155 ± 13 mg/dl with the iLet in the insulin-only configuration using lispro or aspart, 155 ± 11 mg/dl with the iLet in the insulin-only configuration using Fiasp, and 163 ± 26 mg/dl under usual care. The time < 60 mg/dl was 1.2% using lispro or aspart, 1.2% with the iLet using Fiasp, and 1.3% under usual

care. Red lines and circles correspond to data from subjects who used multiple daily injection therapy for their usual care and blue lines and circles correspond to data from subjects who used insulin-pump therapy for their usual care.

The Insulin-Only Bionic Pancreas Bridging Study was unprecedented in several ways. It is the only study of an automated insulin delivery system to test (1) two different CGM devices, (2) an ultra-rapid insulin analog, and (3) a cohort that was comprised subjects coming from multiple daily injection (MDI) therapy and insulin pump therapy. Since only the patient's body weight is required to initialize the iLet, and no other information is required about either insulin therapy regimen (either MDI or insulin pump therapy), the iLet is the only device that can be tested in this way. All other automated insulin delivery systems first require transition to pump therapy and weeks-long run-in periods or device training periods to determine a baseline pump therapy regimen before automated insulin delivery can be initiated. The iLet, on the other hand, requires no run-in periods or device training periods; it is ideally suited, therefore, for use in underserved populations, in insulin-pump-naïve populations, and in populations where endocrinologists and diabetologists are not available or in short supply. The Insulin-Only Bionic Pancreas Bridging Study demonstrated that the iLet performed equally well on subjects coming from MDI therapy as it did on subjects coming from insulin pump therapy (see Figure 7).

A.2.2 The iLet Day-Camp Transitional Study in Pediatrics

The Pediatric Transitional Study was conducted in July and August 2018 at Nemours Children's Health System, the Barbara Davis Center at the University of Colorado, and Stanford University in pediatric subjects 6–17 years old with type 1 diabetes. The study was designed as a random-order, cross-over, outpatient trial that compared the insulin-only configuration of the iLet (using lispro or aspart) to each subject's own usual care (UC) for 5 days each. The study enrolled 20 subjects who used insulin-pump therapy for their UC (n = 6 at Nemours, n = 6 at Colorado, and n = 8 at Stanford). Results from the Pediatric Transitional Study are summarized in Figure 8.

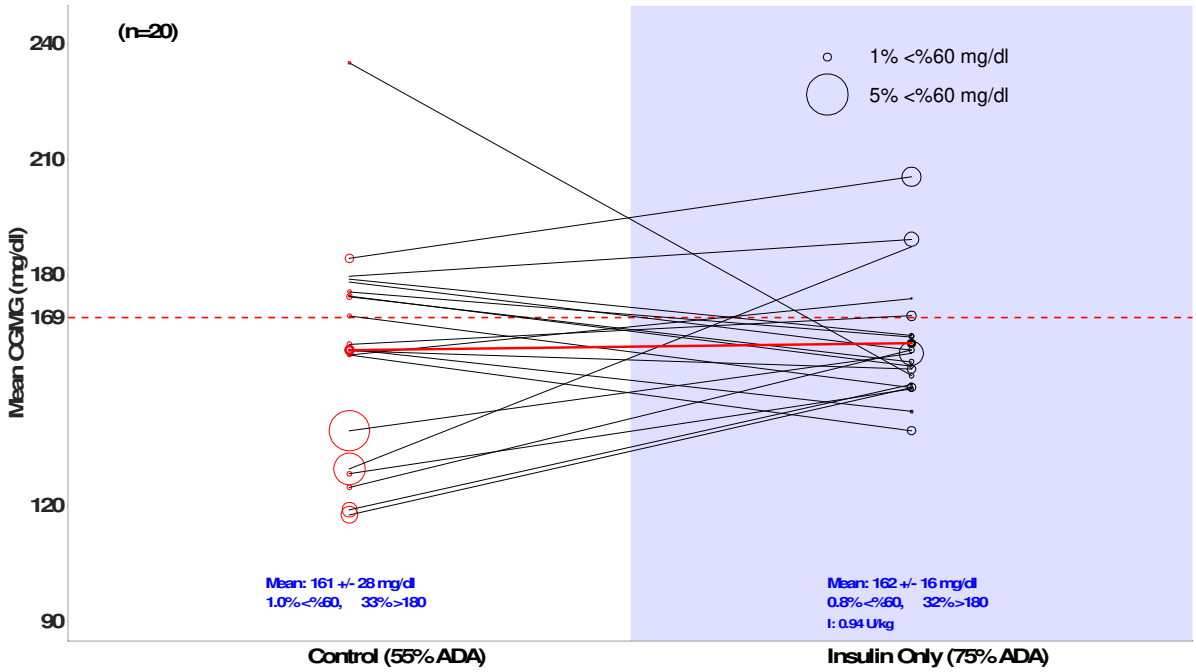


Figure 8. Distribution of mean glucose and hypoglycemia in the Pediatric Day-Camp Transitional Study. Mean CGM glucose level for each subject is shown over Days 2–5 in the control arm, as a red circle on the left side, connected with the corresponding mean CGM glucose level on the iLet, as a black circle on the right. The diameter of each circle is proportional to the percentage time spent < 60 mg/dl for each subject under each study arm over Days 2–5. The mean CGM glucose with the iLet in the insulin-only configuration was 162 ± 16 mg/dl and the CGM glucose was < 60 mg/dl 0.8% of the time, whereas the mean CGM glucose under usual care was 161± 28 mg/dl and the CGM glucose was < 60 mg/dl 1.0% of the time.

A.2.3 The iLet Bihormonal Cross-Over Study

The Bihormonal Cross-Over Study was conducted in May and June 2019 at MGH in adult subjects ≥ 18 years old with type 1 diabetes. The study was designed as a random-order, cross-over, home-use trial that compared the insulin-only configuration of the iLet using lispro or aspart to the bihormonal configuration of the iLet using lispro or aspart and dasiglucagon (4 mg/ml) for 7 days each. The study enrolled 10 subjects who used insulin-pump therapy for their usual care. Results from the Bihormonal Cross-Over Study are summarized in Figure 9.

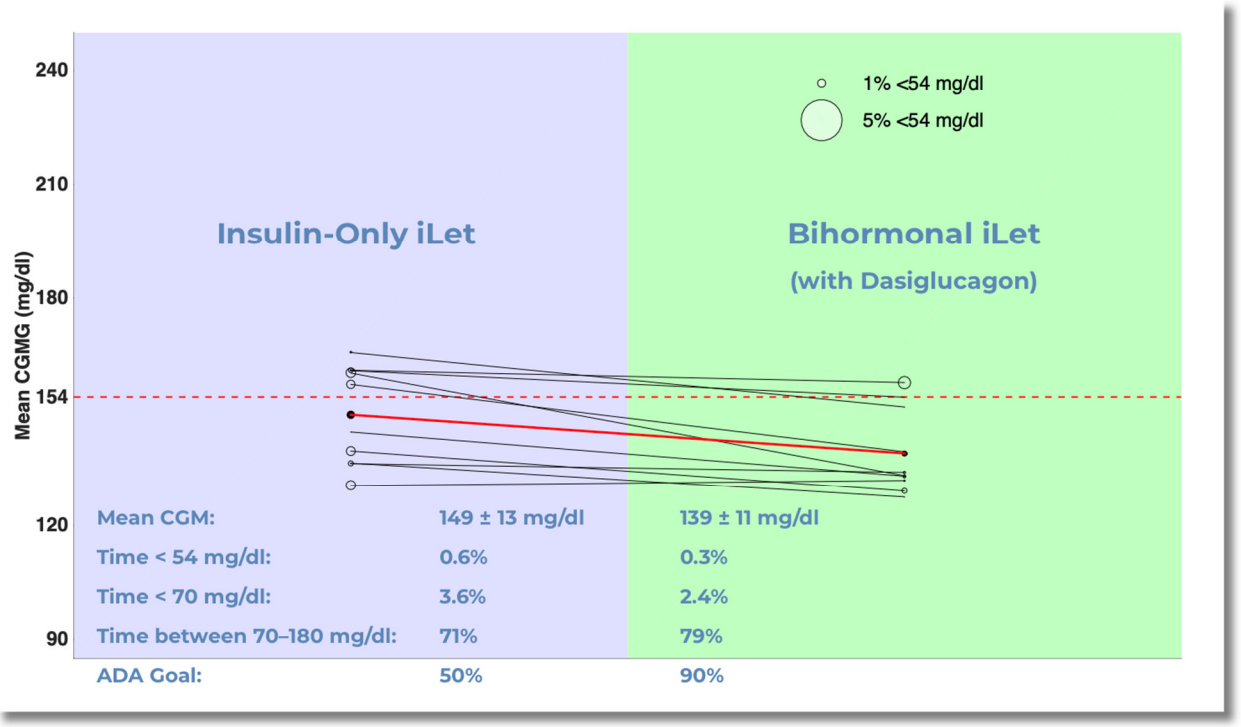


Figure 9. Distribution of mean glucose and hypoglycemia in the Bihormonal Cross-Over Study. Mean CGM glucose level for each subject is shown over Days 2–7 in the insulin-only iLet arm, as a black circle on the left side, connected with the corresponding mean CGM glucose level on the bihormonal iLet with dasiglucagon, as a black circle on the right. The diameter of each circle is proportional to the percentage time spent < 54 mg/dl for each subject under each study arm over Days 2–7. The mean CGM glucose with the iLet in the insulin-only configuration was 149 ± 13 mg/dl and the CGM glucose was < 54 mg/dl 0.6% of the time, whereas the mean CGM glucose with the iLet in the bihormonal configuration with dasiglucagon was 139 ± 11 mg/dl and the CGM glucose was < 54 mg/dl 0.3% of the time.

iPhone bionic pancreas (BP) and iLet BP Studies – Insulin-only exposure only

	Year	Name of Study	Setting, Population, Device exposure[1]	BP Configuration, Set Points tested, Medications used	Protocol Description	Results: Mean CGM glucose, % < 60	Conclusions
1	2015-2016	BP Set Point Study IDE: G150130	Outpatient, unsupervised at home 20 adults aged 18 and older 4 arms, 4 days each	Insulin-only iPhone BP with one Tandem t:slim pump and Dexcom G4 AP CGM Glucose	RCT with 4 insulin-only glucose targets compared with usual care and bihormonal configurations. This was the first testing of	110 mg/dl: 153±15 mg/dl, 1.3% 120 mg/dl: 156±15 mg/dl, 1.1% 130 mg/dl:	The results of this study helped identify the glucose target settings that will be

			7,680 hours	targets: 110 mg/dl 120 mg/dl 130 mg/dl 145 mg/dl Insulin lispro (Eli Lilly) & Insulin aspart (Novo Nordisk)	the insulin-only algorithm. Remote telemetric monitoring	161±17 mg/dl, 0.8% 145 mg/dl: 174±23 mg/dl, 1.0% UC: 158±31 mg/dl, 1.4%	used in future studies. These were set to range from 110 mg/dl to 130 mg/dl, with a default of 120 mg/dl.
2	2015	Stanford Insulin-only Study IDE: G150142	Outpatient, unsupervised at home 16 adults aged 18 and older 2 arms, 7 days each 5,376 hours	Insulin-only iPhone BP with one Tandem t:slim pump and Dexcom G4 AP CGM Glucose targets: 115 to 130 mg/dl Insulin lispro (Eli Lilly) & Insulin aspart (Novo Nordisk)	RCT comparing insulin-only BP with usual care Remote telemetric monitoring	BP: 160±9 mg/dl, 0.9% UC: 151±26 mg/dl, 1.9%	The results of this study helped identify the glucose target settings that will be used in future studies.
3	2017	Monitoring Study IDE: G150130	Outpatient, unsupervised at home 23 adults aged 18 and older 2 arms, 7 days each 7,728 hours	Insulin-only iPhone BP with one Tandem t:slim pump and Dexcom G5 CGM Glucose target: 110 mg/dl Insulin lispro (Eli Lilly) & Insulin aspart (Novo Nordisk)	RCT with the insulin-only BP set at the lowest allowed glucose target for the insulin-only system, repeated with and without monitoring for hypoglycemia, and compared with usual care and the bihormonal BP. Remote telemetric monitoring in	<u>With monitoring:</u> Insulin-only: 151±13 mg/dl, 1.6% UC: 164±29 mg/dl, 1.3% <u>Without monitoring:</u> Insulin-only: 148±11 mg/dl, 1.7% UC: 165±29 mg/dl, 2.0%	The results of this study confirmed that the insulin-only BP set at the lowest possible glucose target (110 mg/dl) was safe to be used in the outpatient setting without any remote monitoring for

					half of the study arms.		hypoglycemia.
4	2018	Adult Bridging study IDE: G180083	Outpatient, unsupervised at home, 2 centers 34 adults aged 18 and older 2 arms, 7 days each 11,424 hours	Insulin-only Gen 3 iLet BP using Senseonics Eversense CGM (MGH) or Dexcom G5 CGM (Stanford) Glucose target: 120 mg/dl Insulin lispro (Eli Lilly), Insulin aspart (Novo Nordisk) & Fiasp PumpCart (Novo Nordisk)	RCT comparing the insulin-only BP in 2 arms with usual care. One BP arm used insulin lispro or aspart, the other BP arm used Fiasp. The BP was set at the default glucose target of 120 and tmax setting of 65 minutes for both arms. Remote telemetric monitoring	BP: 155±13 mg/dl, 1.19% BP with Fiasp: 155±11 mg/dl, 1.19% UC: 163±26 mg/dl, 1.30%	The results of this study demonstrated that the insulin-only iLet BP was safe and effective using both Fiasp or aspart/lispro at the default PK settings consistent with the results of the iPhone BP studies, preparing the path for a larger and longer study using the same device settings and insulins.
5	2018	Day-camp Transitional Study IDE: G180083	Supervised day camp setting followed by unsupervised at home nightly, 2 centers 20 children aged 6-17 5 days 2,400 hours	Insulin-only Gen 3 iLet BP using Dexcom G5 CGM Glucose target: 120 mg/dl Insulin lispro (Eli Lilly) & Insulin aspart (Novo Nordisk)	RCT comparing the insulin-only BP with usual care. Remote telemetric monitoring	BP: 162±16 mg/dl, 0.8% UC: 161±28 mg/dl, 1.0%	The results of this study demonstrated that under stressful conditions, the insulin-only iLet BP was safe and effective to use in adolescent and pre-adolescent

							children, preparing the path for a larger and longer study using the same device settings in this age group.
6	2019	Fiasp Exploratory Study IDE: G180150	48 hour supervised hotel stay, followed by 5 days unsupervised at home 24 adults aged 18 and older 2 arms, 7 days each 8,064 hours	Insulin-only Gen 3 iLet BP using Dexcom G5 CGM Glucose target: 120 mg/dl Fiasp PumpCart (Novo Nordisk)	RCT to compare default insulin PK settings (tmax = 65 minutes) with faster PK settings (tmax = 50, 40 and 30 minutes). Faster PK setting was escalated over three cohorts of 8 subjects Remote telemetric monitoring	Pending analysis.	
7	2019	Bihormonal Crossover Study IDE: G190028	Outpatient, unsupervised at home 10 adults aged 18 and older 7 days 1,680 hours	Insulin-only Gen 3 iLet BP using Dexcom G5 CGM Glucose target: 120 mg/dl Insulin lispro (Eli Lilly) & Insulin aspart (Novo Nordisk)	RCT to compare insulin-only with bihormonal using dasiglucagon, testing bihormonal iLet for the first time Remote telemetric monitoring	Insulin-only: 149±13 mg/dl, 1.25%	The results of this study confirm the insulin-only iLet BP at the lowest target glucose set point is safe and effective in the outpatient setting, consistent with results achieved in the iphone BP studies.

8	2019	MultiPK BP Study IDE: G180254	Outpatient, unsupervised at home 6 adults aged 18 and older completed to date 3 arms, 7 days each 3,024 hours	Insulin-only Gen 3 iLet BP using Dexcom G5 CGM Glucose target: 120 mg/dl Insulin lispro (Eli Lilly), Insulin aspart (Novo Nordisk) & BioChaperone lispro (Adocia)	RCT with one week each on insulin lispro, insulin aspart and BioChaperone lispro using the default tmax setting (65 minutes) for all three insulins Remote telemetric monitoring	Pending analysis, experiments ongoing

1 – Total device exposure is calculated based on cohort size used in the study analysis and includes insulin-only arms only

Pediatric iPhone bionic pancreas (BP) and iLet BP studies – insulin-only and bihormonal (ages 6 to < 18 years)

	Year	Name of Study	Setting, Population, Device exposure[1]	BP Configura-tion, Set Points tested, Medications used	Protocol Description	Results: Mean CGM glucose, % < 60	Conclusions
1	2013	2013 Summer Camp Study IDE: G130065	Supervised summer camp setting 32 adolescents aged 12 to 20 5 days 3,840 hours	Bihormonal iPhone BP with two Tandem t:slim pumps and Dexcom G4 AP CGM Glucose target: 100 mg/dl Insulin lispro (Eli Lilly) & Glucagon (Eli Lilly)	RCT comparing bihormonal iPhone BP with usual care at camp Remote telemetric monitoring	BP: 142±12 mg/dl, 1.3% UC: 158±27 mg/dl, 2.2%	The results of this study demonstrated that under stressful conditions, the bihormonal BP was safe and effective to use in adolescent children.
2	2014	2014 Summer Camp Study IDE: G130065	Supervised summer camp setting 19 pre-adolescents aged 6 to 11 5 days 2,280 hours	Bihormonal iPhone BP with two Tandem t:slim pumps and Dexcom G4 AP CGM Glucose target: 100 mg/dl Insulin lispro (Eli Lilly) & Glucagon (Eli Lilly)	RCT comparing bihormonal iPhone BP with usual care at camp Remote telemetric monitoring	BP: 137±11 mg/dl, 1.2% UC: 168±30 mg/dl, 2.8%	The results of this study demonstrated that under stressful conditions, the bihormonal BP was safe and effective to use in pre-adolescent children