FEASIBILITY OF OUTPATIENT AUTOMATED BLOOD GLUCOSE CONTROL WITH THE ILET BIONIC PANCREAS FOR TREATMENT OF CYSTIC FIBROSIS RELATED DIABETES

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Abbreviations	
ADA	American Diabetes Association
BG	Blood Glucose
BHBP	Bihormonal Bionic Pancreas
BMI	Body Mass Index
BP	Bionic Pancreas
BU	Boston University
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis Related Diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CGM	Continuous Glucose Monitor
CHF	Congestive Heart Failure
DPP-4	Dipeptidyl peptidase-4
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
GLP-1	Glucagon-like peptide-1
GUI	Graphical User Interface
HCG	Human Chorionic Gonadotropin
IOBP	Insulin-only Bionic Pancreas
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	Intrauterine device
IV	Intravenous
MDI	Multiple Daily Injections
OCP	Oral Contraceptives
PK	Pharmacokinetics
RDA	Recommended Dietary Allowances
SC	Subcutaneous
SGLT-2	Sodium-glucose co-transporter-2
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TIA	Transient Ischemic Attack
UC	Usual Care
UI	User Interface

Table 1. *Abbreviations*

Visit Procedures	Screening	Start Visit	Check In Call 1	Check In Call 2	Crossover Visit	Check In Call 3	Check In Call 4	Final Visit
Days from start visit (window):		*0*	*2 (±1)*	*5 (±1)*	*14* (+2)*	*16# (±1)*	*19# (±1)*	*28# (+2)*
Informed Consent	X							
Eligibility Assessment	X							
Height	X							
Weight	X	X			X			X
Urine pregnancy test	X	X			X[1]			
Adverse Event querying		X	X	X	X	X	X	X
Psychosocial questionnaires		X			X			X
Sputum collection		X			X[2]			X[2]
CGM insertion		X			X[3]			
iLet initiation		X[4]			X[4]			
Data download					X			X

* visit may be split into separate shutdown and start up visit; start up visit must occur within 14 days of shutdown visit
# may differ based on length of window between study arms

1 if separate startup visit occurs 14 days after shutdown visit
2 if sputum wasn't collected at start visit and this is the next in person visit
3 if applicable, based on randomization
4 as needed

Table 2. *Visit Procedures*

1. Background and Significance

1.1 Background

Cystic fibrosis (CF) affects 1 in 2000 to 3000 live births in the United States and is the most common life-shortening autosomal recessive disease among those of Northern European ancestry. Clinical management of cystic fibrosis continues to improve and there has been a substantial increase in life expectancy(1). As a consequence, there has been an increase in prevalence of non-pulmonary sequelae of CF that can negatively impact outcomes. Cystic fibrosis-related diabetes (CFRD) is the most common co-morbidity of cystic fibrosis, affecting up to 50% of adults with CF (2), and has been associated with worsening decline of pulmonary function and increased mortality (3, 4).

CFRD pathogenesis is related to abnormal chloride channel functioning which results in thick viscous secretions that cause obstruction and damage to the exocrine pancreas. This damage leads to progressive pancreatic fibrosis, which subsequently can disrupt and destroy pancreatic islet cells (both beta and alpha cells) leading to both a decrease of insulin and glucagon secretion (5). Islet cell destruction is further intensified by insulin resistance from stress hormones and pro-inflammatory cytokines (5). Data also suggest that cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction may also directly contribute to glucose intolerance (7-9).

Although CFRD shares characteristics of both type 1 and type 2 diabetes, CFRD is a unique disease with a distinct clinical course, management approach, and complications. Unlike both type 1 and type 2 diabetes, morality in those with CFRD is nearly always secondary to pulmonary failure rather than from the macrovascular or microvascular disease (10). Distinct from other forms of diabetes where glucose control is to primarily to prevent microvascular and macrovascular complications, the main goal treatment of CFRD is prevention of the decline of pulmonary function and improve nutritional status (11)). CFRD is associated with significant clinical deterioration. The development of CFRD directly correlates with declining pulmonary function (11-14)), potentially related to effects of hyperglycemia on airway surfaces (15, 16)sputum microbiome in patients with CF (17-19). In addition, CFRD is associated with poor nutritional status and a decline in BMI that can be reversed with initiation of insulin (2, 20). Patients with CFRD are at risk for the same microvascular complications (diabetic retinopathy, neuropathy, nephropathy and

gastroparesis) as patients with type 1 and 2 diabetes (21, 22) but do not appear to have the same risk for macrovascular complications, although this may change with continued increasing life expectancy. Early diagnosis and treatment of CFRD has been shown to improve BMI, pulmonary status, and mortality rates (2, 23-25).

Insulin therapy is the only recommended treatment for CFRD(11) . Most patients with CFRD are treated with multiple daily insulin injections, which can be a further burden for CF patients who already require complex care (11). Those with CFRD are directed to attain the same target plasma glucose goals that are recommended by the ADA for people with other types of diabetes (10). Although targets of care may be the same, there are many unique aspects of CFRD that can complicate management. The dietary recommendations for CFRD dramatically differ from those with type 1 and type 2 diabetes. Those with CF, including those with CFRD, require a high calorie diet (26). The recommendation is to consume 120-150% of the RDA for age and sex in order to maintain weight. To meet this goal, patients with CF often consume several high-carbohydrate-containing meals and snacks throughout the day (27). Frequent insulin injections are required, which can discourage patients and may reduce carbohydrate intake (28). Consumption of frequent of high carbohydrate meals and snack without appropriate insulin coverage can lead to poor control of CFRD. CFRD's relative insulin deficient state can be exacerbated by periods of increased insulin resistance. Patients with CF are at risk for infections which can cause an acute increase insulin resistance, and patients with CF are often treated with courses of glucocorticoids, both of which can result in hyperglycemia (29).

Conventional therapy for treatment of CFRD requires a relentless daily effort related to diabetes care on top of the already burdensome management of cystic fibrosis. A promising approach to meeting these challenges and achieving consistent blood glucose (BG) control consists of an integrated artificial or bionic pancreas (BP) system, comprising a continuous glucose monitor (CGM), an infusion pump (with insulin and in some configurations glucagon), and a control algorithm that actuates the pump based on CGM glucose data. Such a system may be able to automate diabetes management, vastly improve glycemic control relative to the current standard of care, and ease the additional burden of diabetes care in patients with CF.

1.2 Bionic Pancreas System

We have developed an autonomous, self-learning BP that requires only the participant's weight for initialization, then autonomously adapts to cope with the wide range of insulin requirements. This system has been studied in adults, adolescents, and pre-adolescents with type 1 diabetes (T1D), and as well as patients with insulin dependent type 2 diabetes (T2D) (30-36). The BP obviates the need for the patient to know their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate-to-insulin ratios, basal rates, or insulin correction factors. We propose utilizing this system for the management of CFRD.

The core technology is the insulin controller, which orchestrates all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control algorithm, which bases insulin doses on glucose data and insulin absorption and clearance kinetics. The bionic pancreas algorithm was the first to incorporate insulin pharmacokinetics (PK) into the algorithm by augmenting the insulin controller with a mathematical formulation for estimating the concentration of insulin in the blood and predicting its future concentration. It is essential to compensate for the slow absorption rate of SC insulin analogs (peak time in blood of 30–90 min, clearance in 4–8 hr), and to enable the algorithm to refrain from stacking and overdosing insulin. Furthermore, the MPC algorithm automatically adjusts its insulin-dosing aggressiveness continuously and in real-time to different insulin needs between individuals and variable needs within the same individual.

Running in parallel with the MPC algorithm is an algorithm that automatically modulates basal insulin delivery over multiple time scales, and another algorithm that automatically adapts insulin doses in response to optional meal announcements. Unlike current insulin pumps, and all of the other insulin-only control algorithms of which we are aware, the adaptive basal insulin algorithm obviates the need for the user to set, or even know, his or her basal-rate profile. Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, such as might occur over a period of hours, days, or weeks (e.g. circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or as might occur over a period of months or years due to developmental changes (e.g. hormonal changes that occur during puberty or menopause). The 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. The bihormonal configuration of the BP also includes a proportional-derivative algorithm governing SC micro-doses of glucagon to help prevent impending hypoglycemia. Glucagon dosing is based on the glucose level and rate of descent. It could occur preemptively even if glucose is above range and it includes a feedback term to account for the pending effects of recent glucagon doses.

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

1.2.1 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 announce-ments (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 **Table 3** and described with more detail in Appendix A.

	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 BP configurations testing different glucose target set points in addition to

	Year	Name of Study	Setting	N	Duration of Use	BP Configuration	Monitoring	Protocol Description
								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

Table 3. *iPhone BP System Studies*

1.2.2 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 **Table 4** and described in Appendix A.

	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
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	
5	2019	MultiPK BP Study	Outpatient, unsupervised at home	Ongoing	3 arms, 7 days each	Insulin-only	Remote telemetric monitoring	

***Table 4**. iLet BP System Studies*

1.3 The Bionic Pancreas in Participants with CFRD

We have obtained IRB and FDA approval for a protocol evaluating the BP in adults with CFRD (IDE G150130/S009) with the previous phone-based configuration of the bionic pancreas. We completed a pilot study of three adult participants with CFRD with the BP in both insulin-only (IOBP) and bihormonal (BHBP) configurations compared to Usual Care (UC) in a three-week, random-order, crossover trial (37). The results of the study are summarized in **Figure 2**. The mean glucose was nominally lower in both the IOBP (149±10 mg/dl) and BHBP arms (139±15 mg/dl) relative to the usual care with insulin pump or multiple daily injection therapy (159±56 mg/dl). During the BHBP arm, all participants achieved a mean

consistent with a hemoglobin A1C under the ADA target, compared to two participants in the IOBP arm and one participant during UC. The % of time <54 mg/dL was low in all three arms (0.2%, 0.5%, and 0.3% respectively) without statistically significant differences between arms for any participant ($p \geq 0.45$) according to time series analysis. No adverse events were reported during the study period. These test participants found the BP easy to use and surveys suggested improved satisfaction and reduced burden of diabetes treatment. Notably, participants rarely announced meals during both BP arms, instead relying on fully automating glycemic control. This provides an example of the reduction in effort that the bionic pancreas may provide. Participants also reported eating more carbohydrates during the BP arms because they felt they could do so while still having good glycemic control. Although this would not be ideal in some patient populations, increased carbohydrate intake combined with adequate insulinization could result in desirable weight gain for CF patients. In addition, one of the participants studied in this pilot study was recently diagnosed with CFRD within the past year and had significant residual beta cell function, as indicated by a low insulin requirement of 0.19 units/kg/day. The fact that the BP worked well for this participant supports the robustness of the dosing algorithm in the setting of significant endogenous insulin production and suggests that it would perform similarly well in patients with lower insulin needs.

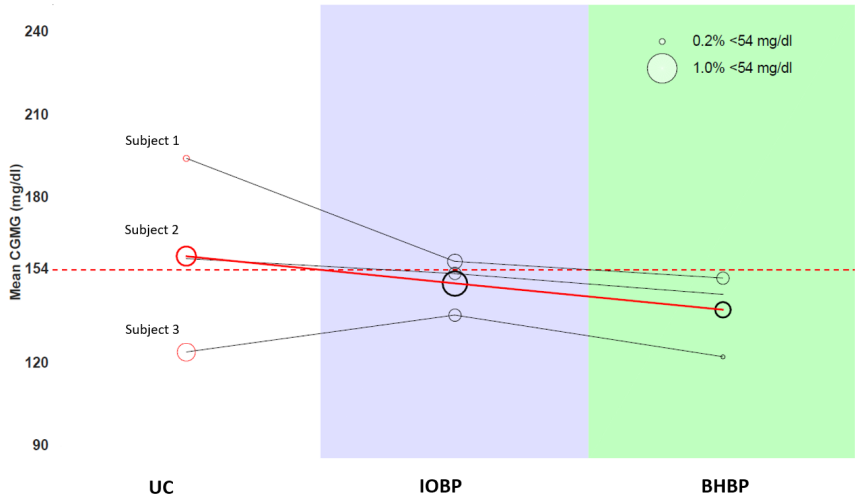

Figure 2. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP bihormonal BP, and usual care comparator arms. Mean CGM glucose levels for each participant in each arm (shown as a black circles) are connected by black lines. For each participant, the circle diameter is proportional to the percentage of CGM glucose values < 54 mg/dl. The heavy circles and heavy red line represent the group means. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal 154 mg/dl (HbA1c <7%).*

1.4 Rationale and Potential Benefits

The experiments to date in human participants with type 1 diabetes have demonstrated the practicality of a wearable automated, bionic pancreas control system for robust glucose regulation using continuous glucose monitoring devices as input to the controller. Given this data in those with type 1 diabetes, we propose to evaluate the bionic pancreas for glycemic control in those with CFRD. We have shown that bionic pancreas is capable of achieving good BG control automatically with minimal hypoglycemia in the face of unrestrained meals and exercise and with trivial patient input (electively announcing meals) in both its insulin-only and bihormonal configurations. Control was particularly good at night, achieving mean BG values in the normal range with almost no hypoglycemia. The studies to date have paved the way for longer-term out-patient studies in a broader population.

The iLet bionic pancreas BG control system was able to provide automatic BG regulation and reduce hypoglycemic episodes. Additionally, the system spares the wearer the relentless tasks of carbohydrate counting, frequent BG monitoring, estimating the effects of specific meals and exercise activity on blood glucose levels, and manual drug administration, which are inexact, demanding, aggravating, and require continuous diligence and vigilance and increases the burden of an already complex management of those with CF. If the bionic pancreas achieves the same degree of glycemic control as those we have seen in

participants with type 1 diabetes, we hypothesize that it may reduce the deleterious complications of CFRD.

The current study is designed to test the capabilities of the insulin-only configuration of the iLet bionic pancreas system in adults with cystic fibrosis related diabetes while they go about their normal daily routines. The primary purpose of this pilot is to assess the feasibility of use in management of CFRD. The logical endpoint in the evolution of exogenous insulin therapy is to treat CFRD with an automated, integrated closed-loop glucose-control system.

2. Hypothesis and Specific Aims

We hypothesize that the wearable iLet bionic pancreas system in the insulin-only configuration can provide superior BG control in participants with CFRD compared to usual care. We hypothesize that glycemic control as measured by CGM time in target range 70-180 mg/dl will be superior with the bionic pancreas compared to usual diabetes care. The specific aims of the study are:

Aim 1. To conduct an outpatient study testing the insulin-only configuration of the iLet bionic pancreas in participants ≥10 years of age with cystic fibrosis and CFRD in a random-order crossover study versus usual care.

The study will consist of two 14-day study arms in random order: one using the insulin-only iLet bionic pancreas and one where the participants follow their usual diabetes care. We will include patients who manage their CFRD with either an insulin pump or multiple daily injections of insulin. We will use the default target glucose for the insulin-only iLet, 120 mg/dl, to start. The glucose target may be adjusted upward or downward, which will only be done in consultation with the study staff and based on the participant's glycemic control.

The primary outcome will be the percentage of time in glucose target range, 70 – 180 mg/dl in the last twelve days of each arm. The first two days will be excluded from the primary outcome and analyzed separately to allow for adaptation of the algorithm and washout of any long-acting insulin. The last twelve days are expected to more be predictive of outcomes in long term use.

Aim 2. To document the satisfaction of participants with the iLet bionic pancreas versus usual care. Questionnaires will be administered at the beginning of the study and the end of each arm to gather data on attitudes towards bionic pancreas BG control, quality of life and treatment satisfaction. We hypothesize that treatment satisfaction with the BP will be superior to usual care.

Aim 3. To explore the composition of sputum microbiome in participants with CFRD. We hypothesize that patients with CFRD have a unique microbiome that explains their increase in CF exacerbations. This protocol will serve as an exploratory Aim to provide preliminary data for future studies.

3. Participant Enrollment

3.1 Participant Recruitment

Patients will be recruited from the patient population of co-investigator Melissa Putman, MD, who sees patients in the MGH Cystic Fibrosis clinic, Dr. Putman is the CF endocrinologist at the MGH Adult CF Program and the Pediatric program at Boston Children's Hospital and has direct access to patients and resources at both centers. We reviewed the number of patients seen in the MGH CF Center who would be eligible for participation in this study. Of the 196 patients with CF ≥18 years old who receive their care at MGH, 45 have CF-related diabetes and have not had a prior lung transplant, suggesting that roughly 45

patients with CF seen at MGH would be eligible for enrollment in the study, not counting patients newly referred to the center (approximately 10 – 15 per year). Removing the exclusion criteria for patients with a history of lung and liver transplant will give us access to an additional 15-20 adults and children with CFRD.

Study recruitment methods may consist of the following:

- IRB approved paper and digital advertisements, brochures, postcards, flyers and/or newsprint advertisements
- Culling of pre-existing databases held by the investigators of patients who have expressed interest in the bionic pancreas.
    - Those identified will be sent one of the aforementioned IRB approved materials via US mail or e-mail, or contacted via phone, and will be provided information about how to complete the consent process.
- Contacting participants enrolled in an approved CFRD Screening Protocol (PHRC IRB # 2020P003149)
- Research Invitations: Patient Gateway Personalized Letters
    - Study staff will review medical records to identify potential participants that meet inclusion and exclusion criteria. Research invitations will be sent electronically using the EPIC Patient Gateway system or via US mail to participants who have not opted out of receiving invitations and meet basic inclusion criteria based on medical record review. These letters will include an opt out period, after which the study team may call participants to gauge their interest in participating if they have not previously indicated they did not wish to be contacted.

All recruitment materials will be approved by the IRB prior to their implementation.

Every attempt will be made to arrange for informed consent to be obtained by an investigator that is not directly involved in the participant's clinical care. If the physician who first discussed the study with the potential participant is their own physician, that physician will be instructed to give the participant the consent form to take home and review and to tell the participant to call back if they wish to participate. Additionally, a different member of the research team that is not involved in the participant's care will contact the potential participant after the investigator has presented the study to them.

Prospective participants will be briefed by a study staff member regarding the study procedures and the inclusion and exclusion criteria. Informed consent will not be obtained at this time. Potential participants will be sent an informed consent document by mail, fax, or e-mail to review prior to their initial consent and screening visit.

3.2 Number of Participants

It is expected that 20 adult participants ≥18 years and up to 10 pediatric participants 10 – 17 years will complete the main study. We expect that the experiments and analysis can be accomplished over a period of 1 to 2 years. Up to 60 participants will be enrolled. The bound is based on the expectation that some volunteers will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or participant withdrawal).

3.3 Enrollment and Consent Procedures

Potential participants, and their parent/guardian if applicable, will be asked to read and review the consent form. Once potential participants, and their parent/guardian if applicable, have had time to review the

consent document, they will meet with a study provider (MD or NP) that will explain the study, answer any questions, and administer informed consent. All participants and parents/guardians 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. The participants will be encouraged to discuss participation with their family and medical providers. If a nurse practitioner is administering the consent, participants and/or their parents/guardians will be offered the chance to speak with a study MD if they wish. A licensed physician investigator will be available to speak with the participants during the consent process.

For potential participants 10 – 17 years old, assent will be obtained. Consent from only one parent/guardian will be required for pediatric participants. Participants that turn 18 years old during the study will provide informed consent at the next available opportunity.

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 Enterprise or Healthcare Secure Zoom. For consent obtained virtually, study staff will implement the Mass General Brigham REDCap eConsent.

Study staff will answer any questions that the participants may have during their participation. They will share any new information in a timely manner that may be relevant to the participant's willingness to continue participating in the trial. The participants may choose to discontinue their participation at any time.

4. Eligibility and Exclusion Criteria

To be eligible for the study, a participant must meet all of the following inclusion criteria and none of the exclusion criteria at the time of screening. No participants will be excluded on the basis of gender or race. An equal distribution of gender is anticipated. A study goal will be to include a variety of races/ethnicities and a spectrum of participants using different diabetes management methods.

4.1 Inclusion Criteria

- Age ≥ 10 years and have had a diagnosis of CFRD managed using either an insulin pump or multiple daily injections (MDI).
    - If < 18 years of age, they must have someone over 18 years of age who lives with them (adult guardian) and has knowledge of hypoglycemia treatment
- Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 1 month prior to screening, with no plans to change regimen before or during the study
- Mean CGM glucose ≥125 mg/dl as determined by the participant's personal CGM 30-day download if CGM is used as part of their usual care. If the participant does not use CGM, hemoglobin A1c ≥ 6% within the last 6-months from available medical records will be required.
    - Study participants who are transplant recipients must have a hemoglobin A1c < 9%
- Minimum insulin requirement of ≥0.1u/kg/day. To ensure that participants with a wide range of insulin requirements are included, participants whose insulin requirement is <0.3u/kg/day will be limited to approximately ~1/3 of the enrolled ≥18 year old adult cohort.
- Willing to wear iLet infusion sets and one Dexcom CGM sensor and change sets at least every 3 days in the iLet arm
- Assent will be obtained for patients <18 of age
- The Investigator believes the participant can safely use the iLet and will follow the protocol

4.2 Exclusion Criteria

- Unable to provide informed consent (e.g. impaired cognition or judgment)
- Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory, unable to speak and read English)
- Current participation in another clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the participant
- Current use of a non-FDA approved closed-loop or hybrid closed-loop insulin delivery system
- Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the next 3-months, or sexually active without use of contraception
    - Participants must use acceptable contraception for the two weeks prior to the study, throughout the study and for the two weeks following the study.
    - Acceptable contraception methods include:
        - Oral contraceptive pill (OCP)
        - Intrauterine Device (IUD, hormonal or copper)
        - Male condoms
        - Female condoms
        - Diaphragm or cervical cap with spermicide
        - Contraceptive patch (such as OrthoEvra)
        - Contraceptive implant (such as Implanon, Nexplanon)
        - Vaginal ring (such as NuvaRing)
        - Progestin shot (such as Depo-Provera)
- History of hypoglycemic seizures (grand-mal) or coma in the last year
- Unable to avoid hydroxyurea for duration of study (interferes with accuracy of Dexcom G6 CGM)
- Unable to avoid taking higher than the maximum dose of acetaminophen from all sources for the duration of the study (interferes with accuracy of Dexcom G6 CGM)
    - Adult: 1 g every 6 hours, up to 4 g every 24 hours
    - Pediatric: 75 mg/kg/day in up to 5 doses, not to exceed 4000 mg/day
- Have started or stopped a CFTR modulator in the past 4 weeks.
- Established history of allergy or severe reaction to adhesive or tape that must be used in the study
- Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) or non-insulin injectable (GLP-1 agonists, amylin) anti-diabetic medications
- History of severe liver disease, including cirrhosis or portal hypertension
- Anticipated lung transplant (on transplant list)
- If the participant has already received a lung or liver transplant:
    - Hemoglobin A1c < 9%
    - Doses of steroids and/or calcineurin inhibitors have been stable for one month prior to enrollment and are not expected to change significantly over the course of the study
- No acute pulmonary exacerbation or hospitalizations within the past 4 weeks or treatment with IV antibiotics in the past 4 weeks.
- History of a complete pancreatectomy
- Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study
- Presence of a medical condition or use of a medication that, in the judgment of the investigator, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following:

- Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or other substance abuse (use within the last 6 months of controlled substances other than marijuana without a prescription)
- Unwilling or unable to refrain from drinking more than 2 drinks in an hour or more than 4 drinks in a day during the trial
- Unwilling or unable or to avoid use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study (use of beta blockers will be allowed as long as the dose is stable and the participant does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator)
- Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation.
- History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
- Renal failure requiring dialysis
- Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
- Congestive heart failure (established history of CHF, lower extremity edema, paroxysmal nocturnal dyspnea, or orthopnea)
- History of TIA or stroke
- Seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants
- History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment

- 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 a 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 trial

4.3 Eligibility Assessment and Baseline Data Collection

Potential participants will be evaluated for study eligibility through the elicitation of a medical history and review of their medical records. This will be conducted virtually via videoconferencing or in person.

4.4 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, cystic fibrosis history and management, other past and current medical problems, past and current medications, and any known allergies.

4.5 Screening Testing and Procedures

Screening Visit (visit 1)

- Once informed consent/assent has been obtained, all participants will have a screening visit to confirm eligibility.
- The participant will be interviewed, and the case report form will be completed by study staff to establish whether the participant is eligible to continue with the screening.
- 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, cystic fibrosis history and management, other past and current medical problems, past and current medications, and any known allergies.
- A urine pregnancy test will be performed in female volunteers who are post-menarche, premenopausal and have not been surgically sterilized. If the test is positive, the volunteer will be informed of the result and the visit will be ended.
    - *If the visit is being conducted virtually, a pregnancy test will be provided to the participant and verbal report of the result will be acceptable.*
- Height and weight will be measured.
    - *If the visit is being 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.*

4.6 Screen Failures

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

4.7 Screening data to be obtained after consent

- Age
- Sex
- Race and ethnicity
- Date of diabetes diagnosis
- Date of last menstrual period in female volunteers
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription)
- Medical questionnaire (medication use, oral glucocorticoid exposure, hospitalizations, pulmonary exacerbations)
- Chart review for most recent FEV1, CFTR genotype, number of CF exacerbations in the preceding year, and any interval HbA1c levels obtained for clinical purposes
- Insulin regimen, including type of insulin and/or pump used and duration of injections or pump use
- Average total daily dose of insulin in the last 30 days for participants using an insulin pump or smart pen – for comparison with insulin dosing during the usual care and bionic pancreas arms of the study
- Usage of CGM, if any (type of CGM, days per month worn, usage of data, whether insulin is dosed based on CGM alone, alarm settings).
- Mean CGM glucose, time with glucose <54 mg/dl, time with glucose <70 mg/dl, and time in the 70-180 mg/dl range for the most recent 30- and 90-day periods available
- Height and weight (via in-clinic measurement, chart review or self-report)
- Urine HCG (post-menarche and pre-menopausal females)

5. Drugs

The study involves subcutaneous administration of insulin lispro (Humalog, Lilly) or insulin aspart (Novolog, Novo Nordisk). These are commercially available by prescription and are indicated for adult and pediatric patients with diabetes, but not for use in a bionic pancreas. Participants will be provided with and use whichever analog of rapid acting insulin they usually use during all arms of the study. Participants who use Apidra or Fiasp will be offered Novolog or Humalog. The default t_{max} setting of 65 minutes will be used for all participants using the iLet and will not be adjusted during the study.

The control system can administer bolus doses of each drug up to every five minutes. A single automated bolus of insulin will not exceed 3 units per 5-minute dose [30 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 bionic pancreas can administer as little as 0.10 µl (0.01 units of U-100 insulin) in single programmable bolus doses.

6. Devices

Continuous glucose monitor: One transcutaneous glucose sensor for the Dexcom G6 will be inserted in the subcutaneous tissue. The Dexcom G6 CGM will provide input to the iLet bionic pancreas and, in the Usual Care arm, be used to collect data on the primary outcome. The sensor is powered by the battery within the transmitter that clips to the sensor. The whole assembly is held to the skin with an adhesive patch and communicates wirelessly via Bluetooth Low Energy with iLet bionic pancreas. If the sensor fails for any reason during the experiment, it will be replaced promptly. A blinded version of the device in which glucose values are masked, the Dexcom G6 Pro, will be used during the Usual Care arm for participants who do not typically wear a Dexcom G6 CGM.

InPen: The InPen is an FDA approved insulin smart pen that is compatible with insulin lispro (Humalog, Lilly) or insulin aspart (Novolog, Novo Nordisk). The InPen is currently approved for adults and children. Participants who are on multiple daily injections in their usual diabetes care will be provided an InPen for use of insulin delivery in the Usual Care arm with the same insulin analog they use during their usual care. This will allow us to accurately collect data on insulin usage during the Usual Care arm.

iLet Bionic Pancreas: The iLet bionic pancreas system receives the same CGM glucose values from the Dexcom transmitter worn on the body. The iLet has an integrated graphical user interface (GUI) and touchscreen display that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin delivered by the control algorithm. The GUI can also be used to input optional meal announcements, designating the type of meal as Breakfast, Lunch, or Dinner, and the size of the meal as Usual for Me, More, or Less. This will trigger a partial meal-priming bolus, the size of which will adapt throughout the course of the trial to meet a target of 75% of the insulin needs for that size and mealtime.

The factory-set Usual glucose target level for the bionic pancreas in the insulin-only mode is 120 mg/dl. The glucose target can be changed by the user to be Lower (110 mg/dl) or Higher (130 mg/dl) target. This can be done on a permanent basis, or for a recurring overnight period. Participants will be trained not to change the permanent target without consulting with the study team. A change in the permanent target will be made only if, in the judgement of the investigator, this is important for participant safety. For example, the permanent target may be lowered after 72 hours if the mean CGM glucose is >154 mg/dl and there is minimal hypoglycemia (% time <54 mg/dl is <1% and there is minimal need for carbohydrate treatment for hypoglycemia). Similarly, the permanent target may be raised in an individual participant if there is excessive hypoglycemia (% time <54 mg/dl is >1%, there is frequent need for carbohydrate treatment for

hypoglycemia, or an episode of severe hypoglycemia). This is consistent with the intended clinical use of the iLet, in which a health care provider will consult with the user on the appropriate target.

The bionic pancreas will be configured to use the default t_{max} setting, 65 minutes, for all participants regardless of the type of insulin used and will not be adjusted during the study.

During periods when the Dexcom CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated, the GUI can be used to manage meal boluses as usual and will administer correction boluses in response to entered BG values, During these times the control algorithm will determine and direct the administration of insulin basal rates either based on the participant's weight early in the course 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 will also administer insulin in response to any entered BG values just as if they were Dexcom CGM values.

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

iLet Infusion Set: While in the iLet arm of the study, participants 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 3 days.

iLet Ready-to-Fill Insulin Cartridges: Participants in the iLet arm will be provided with iLet Ready-To-Fill insulin cartridges for the system and a syringe for transferring insulin from a vial to the cartridge. Study staff will work with the participants to ensure they are comfortable with the fill process. Participants will be instructed to replace their insulin cartridge as needed or a minimum of every 3 days.

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

Abbott Precision Xtra Ketone Meter: The Precision Xtra is FDA approved and commercially available. Blood ketone measurements for hyperglycemia management will be obtained via finger stick with the Precision Xtra ketone meter in the bionic pancreas arm.

7. Experimental Procedures and Data Collection

7.1 Randomization of Study Visit Order:

Once the participant has been enrolled and eligibility has been established, participants will be randomized to one of the possible 2 visit-order schedules. We will schedule in-clinic visits so that infectious disease isolation protocols for these participants are not breached.

7.2 Study Start Visit (Visit 2)

Participants will receive one-on-one training on the operation of all study devices. Both the participant and

the study staff must be satisfied that the participant is comfortable with the operation of all study devices before he/she begins the study. Additional training sessions may be arranged as needed.

Training on the use of the glucose and ketone meters, the iLet, insertion of infusion set, insertion of CGM sensors, recognition of failed infusion sets, and the ketone action plan will only be performed by study personnel with the appropriate training and experience, such as a Certified Diabetes Educator, Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician.

If the visit is being conducted virtually, all supplies will be provided to the participant in advance of the visit, and the study team will ensure the participant has the capability to join a video call, providing assistance or equipment as needed.

- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility.
- Participants will complete their baseline psychosocial questionnaires. Detailed information about the psychosocial questionnaires can be found in Appendix B.
- The body weight of the participant will be documented.
    - *If the visit is conducted virtually, the participant will measure body weight at home and a verbal report of the participant's weight will be acceptable. A scale will be provided for participants who do not already have a scale at home*
- A urine pregnancy test will be performed in female volunteers. If the test is positive, the volunteer will be informed of the result and the visit will be ended.
    - *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 2 ml of sputum for microbiology testing.
    - Sputum is routinely collected during outpatient visits for this clinical population in order to perform microbiology testing including identification of pathogen and determining antimicrobial resistance patterns. Most patients with cystic fibrosis or bronchiectasis produce large amounts of sputum. At the initial study visit, we will request ~½ teaspoon of sputum. Sputum will be aliquoted into 1) a preservative such as RNA/DNA Shield (Zymo R1100-50) to prevent further microbial growth and to stabilize nucleic acids for shotgun metagenomics and transcriptomics studies; 2) sterile specimen container for metabolomics and culture-based microbiological studies.
    - *If the visit is conducted virtually, sample collection will be skipped. Sputum may be collected at the next in person visit.*
- The participants will place a Dexcom CGM sensor and study staff will confirm they are doing it properly.
    - If participants use a Dexcom G6 CGM as part of their standard care, they will continue to use the Dexcom G6 CGM during the iLet bionic pancreas arm and the Usual Care arm.
    - If the participant does not use a CGM, or uses a different type of CGM, they will use the Dexcom G6 Pro CGM during the Usual Care arm and the Dexcom G6 CGM during the iLet bionic pancreas arm.
- Study staff will provide supplies and review the study procedures.

For the iLet bionic pancreas arm:

- Study staff will supervise the setup of the insulin cartridge and infusion set.
- The control algorithm will be initialized with only the participant's weight.
- The participant's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed. For participants using multiple daily injections of insulin, they will take their

insulin as usual prior to starting the bionic pancreas, then stop taking any insulin other than delivered by the bionic pancreas once it is started.

- Study staff will verify that the iLet bionic pancreas is functioning properly prior to ending the study visit.
- The participant will be asked to demonstrate their competency by placing at least one practice infusion site and one site in themselves and "teach back" to confirm that they adequately understand when to replace a set. Study staff will be trained that participants who have not previously used an insulin pump or who have not previously used the study infusion set may need additional time for training on pump-related tasks, such as placement of infusion sets and how to recognize when an infusion set needs to be replaced.
- Study start visits for participants who may need more assistance with the iLet and the infusion set, and/or participants who live alone should be scheduled early in the day so that there is sufficient time before bedtime to recognize if the first infusion set is not performing well. Study staff may follow up with participants that need additional support before the end of the first day to confirm everything is working and the participant is comfortable.

7.3 Check In Phone Calls (Visits 3 & 4)

Study staff will call participants at 2 days (±1 day) and 5 days (±1 day) from the start of the arm. Phone contacts will be made according to the contact window, regardless of the day of the week.

Study staff will:

- Review any adverse events or device issues experienced
- Answer any questions the participant may have
- Bionic Pancreas arm:
    - Review glucose control
    - Review study policies and procedures related to glucose management and inquire about any hypoglycemic or hyperglycemic events
    - Review any need for a change in the glucose target setting
    - Assess the participant's ability to follow the protocol and use the device

Study staff may also contact participants in the usual care arm using the Dexcom G6 Pro CGM sensor 10 days after sensor placement, to remind them to replace the study sensor if they haven't already and provide assistance as needed.

7.4 Crossover Visit (Visit 5)

- This visit will occur 14 (+2) days from the start of the first arm. This visit will serve as the shutdown visit for the first arm and the startup visit for the second arm of the study.
- Participants will return to the clinic and answer the post questionnaires for the study arm or will complete the study visit virtually via Zoom.
- The body weight of the participant will be documented.
    - *If the visit is conducted virtually, the participant will measure body weight at home and a verbal report of their weight will be acceptable.*
- Study devices will be downloaded as applicable (CGM, glucometer, InPen, iLet).
    - *If the visit is conducted virtually, device downloads may be skipped. Participants will ship the iLet back to the study site using provided shipping materials for later downloading.*
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility and will document any adverse events that may have occurred since their last study visit.

    - Study staff will specifically ask participants if they had any infusion site or CGM sensor site reactions or other skin irritation during the arm and will document any reactions.
    - Any changes to medications or medical history and any adverse events that may have occurred since their last study visit will be documented.
- Study staff will review all study procedures and policies (including the use of the Dexcom and Contour Next One, and the iLet) and the upcoming visit schedule.
- If the participant is switching to the iLet bionic pancreas arm:
    - The participant will remove their Dexcom G6 Pro sensor if applicable. The participant will a Dexcom G6 CGM sensor if necessary.
    - Study staff will supervise the setup of the insulin cartridge and infusion set.
    - The control algorithm will be initialized with the participant's current weight.
    - The participant's own insulin infusion pump will be stopped and disconnected, and its infusion set will be removed. For participants using multiple daily injections of insulin, they will take their insulin as usual prior to starting the bionic pancreas, then stop taking any insulin other than delivered by the bionic pancreas once it is started.
    - Study staff will verify that the iLet bionic pancreas is functioning properly prior to ending the study visit.
    - The participant will be asked to demonstrate their competency by placing at least one practice infusion site and one site in themselves and "teach back" to confirm that they adequately understand when to replace a set. Study staff will be trained that participants who have not previously used an insulin pump or who have not previously used the study infusion set may need additional time for training on pump-related tasks, such as placement of infusion sets and how to recognize when an infusion set needs to be replaced.
    - Study start visits for participants who may need more assistance with the infusion set, and/or participants who live alone should be scheduled early in the day so that there is sufficient time before bedtime to recognize if the first infusion set is not performing well. Study staff may follow up with participants that need additional support before the end of the first day to confirm everything is working and the participant is comfortable.
- If the participant is switching to the Usual Care arm, a provider will review the last several hours of insulin dosing and glucose trend data and assist the participant in resuming their usual care.
    - The participants will place a Dexcom CGM sensor and study staff will confirm they are doing it properly.
        - If participants use a Dexcom G6 CGM as part of their standard care, they will continue to use the Dexcom G6 CGM during the Usual Care arm.
        - If the participant does not use a CGM, or uses a different type of CGM, they will use the Dexcom G6 Pro CGM during the Usual Care arm.
- All participants will be given additional supplies as needed.
- It is preferred that the second arm be started at this visit. If that is not possible, then the startup for the second arm may be delayed up to 14 days, during which participants will revert to their own usual care. An additional visit will be scheduled for the startup of the second arm. If the startup is delayed the full 14 days, a urine pregnancy test will be repeated at this additional visit.

7.5 Check In Phone Calls (Visits 6 & 7)

Study staff will call participants at 2 days (±1 day) and 5 days (±1 day) from the start of the arm. Phone contacts will be made according to the contact window, regardless of the day of the week.

Study staff will:

- Review any adverse events or device issues experienced
- Answer any questions the participant may have

- Bionic Pancreas arm:
    - Review glucose control
    - Review study policies and procedures related to glucose management and inquire about any hypoglycemic or hyperglycemic events
    - Review any need for a change in the glucose target setting
    - Assess the participant's ability to follow the protocol and use the device

Study staff may also contact participants in the usual care arm using the Dexcom G6 Pro CGM sensor 10 days after sensor placement, to remind them to replace the study sensor and provide assistance as needed.

7.6 Final visit (Visit 8)

- This visit will occur 14 (+2) days from the start of the second arm.
- Participants will return to the clinic and answer the post questionnaires for the study arm or will complete the study visit virtually via Zoom.
- The body weight of the participant will be documented.
    - *If the visit is conducted virtually, the participant will measure body weight at home and a verbal report of their weight will be acceptable.*
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility and will document any adverse events that may have occurred since their last study visit.
    - Study staff will specifically ask participants if they had any infusion site or CGM sensor site reactions or other skin irritation during the arm and will document any reactions.
    - Any changes to medications or medical history and any adverse events that may have occurred since their last study visit will be documented.
- Study devices will be downloaded as applicable (CGM, glucometer, InPen, iLet).
    - *If the visit is done virtually, participants will ship study devices back to the site in the provided shipping materials.*
- All equipment will be collected.
- A study provider will review the last few hours of glucose trend data and insulin on board from the iLet and assist the participants in resuming their usual diabetes management.

7.7 General Study Policies for both Study Arms:

- Participants will keep their study issued Contour Next One glucometer easily accessible at all times. They will keep a glucometer, fast-acting carbohydrates, and a glucagon emergency kit easily accessible.
    - Participants will be encouraged to check their BG as often as they wish to confirm the accuracy of the Dexcom CGM and for safety, as well as to maintain adequate control of glycemia in the Usual Care arm. However, they should use the study provided glucose meter for all checks.
- Participants may not take hydroxyurea during all study arms due to potential interference with CGM sensing. Hydroxyurea is known to interfere with the accuracy of the Dexcom CGM.
- Participants are not allowed to exceed the maximum daily doses of acetaminophen from all sources during the study due to potential interference with the Dexcom G6 CGM.
    - Adult: 1 g every 6 hours, up to 4 g every 24 hours
    - Pediatric: 75 mg/kg/day in up to 5 doses, not to exceed 4000 mg/day
- Any medical advice needed by the participants during their participation, which is not directly related to BG control during the experiment, should be obtained by them in the usual manner with

their primary care physician, pulmonologist, or endocrinologist.
    - If a participant develops an illness during the experiment, they can seek medical care as usual. As long as the participant is not hospitalized, the study can be continued. If the participant is unable to eat for a period exceeding one day, they must notify study staff so that the medical staff can assess the safety of continuing in the study.
        - If a participant requires hospitalization during the experiment, they will discontinue the experiment and their participation in that study arm will end. The data collected up to their admission will not be used for the primary glycemic analysis but will be used in safety analyses. The participant can restart the study arm 2 weeks after discharge, but no later than 4 weeks after discharge.
    - If a participant has exacerbation requiring oral glucocorticoid therapy, they can continue with all study arms as long as they do not require hospital admission.
- Participants may participate in any activities that they wish, as long as they abide by the policies above.
- There are no restrictions of any kind on diet or exercise, although participants should attempt to maintain similar dietary habits and exercise habits during each arm of the study. The iLet bionic pancreas must be kept dry during exercise.
- Participants may choose to withdraw from the study at any time. If they withdraw from the study, they should contact a provider immediately. If they are wearing the bionic pancreas, a provider will help them transition to their own insulin regimen safely. If the participant wishes to discontinue use of the bionic pancreas but is willing to continue in the study, they will be asked to continue to wear the Dexcom G6 CGM for the entire study period and complete the study visits to facilitate full data collection and analysis by the intention to treat principle.
- Participants will be asked to report all hypoglycemia, carbohydrate interventions, any adverse events, time spent exercising, any unscheduled infusion set changes, alcohol use, and other questions through a daily email survey.

7.7.1 Usual Care Arm

- In the Usual Care arm, participants will continue to manage their own BG according to their usual practice. If they routinely use a CGM, they will be encouraged to continue to use it during the Usual Care period. They will be asked not to modify their insulin regimen without consulting their own endocrinologist.
- If a participant does not use the Dexcom G6 as part of their usual care, they will be given blinded Dexcom G6 Pro CGM sensors and transmitters and instructed to change it every 10 days during the usual care arm. If they do use the Dexcom G6 they will be asked to use it throughout the entire study period.
- Participants will be trained to respond to hypoglycemia and hyperglycemia according to their usual practice and best practice recommendations.
- If a participant uses multiple daily injections as part of their usual care, they will be provided with an InPen and taught how to use it.

7.7.2 Bionic Pancreas Study Arm

- Participants will keep their bionic pancreas charged, which will require charging with the study provided charger at least once per day.
- Participants will keep their study issued Precision Xtra ketone meter, extra infusion sets and insulin vials and syringes or insulin pens easily accessible at all times.
    - Participants will be required to check their ketone levels whenever their CGM has been above 300 mg/dl for 90 minutes and to notify study staff if the result is $\geq$ 0.6 mmol/l.

- During the experiment, the iLet bionic pancreas will be worn by the participant at all times to ensure good radio-frequency signal reception.
    - The bionic pancreas is not waterproof and therefore must be removed for water activities, including showering. Participants are urged to take appropriate precautions when they are disconnected from the bionic pancreas, including frequent BG checks and having carbohydrate readily available.
    - The Dexcom CGM transmitter is water resistant and can be left on for bathing and swimming.
    - Participants may not remove the iLet bionic pancreas for more than 1 hour at a time (e.g. for bathing) and may not remove it for more than 2 hours total in any 24-hour period.
- Participants will be asked to change their infusion set and cartridge every 3 days.
    - Participants will be taught to replace their infusion set if there is any doubt that it may not be working. They will be taught how to recognize potential infusion site failures.
    - Participants will be taught to replace their infusion set if their ketones are ≥ 0.6 mmol/l. More details pertaining to hyperglycemia management can be found in Appendix C.
- Participants will receive alerts if Dexcom CGM Bluetooth connection is interrupted for more than 2 hours.
    - If a Dexcom CGM sensor fails during the course of an experiment, the iLet will provide basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated by the algorithm in the same way as Dexcom CGM data and may result in administration of insulin or temporary suspension of insulin delivery. The Dexcom CGM sensor will be replaced as soon as possible and normal bionic pancreas control will resume when the new sensor is online.
- If there is a complete failure of bionic pancreas operation and it is anticipated that restarting it will take more than an hour, participants may take over their own BG control using their own insulin pump or with insulin injections until the bionic pancreas can be brought back online with the help of study staff.
    - 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 until a meeting is possible.
    - If necessary, the bionic pancreas device may be replaced. If the failure occurs at night, every effort should be made to correct the problem as soon as possible, which should almost always be possible within 12 hours.
- Participants will be asked to announce the three major meals of the day, but not snacks, to the iLet bionic pancreas. The meal announcement will consist of choosing the type of meal (breakfast, lunch, dinner) and the size of the meal relative to typical meals for that participant (Usual for me, more than or less than usual).
- The iLet bionic pancreas will generate the following CGM glucose related alarms to the participant:
    - Urgent Low Glucose: ≤55 mg/dl
    - Low Glucose: ≤70 mg/dl
    - Fall Rate Alert: CGMG <100 mg/dl and CGM trend is dropping more than 2 mg/dl/min
    - High Glucose: ≥300 mg/dl for 90 minutes
- Participants will be trained in recognizing and responding to all of these alarms.
- Participants will be trained on troubleshooting for various scenarios that could lead to a low glucose alarms. For instance, a threshold alarm could be due to true hypoglycemia, poor Dexcom CGM calibration, or a compression artifact at the site of the sensor.
    - The first step for all low glucose-related alarms will be to perform a fingerstick BG measurement.
    - If the BG measurement is not consistent with the CGM glucose, the participant will

assess the possibility of a compression artifact (they will be trained in the causes and recognition of these events). If a compression artifact is suspected, they will take steps to relieve the pressure on the transmitter. If compression is not suspected, they will calibrate the Dexcom CGM as long as there has been no food or carbohydrate intake in the last 30 minutes. If a calibration is delayed for this reason, it will be performed at the next opportunity if still necessary.
    - If the BG measurement is consistent with a low glucose: the participant will treat hypoglycemia with carbohydrates. Participants will be instructed to consider using less carbohydrate to treat or prevent hypoglycemia, since due to insulin suspension 5-10 grams is often sufficient and is less likely to lead to hyperglycemia.
- Participants will be trained on troubleshooting for various scenarios that could lead to hyperglycemia. For instance, hyperglycemia could be due to true hyperglycemia or poor Dexcom CGM calibration.
    - The first step in responding to hyperglycemia according to the CGM will be to perform fingerstick BG and ketone measurements.
    - If the BG measurement is not consistent with the CGM glucose: the participant will calibrate the Dexcom CGM as long as there has been no carbohydrate intake in the last 30 minutes and there is no steep rise or fall in glucose (>2 mg/dl/min). If a calibration is delayed for this reason, it will be performed at the next opportunity if it is still necessary. The participant will be taught to continue to monitor CGM and BG measurements to confirm accuracy and normoglycemia.
    - If the BG measurement is consistent with the CGM glucose:
        - Participants will be asked to investigate their insulin infusion set and consider replacing it, check for any occlusions along the fluid path, and check to make sure that the cartridge is not empty.
        - Study staff will recommend the participant continue to monitor their BG until it returns to normoglycemia, and to contact study staff with any questions or concerns.
    - If ketones ≥0.6 mmol/L are present:
        - Participants will be advised to change their pump infusion set and will be reminded that the BP should dose insulin accordingly.
        - Study staff will recommend the participant continue to monitor their ketone levels and BG every 60 minutes until ketones return to < 0.6 mmol/L and BG is < 180 mg/dl, and to contact study staff with any questions.
    - If participants experience persistent hyperglycemia lasting more than 2 hours, they will be instructed to contact study staff for consideration of infusion set replacement and/or correction insulin according to the above protocol.
- If the participant is a transplant recipient taking steroids and/or calcineurin inhibitors, they will be instructed to notify the study team of any dose changes while they are wearing the iLet bionic pancreas. If a change occurs, study staff will review their CGM Clarity data daily for three days after the change to make sure the iLet has adapted well. Based on this review of CGM data, a change in glucose target may be indicated.

7.7.3 Response to Hypoglycemia

- Participants in all study arms are encouraged to check their BG for any symptoms of hypoglycemia and in response to any CGM alarms.
- During the usual care arm, subjects are encouraged to treat hypoglycemia according their usual practice or according to the rule of 15s: take 15 grams of rapid acting carbohydrate and recheck in 15 minutes, then repeat as needed.
- While using the iLet bionic pancreas, participants will be instructed to consider using less

carbohydrate to treat or prevent hypoglycemia, since due to insulin suspension 5-10 grams is often sufficient and is less likely to lead to hyperglycemia.

- If a participant experiences a seizure or unconsciousness associated with hypoglycemia the PI will make a determination regarding whether it will be safe to allow them to continue in the study. A participant using the iLet bionic pancreas when they experienced severe hypoglycemia will suspend use of the device until a determination is made about the safety of having them continue.
    - If the PI concludes that the event is explainable and unlikely to recur, the participant will be allowed to continue to use the system. Further study participation of an individual participant will be discontinued if they experience more than one episode of DKA requiring hospitalization, more than one episode of seizure or unconsciousness associated with hypoglycemia, or one of each.

7.7.4 Response to Hyperglycemia

- Participants in the usual care arm will manage their hyperglycemia in their usual way. They will be taught to contact study staff at any time for assistance as needed.
- Participants in the bionic pancreas arm will be required to check ketones whenever CGM glucose is > 300 mg/dl for 90 minutes, > 400 mg/dl once, or with symptoms of diabetic ketoacidosis.
- Participants will be instructed to check their insulin infusion site and their pump or bionic pancreas for normal operation any time they experience hyperglycemia. If there is any suspicion of insulin infusion set malfunction, the site should be replaced. Participants will be taught how to recognize if an infusion set might be failing and need replacement, including recognizing that the sensor glucose is rising or not falling despite sufficient insulin being pumped by the iLet, that the sensor glucose is >300 mg/dl for more than 90 minutes, or that the sensor glucose is >400 mg/dl.
    - It will be emphasized in participant training to have a low threshold of suspicion to changing out the infusion set, and emphasizing that "when in doubt, change it out." Participants will be told that sufficient supplies are available so that they should not hesitate to change out the infusion set if they have any doubt that it is working well.
- Participants may contact a study provider (MD or NP) for advice at any time, and may contact the troubleshooting support team, as they wish. During the iLet bionic pancreas arm, they will be assisted in checking the bionic pancreas for any malfunction and correcting and problems that are found.
    - If no correctable fault is found, but there is doubt regarding the correct function of the bionic pancreas system, an entirely new backup bionic pancreas system may be brought to the participant's location by study staff.
- Detailed information about the hyperglycemia treatment plan can be found in Appendix C.
- Unlike in patients with type 1 diabetes, diabetic ketoacidosis (DKA) is very rare in patients with CFRD due to underlying residual beta cell function. However, in the unlikely case that a participant experiences diabetic ketoacidosis requiring hospitalization, the PI will make a determination regarding whether it will be safe to allow them to continue in the study. A participant using the bionic pancreas when they experienced diabetic ketoacidosis will suspend use of the device until a determination is made about the safety of having them continue.
    - If the PI concludes that the event is explainable and unlikely to recur, the participant will be allowed to continue to use the system. Further study participation of an individual participant will be discontinued if they experience more than one episode of DKA requiring hospitalization, more than one episode of seizure or unconsciousness associated with hypoglycemia, or one of each.

7.7.5 Response to Other Medical Needs

If the participant experiences any non-emergent medical concerns outside the scope of diabetes care, he or she will see their personal physician. If the participant experiences urgent or emergent medical concerns outside the scope of diabetes care and their primary care physicians, they should visit a walk-in clinic or emergency room, or if necessary, call 911.

7.7.6 Monitoring of Bionic Pancreas Performance

Beta Bionics customer support will be readily available by phone for consultation at all times during the course of the study.

7.7.7 Supervision by Study Staff

A study provider (MD or NP) will be on call at all times during the course of each experiment. All device training will be performed by study personnel with the appropriate training and experience, such as a Certified Diabetes Educator, Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician.

Study staff will emphasize to participants that they must carefully follow study policies, including the ketone action plan, for their safety. They will be instructed to call study staff whenever indicated or needed, regardless of the hour.

Study staff will be trained that if a participant calls and is found to be in Zone 2 of the Ketone Action Plan or has a plasma glucose <54 mg/dl, they must speak directly to a Certified Diabetes Educator, Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician. If a participant calls and is in Zone 3 of the Ketone Action Plan or has had a severe hypoglycemic event requiring assistance from another person, either the participant or someone with them and assisting them must speak directly to a Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician *and the Site PI must be informed*.

Whenever a participant contacts with hyperglycemia and is in Zone 2 or Zone 3 of the ketone action plan or has a glucose <54 mg/dl, study staff with the appropriate training and experience (Certified Diabetes Educator, Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician) must attempt to ascertain whether the participant has the capacity to care adequately for themselves with guidance. If based on their experience and judgement they believe the participant may not be adequately able to care for themselves without assistance, then they must either directly communicate with someone on the scene who they judge to have that capacity, or call 911, or both.

If based on their experience and judgment study staff believes that the participant needs emergency care, they should recommend to the participant that they go to an emergency department. Study staff should determine which emergency department the participant will be taken to and follow up within 15 minutes of the expected arrival time to make sure they have arrived. If the study staff calls 911 they should remain on the telephone with the participant until the ambulance arrives and speak to the Emergency Medical Technicians to provide history and determine where the participant will be taken.

Whenever a participant is sent to the emergency department, study staff must confirm that the participant has arrived at ED within an hour, and study staff member should speak with a member of the medical staff at the emergency department to confirm arrival and provide information about the reason for referral to the ED.

If a participant cannot be reached and there is concern for their wellbeing (e.g. if their Clarity data shows

hypoglycemia or severe hyperglycemia) then study staff should attempt to reach close contacts. If no contacts are available or their contacts do not succeed in reaching them quickly, then 911 should be called and a well-being check should be requested. Study staff must follow up on and document the results of the well-being check.

8. Biostatistical Analysis

8.1 Data Collected During Study Arms:

- CGM glucose (CGM glucose) every five minutes from the Dexcom CGM
- CGM data sufficiency (percentage of possible CGM values captured)
- All fingerstick BG measurements taken by the participant (meter download)
- Information collected from the daily email survey and phone calls including hypoglycemia, carbohydrate interventions, any other adverse events, any unscheduled infusion set changes or Dexcom CGM sensor changes.
- Insulin total daily dose (from the bionic pancreas, insulin pump download, or InPen)
- Timing of meal announcements and size of meals announced (in the bionic pancreas arm)
- Data from a questionnaire about attitudes and expectations regarding the bionic pancreas at baseline and on day 14 of each arm.
- Time under bionic pancreas control with CGM data in bionic pancreas arm
- Time under bionic pancreas control without CGM data in bionic pancreas arm
- Percent of time not under bionic pancreas control during the bionic pancreas arms
- List of technical faults associated with the bionic pancreas including cause and resolution
- Body weight after each arm

8.2 Outcomes

Study endpoints will be calculated for days 3 – 14 so that any long-acting insulin on board has time to clear and therefore does not affect study outcomes. Adverse events will be reported for the entire study period.

The primary analysis of the designated endpoints will be calculated on an intention-to-treat basis, including data from periods when the bionic pancreas was not in use, if available (Dexcom CGM data may not be available in some failure modes). In cases where an arm was not completed, we will use the available data from that arm in the data analysis. We will calculate percentages, means and standard deviations or medians and interquartile ranges as appropriate. We will use paired t-test for comparison of means for normally distributed data and the Wilcoxon signed rank test for non-normally distributed data. We may, in exploratory analyses, also stratify participants for secondary analyses of the pre-specified endpoints by participant characteristics including: sex, age, use of CGM in usual care, baseline A1c, usual care insulin total daily dose, body mass index, FEV1, CFTR genotype, and/or number of CF exacerbations in the preceding year. Given the potential difference in glucose variability, participants under the age 18 will also be analyzed separately from the adult cohort.

8.2.1 Primary Outcome

The primary outcome will be percentage of time in glucose target range, 70 – 180 mg/dl, as determined by CGM on days 3 – 14.

8.2.2 Secondary Outcomes

8.2.2.1 Continuous CGM outcomes for days 3 – 14:

- Key secondary endpoint:
  - Mean CMG glucose
  - Fraction of time spent with CGM glucose <54 mg/dl
- Other secondary endpoints:
  - Fraction of time spent within each of the following glucose ranges:
    - <70 mg/dl
    - >180 mg/dl
    - >250 mg/dl
  - Coefficient of variation
  - Standard deviation

8.2.2.2 Binary CGM outcomes for days 3-14:

- Participants with mean CGM glucose <154 mg/dl (estimated average glucose corresponding to an A1c of 7%)
- Participants with time <54 mg/dl <1%
- Participants with mean CGM glucose ≤154 mg/dl and time <54 mg/dl <1%
- Participants with time in range of 70 – 180 mg/dl of ≥70%

8.2.3 Other outcomes

8.2.3.1 CGM

- Primary and secondary continuous CGM outcomes will additionally be calculated for days 1 – 2
- Primary and secondary continuous CGM outcomes will additionally be calculated for days 3 – 14 for daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM)
- Binary outcomes
  - Participants with time <70 mg/dl <4%
  - Participants with mean CGM glucose ≤154 mg/dl and time <70 mg/dl <4%
  - Fraction of days that CGM was used by participants as part of their usual care
  - 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%

8.2.3.2 Non-glycemic

- Continuous outcomes:
  - From bionic pancreas:
    - Mean total daily dose (TDD)
    - Mean daily basal insulin dose
    - Mean daily bolus insulin dose
    - Mean daily correction insulin dose
    - Mean daily dose from meal announcements
    - Fraction of time bionic pancreas disconnected by the participant (self-report on daily questionnaire)

        - Number of unscheduled infusion set replacements
        - Number of unscheduled Dexcom CGM sensor changes
    - In the UC arm:
        - Insulin total daily dose (TDD) for participants using an insulin pump or smart pen
        - Mean daily basal insulin dose
        - Mean daily bolus insulin dose
    - In both arms:
        - Number of episodes of symptomatic hypoglycemia per 24 hours (reported daily by participants)
        - Amount of carbohydrate taken to treat or prevent hypoglycemia per 24 hours (reported daily by participants)
        - Change in body weight from baseline
        - Questionnaires scores on each questionnaire that is administered

8.2.3.3 Safety Outcomes

- Episodes of diabetic ketoacidosis
- Episodes of severe hypoglycemia

8.3 Power Analysis

The sample size was selected to detect superiority of the iLet bionic pancreas relative to the comparator group of usual diabetes care based on the primary outcome, percentage time of glucose in target range 70 – 180 mg/dl. The mean and SD of the CGM time in target range for the usual care group was derived from unpublished CGM data in patients with CFRD who wore a blinded CGM for 14 – 28 days. Based on the inclusion criteria of mean glucose ≥125 mg/dl (which equates to an expected A1c > 6%), patients had a time in target range of 50 ± 18% in their usual care. The iLet bionic pancreas is expected to achieve a time in rage of 70 ± 12% based on data from patients in type 1 diabetes. Nine subjects would be required in order to detect a difference between arms using a paired t-test for a power of 80% at an alpha of 5% assuming a correlation pre- and post-treatment of 0.3. We increased the sample size to up to 30 subjects (20 adult subjects and up to 10 pediatric subjects) in order to account for the potential increased variability in glycemic control in response to the bionic pancreas in patients with CFRD, to increase the exposure to the treatment to gather data on safety, and to increase power for detecting differences in secondary outcomes.

9. Risks and Discomforts

Participants may experience mild discomfort associated with the insertion of the infusion sets and the Dexcom sensor. The risk of discomfort due to insertion of infusion sets and sensors may be greater than in their lives outside the trial because it may be more infusion sets and sensors than are used in their usual care.

There is a risk of feeling light-headed from coughing to produce a sputum sample.

There is a risk of hypoglycemia. In the Usual Care arm, this risk is expected to be of the same nature and magnitude as during the participants' lives outside of the trial. In the bionic pancreas arm, this risk is expected to be the same or lower than the risk during the participants' lives outside of the trial based on data from earlier trials. All of the previous studies, albeit in type 1 and type 2 diabetes, have shown that hypoglycemia is similar in the insulin-only configuration of the bionic pancreas when compared with usual care. Based on our experience, we believe that the risk of hypoglycemia will be the same for those with

CFRD.

There is a risk of hyperglycemia. In the Usual Care arm, this risk is expected to be of the same nature and magnitude as during the participants' lives outside of the trial. In the bionic pancreas arm, this risk is expected to be similar to or less than the risk during the participants' lives outside of the trial based on data from earlier trials.

Patients with CF are frequently colonized by resistant strains of bacteria and other infectious organisms. Strict precautions will be taken to minimize the risk of transmission of infectious organisms during the study. In accordance with infection control standards set by the MGH CF Centers, all research staff will be required to utilize contact precautions including gloves and gown when in contact with participants. All rooms, supplies, and equipment will be thoroughly cleaned and disinfected after each use. Additionally, study procedures have been designed to allow for all visits to be completed virtually via videoconferencing systems. Study staff will provide Chromebooks, scales and all study supplies, as well as return shipping materials to facilitate remote visits.

Genetic studies include the risk of loss of confidentiality and risk of emotional distress of learning a new genetic diagnosis. As they are not clinically actionable, genetic data from the sputum microbiome will not be released to the participants. Thus, these risks are small. Therefore, the additional risk from the microbiome analysis is the risk of loss of privacy (discussed below).

10. Potential Benefits

Based on evidence from previous trials of the bionic pancreas, participants enrolled in the study may benefit from a better mean glucose and increased time in the target glucose range without an increase in the risk of hypoglycemia during the bionic pancreas arm.

The data derived from this study will allow us to evaluate the effectiveness of the bionic pancreas control system in use of management of CFRD. Participants will be financially compensated for participating in the study.

11. Data and Safety Monitoring

11.1 Monitoring of Source Data

Data will be captured on case report forms, and any original source documentation will be maintained in the participant's study chart or medical record. During the experiment, Dexcom CGM data will be collected in various ways. Dexcom CGM data will be automatically stored in the bionic pancreas device (from which it will be downloaded at intervals). If the participant uses the Dexcom CLARITY app the CGM data will be wirelessly streamed for storage in the cloud, which will provide redundancy in data capture and mitigate the risk of data loss. Daily emails with a link to a survey will be sent to the participant to document events, including any adverse events, in the previous 24 hours; this data will be captured in REDCap on a MGH server. All of the data will be combined in a single database in the Partners Institutional Lab Archives and will be compared against the primary data files for integrity.

A numeric code will be substituted for the participants personal identifying information in the study database, which will be password protected. The key linking the medical record number of the participant with the numeric code, along with case report forms, and all information that is personally identifiable, will be kept in a locked filing cabinet in an investigator's locked office. All electronic records will be kept in a password protected computer database. All printed computer data will be disposed of confidentially when

no longer needed. Only the study staff will have access to the study database. Participants may not withdraw from the de-identified database, but they may elect to have the key linking their medical record to the de-identified database destroyed.

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

All sputum samples will be labeled by study ID number and will be devoid of any identifying information in order to protect patient confidentiality.

The study data may be shared with collaborators at Beta Bionics, but only in a form in which all personally identifiable information has been removed. Shared data will be in the form of a database in which only a number identifies participants.

De-identified data from microbial profiling may be deposited with the National Institutes of Health (NIH) and other central repositories for genomic data. We do not believe that there will be further risks to participants' privacy or confidentiality by sharing this data. There are many safeguards in place to protect participants' information while it is stored and used for research.

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

11.2 Safety Monitoring and Reporting

This study is considered moderate risk. An external Data and Safety Monitoring Board will oversee the conduct of the study and review its results on a regular basis. The DSMB will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. Additionally, the DSMB will be informed of any severe or unexpected adverse events, including but not limited to any severe hypoglycemia or DKA, within 72 hours. A final DSMB meeting will convene after the completion of the study.

11.2.1 Stopping Rules

The participation of individual participants in the bionic pancreas arm of the study may be discontinued if they experience:

- Diabetic ketoacidosis requiring hospitalization during a bionic pancreas arm
- Seizure or unconsciousness associated with hypoglycemia in a bionic pancreas arm

Unlike in patients with type 1 diabetes, diabetic ketoacidosis (DKA) is very rare in patients with CFRD due to underlying residual beta cell function. However, in the case that a participant experiences one of the above events, the PI will make a determination regarding whether it will be safe to allow them to continue in the study. A participant using the bionic pancreas when they experienced the event will suspend use of the device until a determination is made about the safety of having them continue. If the PI concludes that the event is explainable and unlikely to recur, the participant will be allowed to continue to use the system. Further study participation of an individual participant will be discontinued if they experience more than

one episode of DKA requiring hospitalization, more than one episode of seizure or unconsciousness associated with hypoglycemia, or one of each.

If more than 2 participants must be withdrawn from the study for these reasons, the study will stop and a vote of the DSMB will be required to restart it.

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

11.2.2 Adverse Event Reporting

11.2.2.1 Definitions

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

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

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

- **Related:** There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.
- **Possibly Related:** Possibly related to the research means there is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)). Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures
- **Not Related:** Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

The investigator will also classify the event based on expectedness. The event will be classified as **unexpected** if the nature, severity, or frequency of the event is not consistent with known risk information.

Serious adverse event (SAE) means any event temporally associated with the participant's participation in

research that meets any of the following criteria:

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

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.

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).

Expected occurrences that will not be documented as an ADE include: CGM tape adherence issues, CGM sensor lasting fewer days than expected per manufacturer, intermittent device component disconnections/communication failures not requiring system replacement or other resolution not described in the user guide, and any device issues clearly addressed in the user guide that do not require additional troubleshooting.

All ADEs, both expected and unexpected will be documented, and reported as an AE when applicable. ADEs, device complaints and device malfunctions will be documented and reported to regulatory bodies as appropriate.

11.2.2.2 Reporting guidelines

Any serious or unexpected but possibly related adverse events will be communicated to the PI as soon as possible and within 24 hours of the time they are detected. Adverse events and unanticipated problems will be reported to the Partners IRB, the DSMB and Beta Bionics. Reports of adverse events will be made to the FDA in compliance with the terms of IDE.

12. Participant Compensation

Financial compensation will be provided to all participants who complete the screening visit. Participants will be paid $25 for completing the screening visit whether or not they are eligible to participate in the study.

Study participants will be compensated $75 for completing each study visit (study start, crossover, and final). The total compensation for a participant who completes the screening visit and scheduled study visits (study start, crossover, and final) would be $250.

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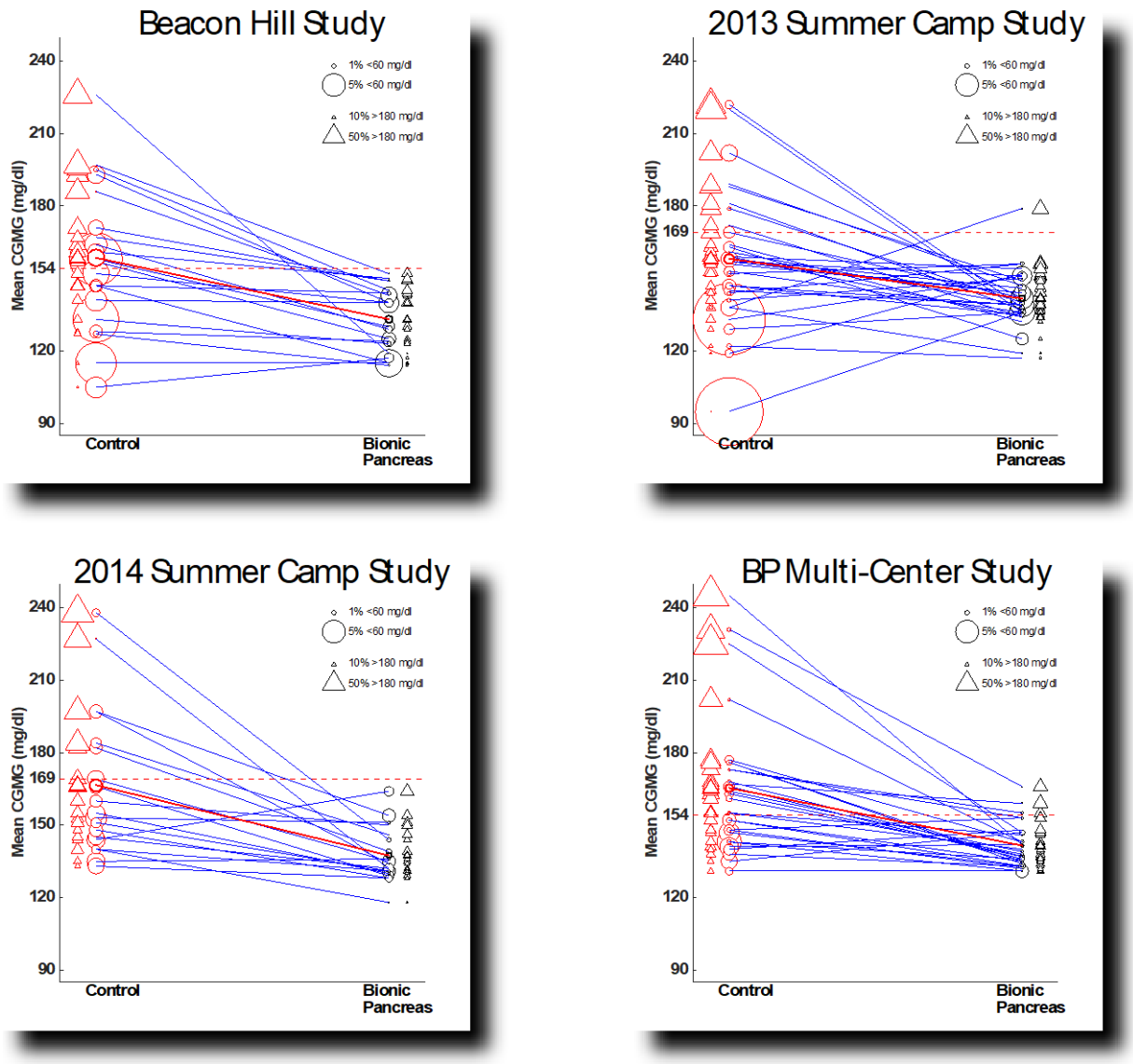
14. Appendices

14.1 Appendix A: Prior Studies Conducted Using the Bionic Pancreas System

14.1.1 Studies Conducted with the iPhone-Based BP System

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 3**.



Study	Age (years)	Bionic Pancreas (BP) Mean CGM glucose level (mg/dl)	Bionic Pancreas (BP) % of CGM glucose levels <50 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 <50 mg/dl (%)	Control % of CGM glucose 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 <50 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 3. *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 3**.

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 3**.

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 3**.

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 4**. Results from the bihormonal BP arms and the usual-care arm are summarized in **Figure 5**.

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.

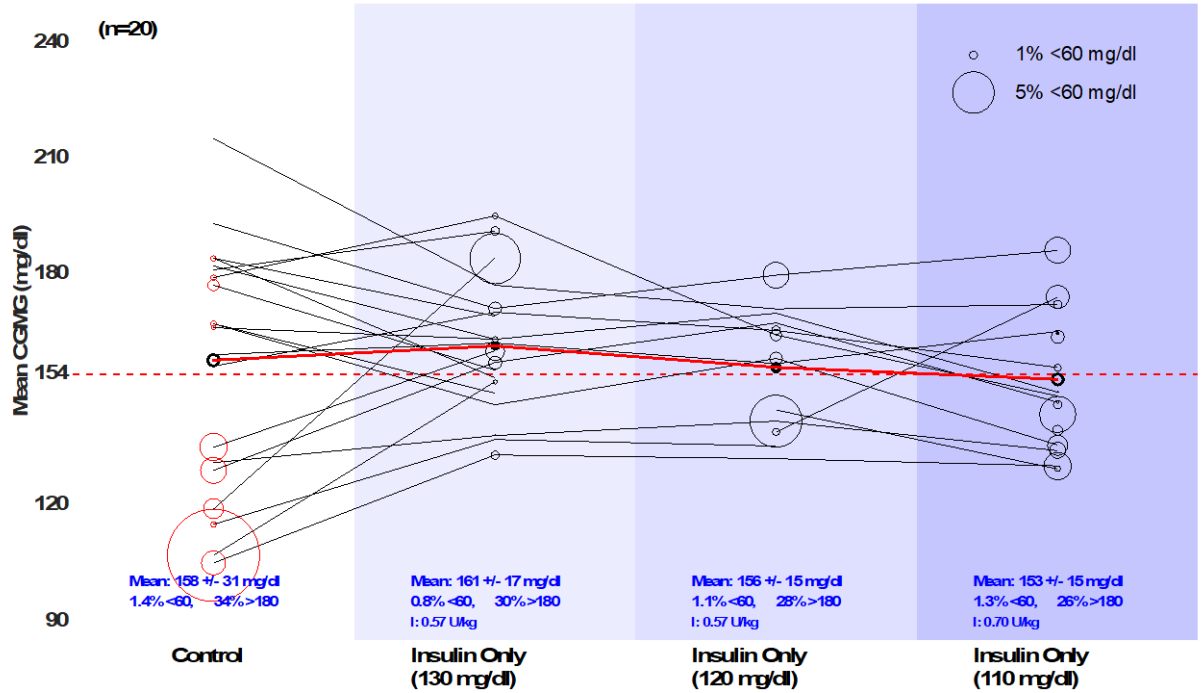


Figure 4. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP arms (with set-points 130, 120, and 110 mg/dl) and usual care arm (control) from the Bionic Pancreas Set-Point Study. Mean CGM glucose levels for each participant in each study 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.*

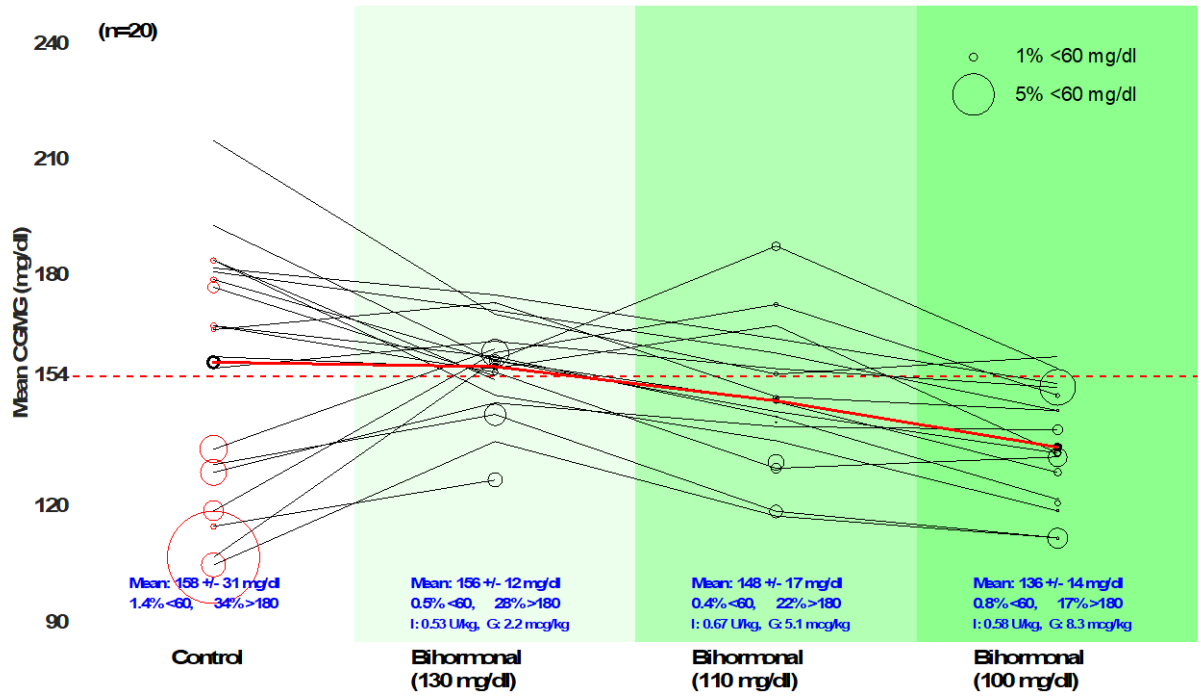


Figure 5. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the bihormonal BP arms (with set-points of 130, 110, and 100 mg/dl) and usual-care arm (control) from the Bionic Pancreas Set-Point Study. Mean CGM glucose levels for each participant in each study 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.*

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 insulin-only 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 6**. 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).

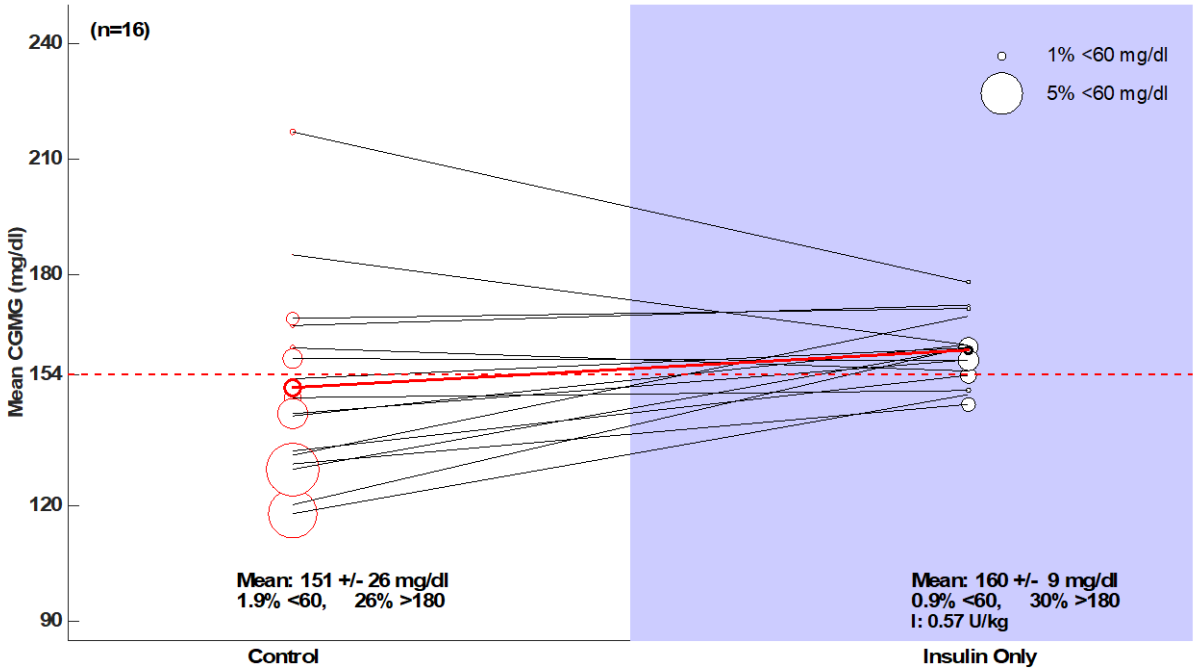


Figure 6. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Stanford Insulin-Only Study. Mean CGM glucose levels for each participant under usual care (shown as a red circle on the left) is connected with the 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.*

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 7**. 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.

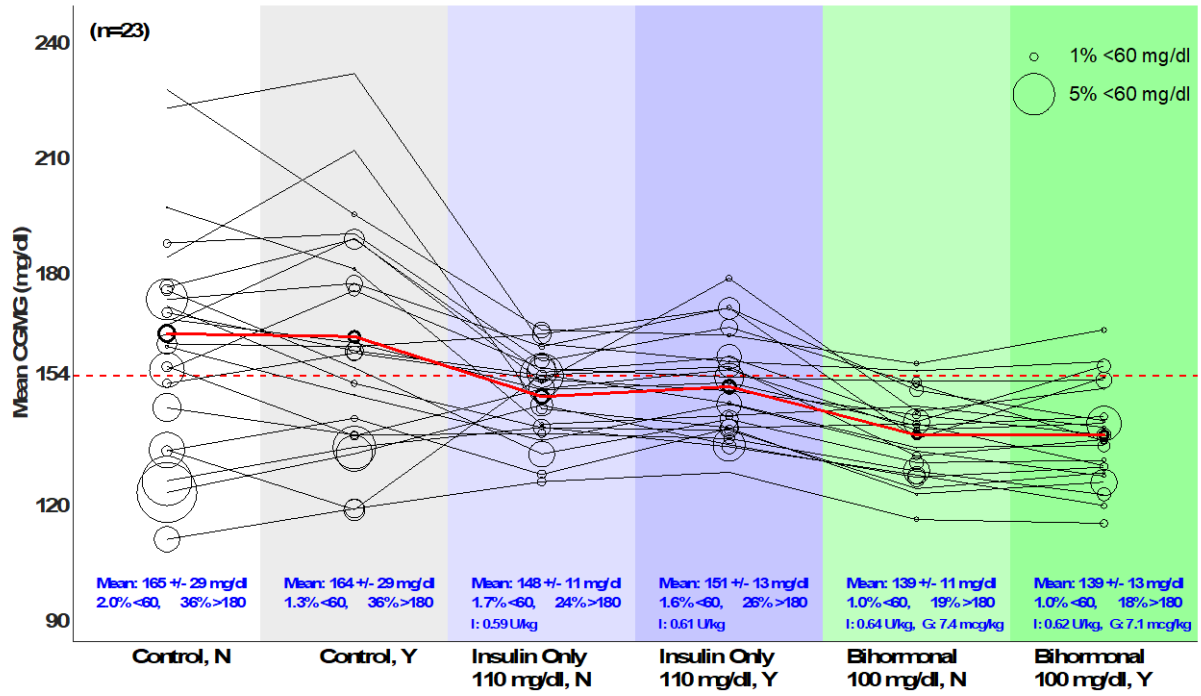


Figure 7. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Bionic Pancreas Monitoring Study. Mean CGM glucose levels for each participant under usual care (shown as a red circle on the left) is connected with 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.*

14.1.2 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.

<u>The iLet Insulin-Only Bionic Pancreas Bridging Study</u>

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 8**.

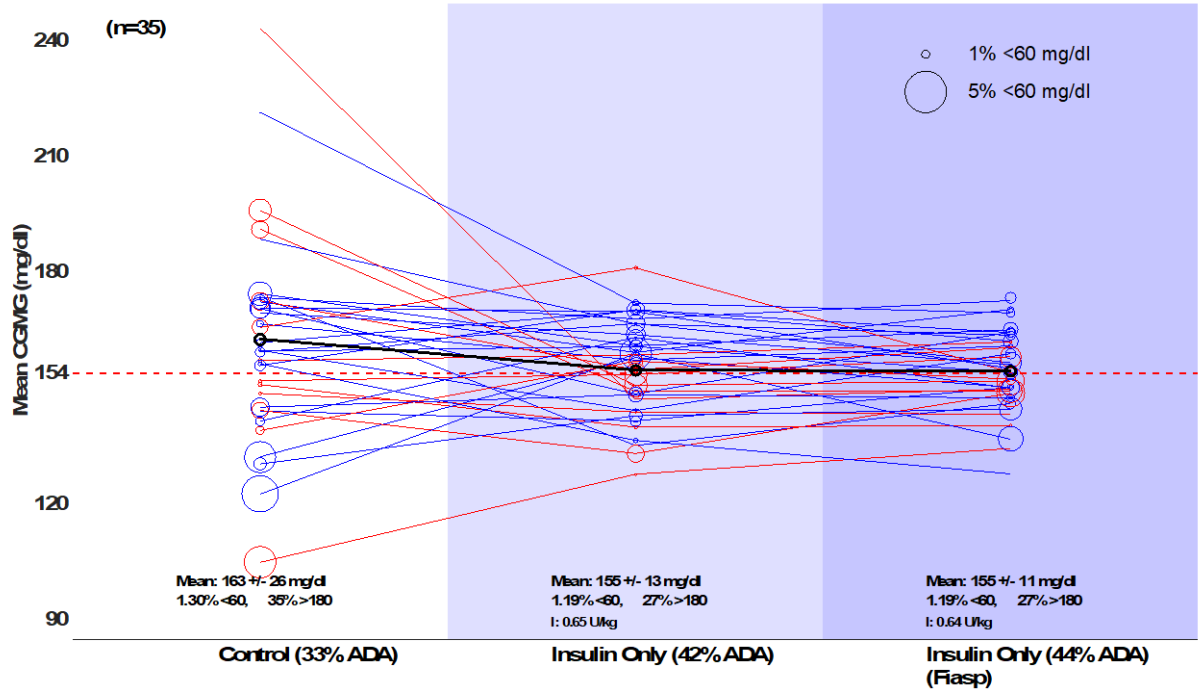


Figure 8. *Distribution of mean glucose and hypoglycemia in the Insulin-Only Bionic Pancreas Bridging Study. Mean CGM glucose level for each subject is shown over Days 3–7 under usual care, (left panel), on the iLet in the insulin-only configuration using lispro or aspart (middle panel), and on the iLet 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 8**).

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 9**.

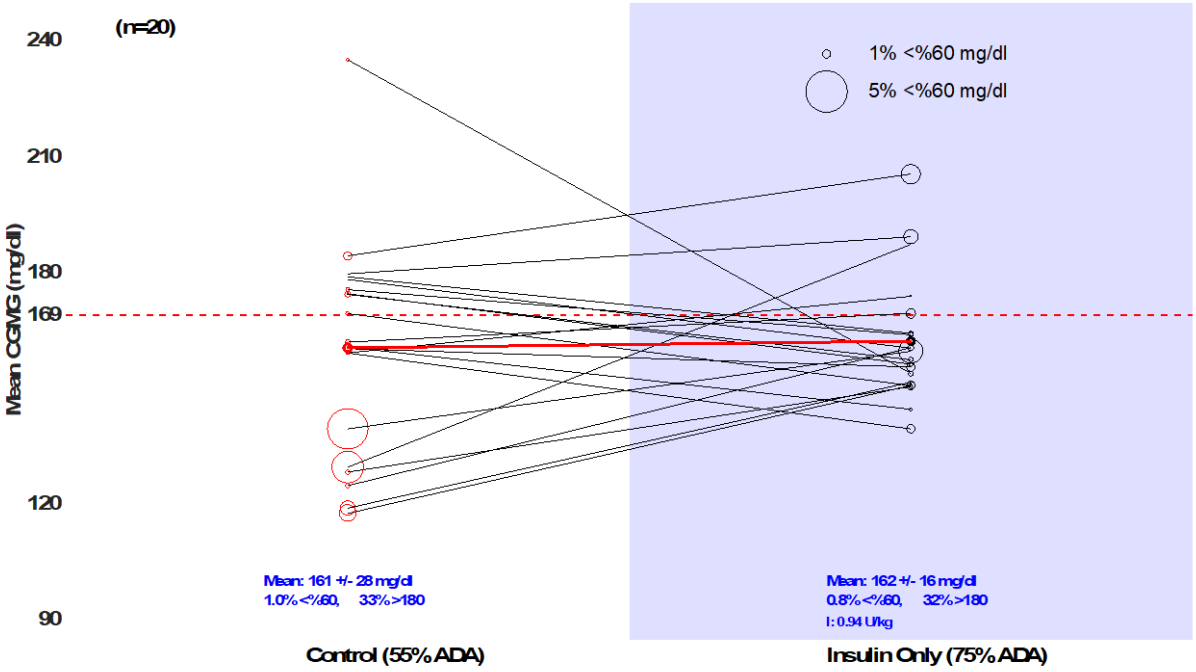


Figure 9. *Distribution of mean glucose and hypoglycemia in the Pediatric Day-Camp Transitional Study. Mean CGM glucose level for each subject is shown over Days 2–5 in the control arm, as a red circle on the left side, connected with the corresponding mean CGM glucose level on the iLet, as a black circle 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.*

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 10**.

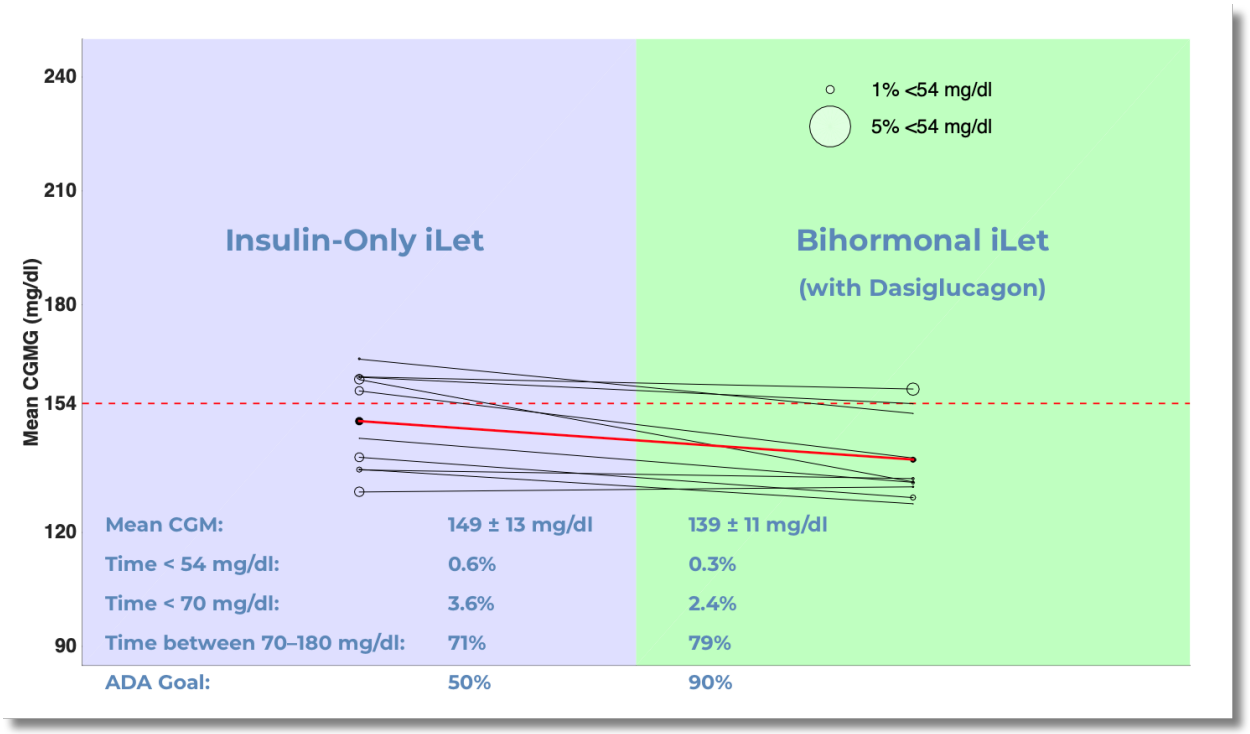


Figure 10. *Distribution of mean glucose and hypoglycemia in the Bihormonal Cross-Over Study. Mean CGM glucose level for each subject is shown over Days 2–7 in the insulin-only iLet arm, as a black circle on the left side, connected with the corresponding mean CGM glucose level on the bihormonal iLet 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.*

14.2 Appendix B: Psychosocial questionnaires

Baseline questionnaires are completed by all participants at the Study Start Visit and then after each arm (or within 1 week leading up to each timepoint).

Each questionnaire is described briefly below. 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.

Brief Description of Questionnaires

Measure	Construct Measured / Relevant Points	Who Completes / Age Range	Timing of Administration in RCT
Diabetes-Specific Emotional Distress • DDS for ≥18 yrs • PAID-C for 10-12 yrs • PAID-T for 13-<18 yrs	Gold standard measures for understanding distress symptoms related to diabetes. • DDS = 28 items • PAID-C = 11 items • PAID-T = 14 items	• DDS: ≥18 yrs • PAID-C: 10-12 yrs • PAID-T: 13-<18 yrs	Baseline, after each arm

Measure	Construct Measured / Relevant Points	Who Completes / Age Range	Timing of Administration in RCT
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 yrs	Baseline, after each arm
Diabetes Technology Attitudes	Subjective questions about attitudes related to diabetes technologies and devices (5 items)	≥18 yrs	Baseline, after each arm
INSPIRE Surveys • Adult (Pre & Post) • Youth (Pre & Post)	Measures psychological expectations and response to closed loop treatment. • Adult (Pre, Post) = 22 items • Youth (Pre, Post) =17 items	• Adult: ≥18 yrs • Youth: 10-<18 yrs	All receive Pre-INSPIRE survey at baseline All receive Post-INSPIRE survey **after the BP arm ONLY**
Fear of Hypoglycemia Scale • Adult Scale • Youth Scale	The HFS measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes. • Adult = Worry (18 items) and behavior (15 items) • Youth = Worry (15 items) and behavior (10 items)	• Adult: ≥18 yrs • Youth: 10-<18 yrs	Baseline, after each arm
EQ5D • 5L Version • Y Version	NICE approved QOL measure that translates into economics (5 items)	• 5L Version: ≥18 yrs • Y Version: 10-<18 yrs	Baseline, after each arm
WHO-5	5 items	≥10 yrs	Baseline, after each arm
Bionic Pancreas User Opinion Survey	35 items	≥10 yrs	**After the BP arm ONLY**
Past Experience with Artificial Pancreas Systems	9 items	≥10 yrs	**After the BP arm ONLY**

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

Measure	Construct Measured / Relevant Points	Child Age Ranges	Timing of Administration in RCT
Diabetes-Specific Emotional Distress • P-PAID-C for 10-12 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: 10-12 yrs • P-PAID-T: 13-<18 yrs	Baseline, after each arm
INSPIRE Surveys • Parent (Pre & Post)	Measures psychological expectations and response to closed loop treatment. • Parent (Pre & Post) = 21 items	10-<18 yrs	Pre-INSPIRE survey at baseline Post-INSPIRE survey **<u>after BP arm ONLY</u>**
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)	10-<18 yrs	Baseline, after each arm
Bionic Pancreas User Opinion Survey	35 items	All youth (6-<18 yrs)	**<u>After BP arm ONLY</u>**
Past Experience with Artificial Pancreas Systems	9 items	10-<18 yrs	**<u>After BP arm ONLY</u>**

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

14.3 Appendix *C*: Hyperglycemia treatment plan

iLet Bionic Pancreas Hyperglycemia and Ketone Action Plan – for study staff

Hyperglycemia assessment:
In <u>*any*</u> time of prolonged hyperglycemia while using the iLet, always confirm with a fingerstick blood glucose reading and then:

- Ask whether the iLet is charged, reading CGM values, has insulin in the cartridge, and is dosing insulin.
    - Insulin doses can be confirmed by viewing the graph, and the algorithm steps in the history.
- Ask whether the infusion set is in place with no signs of leaking (wetness, smell of insulin, adhesive/cannula dislodged).
    - If there is ever any suspicion that the infusion set may not be working, replace it. *When in doubt, change it out!*

- Ask whether there is evidence of leaking anywhere on the fluid pathway.
    - Inspect the tubing to make sure it is patent.
    - Have the participant do the following:
        - Disconnect the tubing at the infusion site first
        - Next, remove the insulin cartridge from the chamber of the iLet.
        - Do NOT disconnect the cartridge connector from the cartridge.
        - Inspect the iLet chamber, the outside of the cartridge and the cartridge connector for signs of leaking (wetness, smell of insulin).
        - If there is no sign of leaking in the cartridge or tubing and no wetness or smell of insulin, insert the cartridge back into the iLet and twist the connector to the closed position. Then connect the tubing back to your infusion site.
    - If you suspect there might be leaking at any place in the tubing, or into the iLet itself, replace the entire cartridge and tubing set as well as the infusion set. Remember, the cartridge and tubing cannot be disconnected from each other, so a whole new cartridge with fresh insulin and new tubing must be used.
- Ask whether there is evidence of air in the tubing.
    - If there are bubbles, disconnect the tubing at the infusion site and prime the tubing until the bubbles are gone.
- Ask about recent carb intake and if a meal announcement was given.
    - If recent carb intake was not announced, was announced late, or had more carbs than originally thought, post-prandial BG will be higher and stay higher longer than if a meal announcement was correctly used. If there is no evidence of any leaking or device issues, the BG should come down on its own. Discuss best practices for meal announcements with the participant to identify any knowledge gaps and educate as needed.
- Ask about any recent disconnections or loss of CGM readings from the iLet that may have disrupted the iLet's ability to dose insulin in the past several hours.
- Ask about any other potential causes of hyperglycemia (hormonal changes, stress, etc).

Check BG if:

- Suspected infusion set failure
- CGMG > 300 mg/dl for 90 minutes
- Participant is sick, vomiting or has diarrhea

Assess and document any symptoms of hyperglycemia (including but not limited to polyuria, polydipsia, nausea and vomiting). Assess and document any device issues that arise.

Ketone Action Plan: repeat testing q90 minutes until in Zone 1

Zone	Glucose	Action
1	Ketones <0.6 mmol/l	1. Assess for any potential causes of hyperglycemia. 2. If CGM is >300 90 minutes later or goes above 400 mg/dl, move to Zone 2
2	Ketones 0.6 - 2.5 mmol/l	1. Change the infusion set, even if there is no obvious leaking or sign of failure. Consider changing the cartridge and tubing if there is reason to suspect they are involved in the failure to deliver insulin.

	(Urine ketones: trace-moderate)	If the infusion set is working and the iLet has a way to get the insulin into the participant, experience has shown that the safest way to bring down BG is to continue to wear the iLet while monitoring BG. 2. Increase fluid intake. Drink 1 oz per year of age each hour for 2 hours up to 12-16 oz per hour. 3. Recheck BG and ketones every 90 minutes until ketones are < 0.6 mmol/l and BG is < 180 mg/dl. 4. If ketones remain > 0.6 mmol/l after 90 minutes, move to Zone 3
3	Ketones > 2.5 mmol/l OR ≥0.6 mmol/l for 90 minutes (Urine ketones: large)	1. Disconnect from the iLet for 2 hours. 2. Give SYRINGE/PEN injection of insulin as follows: a. Help the participant navigate to the iLet Backup Therapy Screen and report what the Correction Factor says (video or picture confirmation is helpful). b. CALCULATE the correction dose: Target a glucose of 120 mg/dl by subtracting 120 mg/dl from the current blood glucose. Divide the result by the Correction Factor on the iLet Backup Therapy screen, then multiply that result by 1.25. Example (for BG of 280 mg/dl, Correction Factor of 32 mg/dl per unit): (280 – 120) ÷ 32 x 1.25 Insulin dose = 280 mg/dl – 120 mg/dl = 160 mg/dl ÷ 32 mg/dl per unit = 5 units x 1.25 = 6.25 units Round to the nearest unit. The participant will take 6 units of insulin. c. Give SYRINGE/PEN correction dose using only rapid-acting insulin. This should be whatever rapid-acting insulin the participant has available, regardless of what they were using in their iLet. 3. Instruct the participant: a. Remain disconnected from the iLet for 2 hours. The iLet will still alarm for high or low CGM glucose. b. Check CGM alarm settings, and suggest they turn on the CGM Falling alarm and the Hypoglycemia alarm if they are off (in addition to the Urgent Low at 55 mg/dl). c. DO NOT reconnect to the iLet before 90 minutes after the injection because the iLet algorithms will not know about the correction injection that was taken and will stack insulin. d. DO NOT take additional correction insulin injections before allowing this injection time to work. e. AVOID high carb snacks or meals while waiting for BG to come down if possible. i. Any meals/snacks with carbohydrates will require an injection of insulin to cover the carbs. Instruct the

		participant to use the carbohydrate ratio in the iLet Backup Therapy screen to decide on a dose of injection insulin if they eat while the iLet is disconnected. f. DO continue to drink fluids with no carbohydrates, continue to monitor CGM glucose, and re-check BG and ketones in 90 minutes. 4. Increase fluid intake. Drink 1 oz per year of age each hour for 2 hours up to 12-16 oz per hour. 5. RECHECK BG and ketones every 90 minutes. 6. 90 minutes later: a. Ketones > 2.5 mmol/l (urine ketones large): Consider a second injection if BG is still elevated. Assess ability to take carbohydrates and fluids by mouth. If unable, refer to ED and follow emergency protocol procedures. b. Ketones 0.6 mmol/l to 2.5 mmo/l (urine ketones moderate or small): Reconnect to the iLet and replace the infusion set, test BG and ketones again in 90 minutes. c. Ketones < 0.6 mmol/l (urine trace or negative): Reconnect to the iLet and replace the infusion set. No further action is necessary, issue is resolved.