Assessing feasibility, safety, and efficacy of deploying a closed-loop automated insulin delivery system by community-based primary care physicians and academic endocrinologists, in person and through telehealth.

Principal Investigators: Tamara K. Oser, MD; Sean M. Oser, MD, MPH

Co-Investigators:
Melissa S. Putman, MD, MMSc

Sponsor: The Leona M. and Harry B. Helmsley Charitable Trust

Address correspondence to:

Colorado:
Tamara K. Oser, MD, Department of Family Medicine, University of Colorado Anschutz School of Medicine, 12631 East 17th Avenue, Mail Code F496, Room 3513, Aurora, CO, 80045, email: *tamara.oser@cuanschutz.edu*, phone: 303-724-9700, fax: 651-666-1415

Sean M. Oser, MD, MPH, Department of Family Medicine, University of Colorado Anschutz School of Medicine, 12631 East 17th Avenue, Mail Code F496, Room 3513, Aurora, CO, 80045, email: *sean.oser@cuanschutz.edu*, phone: 303-724-9700, fax: 651-666-1415

Massachusetts General Hospital:
Melissa S. Putman, MD, MMsc, MGH Diabetes Clinical Research Center, 50 Staniford Street Suite 301, Boston MA, 02114, email: *msputman@mgh.harvard.edu*, phone: 857-218-5017, fax: 617-730-0194

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Table of Acronyms

Abbreviation	Definition
ADA	American Diabetes Association
AE	Adverse Events
AN	As Needed
AP	Artificial Pancreas
APS	Artificial Pancreas System
BG	Blood Glucose
BP	Bionic Pancreas
BU	Boston University
CGM	Continuous Glucose Monitor/ing
CGMG	Continuous Glucose Monitor Glucose
CV	Coefficient of variation
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EN	Endocrinology Group
EN-IP	Endocrinology In Person Group
EN-TH	Endocrinology Telehealth Group
FDA	U.S. Food and Drug Administration
G4	Generation 4
G5	Generation 5
G6	Generation 6
GLP	Glucagon-like peptide 1
GUI	Graphical User Interface
HCG	Human Chorionic Gonadotropin
NCQA HEDIS	National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set

HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IP	In Person
IRB	Institutional Review Board
MARD	Mean Absolute Relative Difference
MD	Doctor of Medicine
MDI	Multiple Daily Injections
METS	Metabolic Equivalent of Task
MGH	Massachusetts General Hospital
MODD	Mean of Daily Difference
MPC	Model-Predictive Control Algorithm
NGSP	National Glycohemoglobin Standardization Program
NP	Nurse Practitioner
NYHA	New York Heart Association
PC	Primary Care
PC-IP	Primary Care In Person Group
PC-TH	Primary Care Telehealth Group
PCP	Primary Care Provider
PI	Principal Investigator
PK	Pharmacokinetic
RCT	Randomized Controlled Trial
RF	Radio-frequency
SC	Subcutaneous
SD	Standard Deviation
SGLT2	Sodium-glucose Cotransporter-2
SMBG	Self-monitoring of blood glucose
T1D	Type 1 Diabetes Mellitus
TDD	Total Daily Dose
TH	Telehealth
TIA	Transient Ischemic Attack
UC	Usual Care
VAS	Visual Analog Scale

Protocol Summary

Title	Assessing feasibility, safety, and efficacy of deploying a closed-loop automated insulin delivery system by community-based primary care physicians and academic endocrinologists, in person and through telehealth.
Precis	This is a study assessing the feasibility of using the insulin-only configuration of the iLet bionic pancreas with initiation in pump-naïve people with type 1 diabetes in a primary care practice with either in-person training and follow-up (PC-IP) or with training and follow-up via telehealth (PC-TH). As a comparison, the iLet will be initiated by an academic endocrinology practice with either in-

	person training and follow-up (EN-IP) or with training and follow-up via telehealth (EN-TH).
Investigational Device	iLet Bionic Pancreas System, which consists of an integrated infusion pump, touchscreen display, Bluetooth radio, and dosing algorithms, that automatically controls insulin delivery based on glucose values obtained by communicating with a Dexcom G6 sensor.
Objectives	**Primary objective** To assess the feasibility of deploying the iLet bionic pancreas system in the insulin-only configuration to pump-naïve MDI users with type 1 diabetes, in the setting of being recruited from community-based primary care practices and being trained and managed by primary care providers (PC group), and in pump- and CGM-experienced (sensor-augmented pump or hybrid closed-loop) users with type 1 diabetes recruited from, trained, and managed by an academic endocrinology practice (EN group). In both practice settings, the exclusive use of telehealth (TH) visits will be assessed, as will use of in-person (IP) visits. We will enroll 40 adult volunteers (≥ 18 years old) with type 1 diabetes, 20 who are insulin pump naïve MDI users enrolled from community primary care practices by University of Colorado Family Medicine (PC group) and 20 who are technology-savvy sensor-augmented pump or hybrid closed-loop users enrolled by the Massachusetts General Hospital Diabetes Clinical Research Center (EN group). Ten of the participants at each center will be trained and managed throughout the trial using in-person visits (PC-IP and EN-IP groups) and the other ten from each center will be trained and managed throughout the trial exclusively via telehealth visits (PC-TH and EN-TH groups). The 40 participants will be evenly divided into these four groups, but not by randomization. Participants will be assigned to either the in-person or telehealth arm based on the participant's preference, the participant's location, and the discretion of the investigator. Subjects in all four groups will each participate, in random order, in one 14-day study arm under their own usual care (UC arm) and one 14-day study arm under the insulin-only configuration of the iLet bionic pancreas (iLet arm). Our hypothesis is that pump naïve community-based primary care participants can be successfully started on the iLet bionic pancreas system by primary care providers in-person and via telehealth and that we will see similar glucose control by the iLet in the primary care and academic endocrinology groups and in the telehealth and in-person groups, with a target mean glucose of < 183 mg/dl in all four groups (PC-IP, PC-TH, EN-IP, and EN-TH). This target of < 183 mg/dl is a functional and clinically meaningful threshold for each group, consistent with a quality indicator of diabetes management (estimated HbA1c < 8.0%) that corresponds to the NCQA HEDIS measure of "HbA1c control" and which is therefore used frequently by many payers, reporting, and accrediting bodies. The outcome is categorical, and the primary outcome is not a direct comparison of the mean CGM glucose between the groups.

	Secondary objectives 1. To obtain preliminary data on the quality of glycemic control among the PC and EN groups, with separate analyses in the IP and TH sub-groups, and in the UC and iLet arms within those groups, which will be used to power a larger study with a glycemic control metric as the primary outcome. Our hypotheses are that glycemic control, with key outcomes being group mean CGM glucose, the group mean time with CGM glucose less than 54 mg/dl, and the group mean time with CGM glucose in the 70–180 mg/dl range, will be similar in the PC-IP group and the EN-IP group, and in the PC-TH group and the EN-TH group in the iLet arm. Additionally, we hypothesize that glycemic control will be similar in the PC-TH group and the PC-IP group, and in the EN-TH group and the EN-IP group in the iLet arm. Further, we hypothesize that there will be a larger difference in glycemic control metrics between the UC arms versus the iLet arm in the PC group than there will be in the EN group. 2. To assess the impact of the insulin-only configuration of the iLet bionic pancreas system on psychosocial outcomes (including quality of life, fear of hypoglycemia, and diabetes distress) among study participants. Secondary analyses will be conducted between the telehealth and in-person arm, the EN and PC groups, and the iLet and UC arms.
Study Design	Random-order cross over trial in a home-use setting with two 14-day study arms
Number of Sites	2; one will be a community-based primary care practice (University of Colorado) and one will be an academic medical center-based endocrinology practice (Massachusetts General Hospital).
Endpoints	**Primary endpoint** • Percentage of individuals with mean CGM glucose <183 mg/dL (corresponding to an estimated HbA1c of <8.0%) on days 3-14, by group. **Secondary endpoints** • Mean CGM glucose on days 3-14 • Percentage of time with CGM glucose <54 mg/dl on days 3-14 • Percentage of time with CGM glucose in the 70-180 mg/dl range on days 3-14 • Percentage of individuals with mean CGM glucose <154 mg/dL (corresponding to an estimated HbA1c of <7.0%) on days 3-14, by group. **Safety endpoints** • Frequency of adverse events • Frequency of severe hypoglycemia

	• Frequency of diabetic ketoacidosis, as defined within this protocol in Section 9.2.
	
	Other endpoints
	• The percentage of time that valid CGM glucose readings are captured by the iLet
	• The percentage of the time that the insulin pump channel of the iLet is available
	• Percentage of time across days 3-14 within each of the following CGM glucose ranges:
	  ○ < 70 mg/dl
	  ○ > 180 mg/dl
	  ○ > 250 mg/dl
	• Percentage of time participants were disconnected from the iLet
	• Number of episodes of symptomatic hypoglycemia (reported daily by participants)
	• Percentage of participants with mean Dexcom CGMG <154 mg/dl (estimated average glucose corresponding to an A1c of <7.0%)
	• Mean total daily dose of insulin in the iLet arms
	  ○ Mean total daily dose of insulin in the usual care arm (pump data in EN group and self-reported in PC group)
	• Mean daily basal insulin dose in the iLet arms and in the EN group usual care arm
	  ○ Mean daily basal insulin dose of insulin in the usual care arm (pump data in EN group and self-reported in PC group)
	• Mean daily bolus insulin dose in the iLet arms and in the EN group usual care arm
	  ○ Mean daily bolus insulin dose of insulin in the usual care arm (pump data in EN group and self-reported in PC group)
	• Mean number of meal announcements in the iLet arms
	• Glucose variability measured with coefficient of variation (CV) and with mean of daily difference (MODD)
	• Number of unscheduled insulin cartridge/infusion set changes in the iLet arms
	• Mean glucose target in the iLet arms
	• Scores from psychosocial questionnaires (including quality of life, fear of hypoglycemia, and diabetes distress). These surveys will be collected at baseline and after each arm. Post-BP measurements, including the bionic pancreas user opinion survey, will be given only after the BP arm

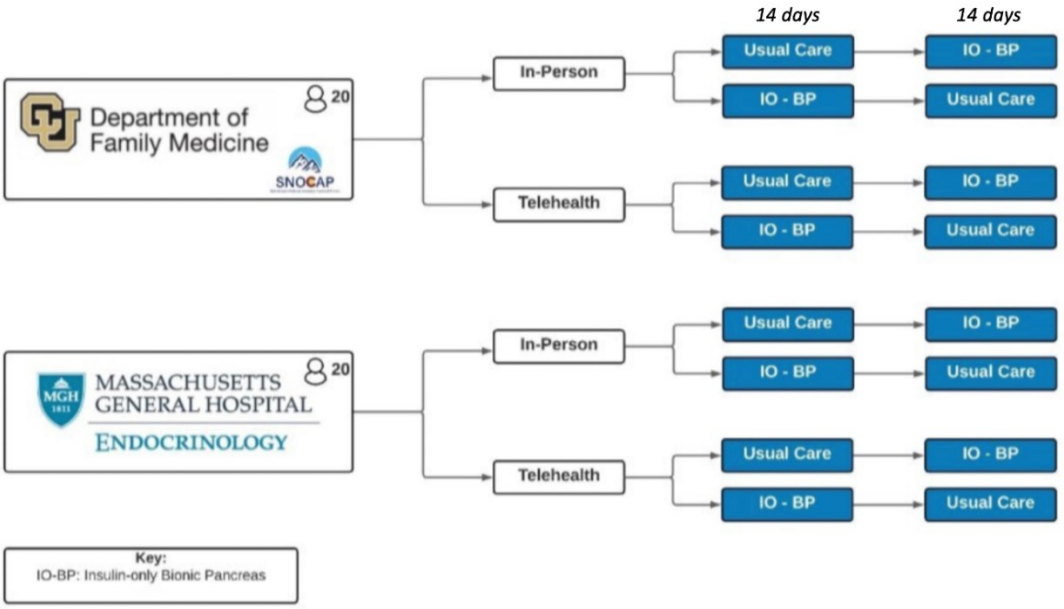
Eligibility Criteria	**Inclusion Criteria** 1. Age 18-85 years, BMI ≥ 18.5, have had clinical type 1 diabetes for at least one year, and have taken insulin for at least 1 year a. Prescription diabetes medication regimen stable for > 1 month, including any adjunctive anti-diabetic medications (except for medications that will not affect the safety of the

	study and are not expected to affect any outcome of the study, in the judgment of the site principal investigator) b. This does not include changes to any insulin doses, including basal rates/long-acting insulin doses, carbohydrate to insulin ratios and correction factors 2. Willing to wear one Dexcom CGM transmitter and sensor (sensor must be changed every 10 days), and one infusion set that must be replaced at least every 3 days. 3. Endocrinology practice criterion is that diabetes is managed using sensor-augmented insulin pump therapy or artificial pancreas therapy for ≥ 3 months) 4. Primary care practice criteria are that diabetes is managed by multiple daily insulin injections (insulin-pump naïve). 5. TH group criterion is that participant must have hardware and internet access capable of 2-way video and audio communication **Exclusion Criteria** 1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English, as iLet BP support materials and device menus are currently available in English only. 4. Plan to change usual diabetes regimen in the next 3 months including before and during participation in the study a. This would include changing from MDI to pump or from pump to MDI, and starting a CGM if not previously used b. This would not include changes to any insulin doses, including basal rates/long acting insulin doses, carbohydrate to insulin ratios and correction factors 5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system (e.g. “Loop” or “Open APS”) 6. Unwilling to switch to lispro or aspart for the duration of the study’s iLet arm (e.g. from Fiasp or Lyumjev) 7. Known hemoglobinopathy (sickle cell trait is not an exclusion) 8. Current participation in another diabetes-related clinical trial, has a medical condition, or use of a medication that, in the judgment of the investigator, could compromise the results of this study or the safety of the participant 9. History of diabetes due to cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy 10. Have a history of intermittently required glucocorticoid treatment (e.g., but not limited to, for the treatment of asthma, inflammatory

	bowel disease). 11. A1c >11.0% (most recent value up to 1 year prior acceptable; if none available or >1 year prior, participant will be instructed to obtain A1c through their usual care provider and to make copy of result available to study team) 12. History of diabetic ketoacidosis (DKA) within the past month 13. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference 14. Established history of allergy or severe reaction to adhesive or tape that must be used in the study 15. Currently treated with GLP-1 analogue, thiazolidinedione (TZD), sulfonylurea, pramlintide, or SGLT-2 inhibitor medication (*use more than 3 months prior to enrollment is acceptable*) a. If using metformin, participants: i. Must be on a stable dose for 1 month prior to enrollment ii. Metformin can be continued while the iLet is used 16. Pregnant (positive urine HCG), breast feeding, plan to become pregnant in the next 6 months, or premenopausal participants who are sexually active without use of contraception 17. Renal failure on dialysis or chronic renal disease with a GFR or eGFR <30mL/min (values within the last two years will be accepted; if none available or >2 years prior, participant will be instructed to obtain GFR or eGFR through their usual care provider and to make copy of result available to study team) 18. Any condition that, in the opinion of the site principal investigator, could interfere with the safe or effective completion of the study. a. Conditions to be considered by the investigator may include, but are not limited to, the following: i. Alcohol or drug abuse ii. Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study iii. Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. exercise of intensity up to 6 METS) despite medical management, or within the last 12 months before screening, a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting iv. Known history of prolonged QTc interval, malignant arrhythmia, or congenital heart disease v. Congestive heart failure with New York Heart

	Association (NYHA) Functional Classification III or IV vi. History of TIA or stroke in the last 12 months vii. Untreated or inadequately treated mental illness viii. History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulimia or omission of insulin to manipulate weight ix. History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment 19. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial 20. Unable to avoid hydroxyurea for duration of study (interferes with accuracy of Dexcom G6 CGM)
Sample size	40 adult participants (18-85 years of age) with type 1 diabetes, 20 PC at the University of Colorado site and 20 EN at the Massachusetts General Hospital Site
Treatment groups	One arm will involve 14 days using the insulin-only iLet bionic pancreas and the other arm will involve insulin delivery via the participants' usual care (multiple daily injections or insulin pump, CGM or SMBG, depending on the study site). Half of the participants will receive care via in-person visits, and the other half will receive care exclusively via telehealth visits. This will result in four study cohorts overall (endocrinology in-person, endocrinology telehealth, primary care in-person, primary care telehealth).
Participant Duration	Up to 3 months

Schematic of Study Design



Schedule of Visit Procedures

	Screening	Start Visit	Mid Period Follow-up #1	Mid Period Follow-up #1	Crossover Visit	Mid Period Follow-up #3	Mid Period Follow-up #4	Final Visit
Days from study start visit (window):		*0*	*1*	*5 (±2)*	*14* (+2)*	*15#*	*19# (±2)*	*28# (+2)*
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Informed Consent	x							
Eligibility Criteria Assessment	x	x[1]						
Review of medications and medical history	x	x	x	x	x	x	x	x
S/AE Querying		x	x	x	x	x	x	x
Psychosocial Questionnaires	x[2]				x			x
HbA1c	x[2]							
Height	x							
Weight	x	x			x			x
Pregnancy Test	x	x			x			
CGM Sensor Insertion		x			x[3]			
Supervised Site Change (Virtual)			x[4]			x[4]		
iLet initiation		x[3]			x[3]			
Data Download					x			x
Randomization		x						

* Visit may be split into separate shutdown and start up visits; startup visit must occur no more than 14 days after shutdown visit
# May differ based on length of previous arm and window between arms

1 Continued eligibility will be confirmed prior to randomization
2 Will be completed between screening & randomization
3 If applicable, based on randomization
4 If necessary

1 Introduction

1.1 Background and Rationale

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

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

We have demonstrated that using the iLet BP system results in better blood glucose control (in terms of reducing average blood glucose levels and/or low blood glucose levels) than can be achieved by usual care involving multiple daily insulin injections. However, this has only been demonstrated through delivery of the iLet BP system by endocrinologists, and only by in-person care. Consequently, access to this level of diabetes management is significantly limited. The ability to expand access to the iLet BP system via primary care providers (PCPs) and via telehealth would be advantageous for several reasons.
Endocrinologists tend to be distributed in more urban locations, making access difficult and limited for many patients. PCPs are more evenly distributed across the nation in a pattern more reflective of the general population. For example, 3,018 of 3,143 (95.9%) U.S. counties have at least one PCP, compared to 777 (24.7%) counties with at least one endocrinologist. Every U.S. county is adjacent to a county with at least one PCP, which is not the case for endocrinologists.[3] Delivery of the iLet BP system through both endocrinology and primary care has the potential to bring this superior, state of the art therapy within reach of many more people.

Although PCP offices lack the extended supports of an endocrinology practice, the movement toward patient-centered medical homes is decreasing this through the addition of diabetes educators, pharmacists, and other healthcare team members. More streamlined, easier to use and support artificial pancreas systems should allow for PCP practices to support this and to achieve outcomes similar to those obtained by their endocrinology colleagues using the same system. Patients have greater access to primary care, and their longitudinal and trusting relationship with their personal physician is associated with better health outcomes, including adherence to treatment.

In addition, telehealth is quickly becoming an additional way to deliver healthcare, even more so in the era of the COVID-19 pandemic, and especially in rural areas can be a valuable alternative care model. Delivery of the iLet BP system through telehealth provides the potential to supplement in-person delivery and allow broader access to this superior therapy.

1.2 Bionic Pancreas System

The BP is a dual infusion pump intended to provide automated control of blood glucose levels via continual subcutaneous infusion of insulin, or a combination of insulin and glucagon (bihormonal), for patients with diabetes or other conditions of glycemic dysregulation. The BP is developed such that it can be used in either configuration as they are both embedded within the same device.

1.2.1 *Key Distinction*

The BP is an autonomous self-learning control system that requires only the participant's weight for initialization, and then autonomously adapts, modestly or dramatically, to cope with the wide range of insulin requirements of adults, adolescents, and pre-adolescents with T1D. The BP obviates the need for the patient to know, or even appreciate, their insulin requirements, and renders obsolete any need for patients or caregivers to know carbohydrate to insulin ratios, basal rates, or insulin correction factors.

1.2.2 *Control Methodology and Philosophy*

The BP's core insulin control algorithm includes three insulin controllers for calculating and orchestrating all subcutaneous (SC) insulin dosing. At its centerpiece is a model-predictive control (MPC) algorithm, which bases insulin doses on the glucose data and insulin absorption kinetics, by 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 h), in order to enable the algorithm to refrain from stacking and overdosing insulin. Furthermore, our MPC algorithm automatically adjusts its insulin-dosing aggressiveness in real time to different insulin needs between individuals or within an individual. A second insulin controller automatically modulates basal insulin delivery over multiple time scales, and a third insulin controller that automatically adapts insulin doses in response to optional meal announcements. The MPC controller provides autonomous control doses that are required above and beyond basal insulin. Unlike insulin pumps and all insulin-only control algorithms of which we are aware, the BP's adaptive basal insulin controller obviates the need for the user to set, or even know their “basal-rate profile”. Instead, it is capable of automatically adapting to, and compensating for, changes in an individual's basal insulin need, whether over hours, days, or weeks (e.g. circadian hormonal fluctuations, intercurrent illness, physical activity, or emotional state) or months or years due to developmental changes (e.g. hormonal changes that occur during puberty or menopause). The BP's adaptive meal dose controller obviates the need for the user to set, or even know, their “carbohydrate-to-insulin ratios”, as it makes automatic adjustments to customize the individual’s meal dose based on dosing history for meal announcements on previous days.

In the bihormonal configuration, the BP also uses a proportional-derivative algorithm to issue 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.

1.2.3 *Autonomy*

The BP design’s primary consideration is autonomy. Apart from body weight for initialization, the BP requires no quantitative input from, or participation by, the user. The BP also remains autonomous in dose handling when the CGM is offline, whereby it (i) invokes a high-resolution ``basal-rate profile'' that it had recently learned when the CGM was online, (ii) responds to meal announcements based on what is

had learned about them when the CGM was online, and (iii) automatically responds to user-entered BG values by issuing a correction dose of insulin or glucagon. Thus, the BP never relies on the user with dose determination decisions and provides a turnkey glucose-control solution across a broad range of individual needs.

1.2.4 *Insulin-only Versus Bihormonal Configurations*

In the insulin-only configuration, all features of the BP operate as usual except that glucagon is not given. In addition, the lowest glucose target that can be chosen by the user is increased from 100 mg/dl in the bihormonal configuration to 110 mg/dl in the insulin-only configuration. This works to reduce the aggressiveness of insulin dosing in the insulin-only configuration relative to the bihormonal configuration, with the aim of keeping the amount of hypoglycemia low even at the potential cost of relatively raising the mean glucose level. On the other hand, the synergy of having both insulin and glucagon administration capabilities activated in the bihormonal configuration is expected to provide better glucose control with reduced hypoglycemia.

The primary intended use for the insulin-only configuration of the BP system is to provide automated glucose control prior to commercial availability of a stable glucagon analog. Moreover, when in the bihormonal configuration, the BP will automatically invoke the insulin-only configuration during periods whenever glucagon delivery is not possible.

1.3 BP System Embodiments

The BP hardware platform began as a laptop-driven system, which we used in all of our inpatient studies (2008–2012) at MGH. The BP embodiment was then transformed to a mobile wearable iPhone-Based system, which was used in our initial outpatient and home-use studies (2013–2017). From 2018 onwards, Beta Bionics transformed the system design into the iLet® Bionic Pancreas System (iLet), a fully integrated wearable device intended to undergo final clinical studies in order to be commercialized. Below are descriptions of and the outpatient clinical results that were obtained using the iPhone-based BP and the iLet.

1.3.1 *iPhone-Based BP System*

The iPhone-Based BP system consisted of the t:slim infusion pump (Tandem), a G4 or G5 CGM (Dexcom), and the BP control algorithms running on an iPhone app that has a graphical user interface (GUI). The iPhone and the Dexcom CGM receiver were hardwire connected and housed together in a custom enclosure, with the iPhone controlling the t:slim pump through Bluetooth. The BP app provided a user interface to make meal announcements by selecting the meal type (as “breakfast,” “lunch,” or “dinner”) and meal size (qualitatively as “larger than typical,” “typical,” “smaller than typical,” or “just a bite”). The BP app also reported associated system alarms and communicated to a server that allows remote telemetric study monitoring.

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. Additionally, the iPhone-based BP was used in the bihormonal configuration in subjects with

congenital hyperinsulinism after subtotal pancreatectomy, in the glucagon-only configuration as an adjunct to patient-controlled insulin dosing in adults with T1D or as an adjunct to usual therapy in adults with post-bariatric hypoglycemia, in the insulin-only configurations in adults with insulin-dependent type 2 diabetes, and in both configurations in adults with cystic fibrosis-related diabetes.

Table 1. iPhone BP System Studies

Year	Name of Study	Setting, Date span	Cohort studied	Duration & device exposure*	Configuration & Set Points	Medications used	Protocol Description, Outcome, if applicable.	Result: Mean CGM, % CGM < 60 mg/dl
2013	Beacon Hill IDE: G120255 11-2012	Supervised hotel stay Start–End: 02-2013– 09-2013	20 adults aged ≥21	5 days 2,400 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at home Direct supervision	BP: 133±13 mg/dl, 1.5% UC: 158±30 mg/dl, 3.7%
2013	2013 Summer Camp IDE: G130065 04-2013	Supervised summer setting Start–End: 07-2013– 08-2013	32 adolescents aged 12–18	5 days 3,840 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at camp Remote telemetric monitoring	BP: 142±12 mg/dl, 1.3% UC: 158±27 mg/dl, 2.2%
2014	2014 Summer Camp IDE: G130065 04-2013	Supervised camp setting Start–End: 07-2014– 08-2014	19 pre-adolescents aged 6–11	5 days 2,280 hours	Bihormonal 100 mg/dl iPhone + two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at camp Remote telemetric monitoring	BP: 137±11 mg/dl, 1.2% UC: 168±30 mg/dl, 2.8%
2014	BP Multi-center IDE: G140045 04-2014	Outpatient, home, 4 study sites Start–End: 05-2014– 03-2015	39 adults aged ≥18	11 days 10,296 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with usual care Remote telemetric monitoring	BP: 141±10 mg/dl, 0.6% UC: 162±29 mg/dl, 1.9%
2015 - 2016	BP Set Point IDE: G150130 JUL-2015	Outpatient, unsupervised at home Start–End: 08-2015– 12-2016	20 adults aged ≥18	8 arms, 4 days each 15,360 hours	Bihormonal and Insulin-only Bihormonal: 100, 110, 115, 130 mg/dl Insulin-only: 110, 120, 130, 145 mg/dl iPhone and one or two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with usual care and 8 different BP configurations testing different glucose target set points in addition to insulin only for the first time Both configurations at 110 mg/dl and 130 mg/dl included an exercise challenge to induce hypoglycemia under direct observation in the clinic Results helped identify the glucose target settings that will be used in future studies. These were set to range from 110 mg/dl to 130 mg/dl, with a default of 120 mg/dl in the insulin-only configuration, and set to range from 100 mg/dl to 120 mg/dl, with a default of 110 mg/dl in the bihormonal	Bihormonal: 100 mg/dl: 136±14 mg/dl, 0.8% 110 mg/dl: 148±17 mg/dl, 0.4% 115 mg/dl: 146±15 mg/dl, 0.9% 130 mg/dl: 156±12 mg/dl, 0.5% Insulin-only 110 mg/dl: 153±15 mg/dl, 1.3% 120 mg/dl: 156±15 mg/dl, 1.1% 130 mg/dl:

							configuration Remote telemetric monitoring	161±17 mg/dl, 0.8% 145 mg/dl: 174±23 mg/dl, 1.0% UC: 158±31 mg/dl, 1.4%
2015 - 2016	Stanford Insulin-only IDE: G150142 JUL-2015	Outpatient, unsupervised at home Start–End: 10-2015–01-2016	16 adults aged ≥18	2 arms, 7 days each 5,376 hours	Insulin-only 115 to 130 mg/dl iPhone and one Tandem t:slim pump	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk)	RCT with usual care Results helped identify the glucose target settings that will be used in future studies Remote telemetric monitoring	BP: 160±9 mg/dl, 0.9% UC: 151±26 mg/dl, 1.9%
2017	Monitoring IDE: G150130 JUL-2015	Outpatient, unsupervised at home Start–End: APR-2017–MAY-2017	23 adults aged ≥18	4 arms, 7 days each 15,456 hours	Bihormonal and Insulin-only Bihormonal: 100 mg/dl Insulin-only: 110 mg/dl iPhone and one or two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with one usual care arm and two BP arms, each repeated with and without remote monitoring Each arm repeated with and without remote telemetric monitoring Results confirmed that the insulin-only and bihormonal BP set at their lowest targets (110 and 100 mg/dl, respectively) are safe to be used in outpatient setting without remote monitoring for hypoglycemia	With monitoring: Insulin-only: 151±13 mg/dl, 1.6% Bihormonal: 139±13 mg/dl, 1.0% UC: 164±29 mg/dl, 1.3% Without monitoring: Insulin-only: 148±11 mg/dl, 1.7% Bihormonal: 139±11 mg/dl, 1.0% UC: 165±29 mg/dl, 2.0%
2016 - 2017	Zealand Feasibility Study IDE: G160012 FEB-2016	Supervised, in clinic Start–End: 12-2016–03-2017	10 adults aged ≥18	2 arms, 8 hours each 160 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Lilly) Insulin aspart (Novo Nordisk) Glucagon, 1 mg/ml (Lilly) Dasiglucagon, 1 mg/ml (Zealand)	RCT comparing Eli Lilly glucagon with dasiglucagon in clinic setting BP was challenged with participants wearing their own insulin pump in addition to the BP insulin dosing, with up to two times their normal basal running and a full meal bolus via their own pump. There was an exercise challenge in the late post-prandial period Direct supervision	Dasiglucagon: 110±29 mg/dl, 13% Lilly glucagon: 99±22 mg/dl, 20%

*Total device exposure is calculated based on cohort size used in the final study analysis

1.3.2 *Fully Integrated iLet® BP System (Beta Bionics)*

The iLet® Bionic Pancreas System (iLet) is a wearable device that integrates CGM technology via its built-in Bluetooth radio, two independent motor–drivetrain pumping mechanisms, which independently deliver insulin and glucagon from glass cartridges, and embedded software that includes our adaptive control algorithms. 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 provides a custom graphical user interface. 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, each with a proprietary connector to connect to its respective. Figure 1 illustrates the iLet's system components and a summary of its virtues and capabilities.

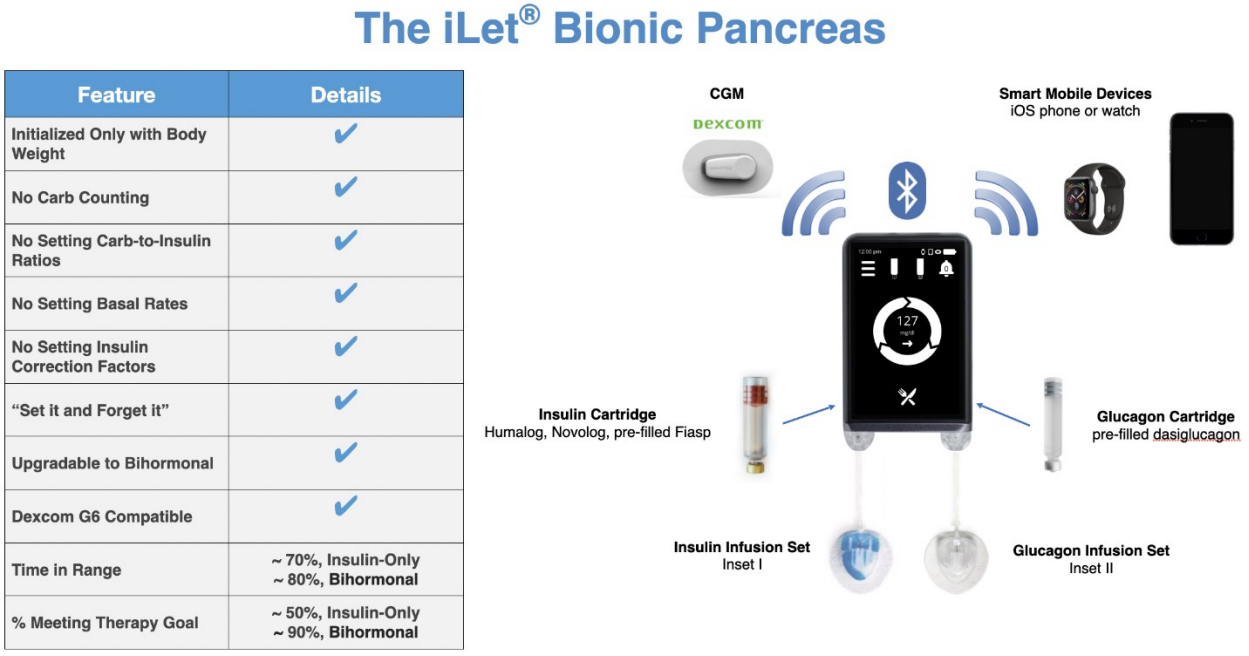


Figure 1 *Illustration of the iLet (Beta Bionics, Inc.) system components and capabilities. It is interoperable with one of two CGM devices and is compatible with three insulin analog formulations and one glucagon analog.*

Additionally, the iLet continually provides daily insulin dosing recommendations (for temporary self-management, should the iLet become temporarily unavailable, e.g. broken or lost), specifically (i) four 6-h basal rates for pump therapy or a 24-h long-acting basal dose for MDI therapy, (ii) a ``correction factor'' for insulin doses, and (iii) prandial insulin doses for the three main meals of the day. These are direction outcome of the autonomous learning capability of the iLet's three insulin controllers (basal, correction, and meal-dose controllers).

1.3.3 *Table 2.* ***iLet BP System Studies***

Year	Name of Study	Setting, Date span	Cohort studied	Duration & device exposure [1]	Configuration & Set Points	Medications used	Protocol Description, Outcome, if applicable.	Result: Mean CGM, % CGM < 60 mg/dl
2018	Adult Bridging study IDE: G180083 MAY-2018	Outpatient, unsupervised at home, 2 centers Start–End: MAY-2018–OCT-2018	34 adults aged ≥18 completed all three arms (36 started)	3 arms, 7 days each 11,424 hours	Insulin-only 120 mg/dl Gen 3 iLet MGH used Senseonics Eversense CGM, Stanford used	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Fiasp PumpCart (Novo Nordisk)	RCT with one usual care arm and 2 BP arms, where one BP arm used insulin lispro/aspart, the other BP arm used Fiasp. The BP was set at the default glucose target of 120 and tmax setting of 65 minutes for both arms Remote telemetric monitoring Remote telemetric monitoring. Results demonstrated that the insulin-only iLet BP was safe and	BP: 155±13 mg/dl, 1.2% BP with Fiasp: 154±11 mg/dl, 1.3% UC: 163±26 mg/dl, 1.3%

					Dexcom G5 CGM		effective using both Fiasp or lispro/aspart at the default PK settings, consistent with results of the iPhone BP studies, paving the path for a larger & longer study with same device settings and insulins	
2018	Day-camp Transitional Study IDE: G180083 MAY-2018	Supervised day camp, followed by unsupervised home nightly, 2 centers Start–End: JUL-2018–AUG-2018	20 children aged 6-17	5 days 2,400 hours	Insulin-only 120 mg/dl Gen 3 iLet	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk)	RCT comparing usual care with BP Remote telemetric monitoring Results demonstrated that under stressful conditions, the insulin-only iLet BP was safe and effective to use in adolescents and pre-adolescents, preparing the path for a larger and longer study using the same device settings in this age group	BP: 163±15 mg/dl, 0.9% UC: 160±27 mg/dl, 0.9%
2019	Fiasp Exploratory Study IDE: G180150 JUL-2018	48 hour supervised hotel stay, followed by unsupervised home, 5 days Start–End: MAR-2018–MAY-2018	24 adults aged ≥18, 8, Tmax=65, 8, Tmax=50 8, Tmax=40	3 cohorts, 8 subjects ≥18 each. 2 arms, 7 days each 8,064 hours	Insulin-only 120 mg/dl Gen 3 iLet	Fiasp PumpCart (Novo Nordisk)	RCT to compare default insulin PK settings (tmax = 65 minutes) with faster PK settings (tmax = 50, 40 and 30 minutes). Faster PK setting was escalated over three cohorts of 8 subjects Remote telemetric monitoring	Cohort #1, Tmax=65 157.7 mg/dl, 0.89% Cohort #1, Tmax=50 150.3 mg/dl, 0.98% Cohort #2, Tmax=65 157.6 mg/dl, 0.50% Cohort #2, Tmax=40 150.1 mg/dl, 0.69% Cohort #3, Tmax=65 152.5 mg/dl, 0.37% Cohort #3, Tmax=30 144.1 mg/dl, 0.61%
2019	Bihormonal Crossover Study IDE: G190028 FEB-2019	Outpatient, unsupervised at home Start–End: MAY-2019–JUN-2019	10 adults aged ≥18	2 arms, 7 days each 3,360 hours	Bihormonal and Insulin-only Bihormonal: 110 mg/dl Insulin-only: 110 mg/dl Gen 3 iLet	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Dasiglucagon, 4 mg/ml (Zealand Pharma)	RCT to compare insulin-only with bihormonal using dasiglucagon, testing bihormonal iLet for the first time Remote telemetric monitoring	Bihormonal: 139±11 mg/dl, 0.69% Insulin-only: 149±13 mg/dl, 1.38%

*Total device exposure is calculated based on cohort size used in the final study analysis

2 Objectives

2.1 Primary objective

To assess the feasibility of deploying the iLet bionic pancreas system in the insulin-only configuration to

pump-naïve MDI users with type 1 diabetes, in the setting of being recruited from community-based primary care practices and being trained and managed by primary care providers (PC group), and in pump- and CGM-experienced (sensor-augmented pump or hybrid closed-loop) users with type 1 diabetes recruited from, trained, and managed by an academic endocrinology practice (EN group). In both practice settings, the exclusive use of telehealth (TH) visits will be assessed, as will use of in-person (IP) visits.

We will enroll 40 adult volunteers (18-85 years old) with type 1 diabetes, 20 who are insulin pump naïve MDI users enrolled from community primary care practices by University of Colorado Family Medicine (PC group) and 20 who are technology-savvy sensor-augmented pump or hybrid closed-loop users enrolled by the Massachusetts General Hospital Diabetes Clinical Research Center (EN group). Ten of the participants at each center will be trained and managed throughout the trial using in-person visits (PC-IP and EN-IP groups) and the other ten from each center will be trained and managed throughout the trial exclusively via telehealth visits (PC-TH and EN-TH groups). The 40 participants will be evenly divided into these four groups, but not by randomization. Participants will be assigned to either the in-person or telehealth arm based on the participant's preference, the participant's location, and the discretion of the investigator. Subjects in all four groups will each participate, in random order, in one 14-day study arm under their own usual care (UC arm) and one 14-day study arm under the insulin-only configuration of the iLet bionic pancreas (iLet arm).

Our hypothesis is that pump naïve community-based primary care participants can be successfully started on the iLet bionic pancreas system by primary care providers in-person and via telehealth and that we will see similar glucose control by the iLet in the primary care and academic endocrinology groups and in the telehealth and in-person groups, with a target mean glucose of < 183 mg/dl in all four groups (PC-IP, PC-TH, EN-IP, and EN-TH). This target of < 183 mg/dl is a functional and clinically meaningful threshold for each group, consistent with a quality indicator of diabetes management (estimated HbA1c < 8.0%) that corresponds to the NCQA HEDIS measure of "HbA1c control" and which is therefore used frequently by many payers, reporting, and accrediting bodies. The outcome is categorical, and the primary outcome is not a direct comparison of the mean CGM glucose between the groups.

2.2 Secondary objectives

1. To obtain preliminary data on the quality of glycemic control among the PC and EN groups, with separate analyses in the IP and TH sub-groups, and in the UC and iLet arms within those groups, which will be used to power a larger study with a glycemic control metric as the primary outcome. Our hypotheses are that glycemic control, with key outcomes being group mean CGM glucose, the group mean time with CGM glucose less than 54 mg/dl, and the group mean time with CGM glucose in the 70–180 mg/dl range, will be similar in the PC-IP group and the EN-IP group, and in the PC-TH group and the EN-TH group in the iLet arm. Additionally, we hypothesize that glycemic control will be similar in the PC-TH group and the PC-IP group, and in the EN-TH group and the EN-IP group in the iLet arm. Further, we hypothesize that there will be a larger difference in glycemic control metrics between the UC arms versus the iLet arm in the PC group than there will be in the EN group.

2. To assess the impact of the insulin-only configuration of the iLet bionic pancreas system on psychosocial outcomes (including quality of life, fear of hypoglycemia, and diabetes distress) among study participants. Secondary analyses will be conducted between the telehealth and in-

person arm, the EN and PC groups, and the iLet and UC arms.

3 Participant Selection

3.1 Inclusion Criteria

1. Age 18-85 years, BMI ≥ 18.5, have had clinical type 1 diabetes for at least one year, and have taken insulin for at least 1 year
    a. Prescription diabetes medication regimen stable for > 1 month, including any adjunctive anti-diabetic medications (except for medications that will not affect the safety of the study and are not expected to affect any outcome of the study, in the judgment of the site principal investigator)
    b. This does not include changes to any insulin doses, including basal rates/long-acting insulin doses, carbohydrate to insulin ratios and correction factors
2. Willing to wear one Dexcom CGM transmitter and sensor (sensor must be changed every 10 days), and one infusion set that must be replaced at least every 3 days.
3. Endocrinology practice criterion is that diabetes is managed using sensor-augmented insulin pump therapy or artificial pancreas therapy for ≥ 3 months)
4. Primary care practice criteria are that diabetes is managed by multiple daily insulin injections (insulin-pump naïve).
5. TH group criterion is that participant must have hardware and internet access capable of 2-way video and audio communication

3.2 Exclusion Criteria

1. Unable to provide informed consent (e.g. impaired cognition or judgment)
2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory)
3. Unable to speak and read English, as iLet BP support materials and device menus are currently available in English only.
4. Plan to change usual diabetes regimen in the next 3 months including before and during participation in the study
    a. This would include changing from MDI to pump or from pump to MDI, and starting a CGM if not previously used
    b. This would not include changes to any insulin doses, including basal rates/long acting insulin doses, carbohydrate to insulin ratios and correction factors
5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system (e.g. “Loop” or “Open APS”)
6. Unwilling to switch to lispro or aspart for the duration of the study’s iLet arm (e.g. from Fiasp or Lyumjev)
7. Known hemoglobinopathy (sickle cell trait is not an exclusion)
8. Current participation in another diabetes-related clinical trial, has a medical condition, or use of a medication that, in the judgment of the investigator, could compromise the results of this study or the safety of the participant
9. History of diabetes due to cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy
10. Have a history of intermittently required glucocorticoid treatment (e.g., but not limited to, for the treatment of asthma, inflammatory bowel disease).

11. A1c >11.0% (most recent value up to 1 year prior acceptable; if none available or >1 year prior, participant will be instructed to obtain A1c through their usual care provider and to make copy of result available to study team)
12. History of diabetic ketoacidosis (DKA) within the past month
13. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference
14. Established history of allergy or severe reaction to adhesive or tape that must be used in the study
15. Currently treated with GLP-1 analogue, thiazolidinedione (TZD), sulfonylurea, pramlintide, or SGLT-2 inhibitor medication (*use more than 3 months prior to enrollment is acceptable*)
    a. If using metformin, participants:
        i. Must be on a stable dose for 1 month prior to enrollment
        ii. Metformin can be continued while the iLet is used
16. Pregnant (positive urine HCG), breast feeding, plan to become pregnant in the next 6 months, or premenopausal participants who are sexually active without use of contraception
17. Renal failure on dialysis or chronic renal disease with a GFR or eGFR <30mL/min (values within the last two years will be accepted; if none available or >2 years prior, participant will be instructed to obtain GFR or eGFR through their usual care provider and to make copy of result available to study team)
18. Any condition that, in the opinion of the site principal investigator, could interfere with the safe or effective completion of the study.
    a. Conditions to be considered by the investigator may include, but are not limited to, the following:
        i. Alcohol or drug abuse
        ii. Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study
        iii. Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. exercise of intensity up to 6 METS) despite medical management, or within the last 12 months before screening, a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting
        iv. Known history of prolonged QTc interval, malignant arrhythmia, or congenital heart disease
        v. Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV
        vi. History of TIA or stroke in the last 12 months
        vii. Untreated or inadequately treated mental illness
        viii. History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulimia or omission of insulin to manipulate weight
        ix. History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
19. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.);

or having a first-degree relative who is directly involved in conducting the clinical trial

20. Unable to avoid hydroxyurea for duration of study (interferes with accuracy of Dexcom G6 CGM)

3.3 Source of Participants

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

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

All recruitment methods and specific advertising materials will be IRB approved prior to their implementation. No individuals will be excluded based on gender or race. An equal gender distribution is anticipated.

4 Participant Enrollment

4.1 Number of Participants

It is expected that we will have 40 participants complete the study with a consistent protocol, with 20 participants at each site. We estimate that there are, at a minimum, 6700 adults with T1D in Colorado who use MDI, and that there are at least 1100 potential participants who are active patients at just a fraction of the primary care clinics from which we will be recruiting; we therefore expect that recruitment, the experiments, and the analysis can be accomplished over a period of 9-18 months. Up to 80 participants may be screened and enrolled. The upper bound is based on the expectation that some volunteers will be excluded after the screening visit and the possibility that some experiments may have to be discontinued before completion (due to, for instance, intercurrent illness or participant withdrawal).

4.2 Enrollment and Consent Procedures

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

Once potential participants have had time to review the consent document, they will meet with a study

provider (MD or NP) in person, over the phone, or over video conference. They will explain the study, answer any questions, and administer informed consent prior to any data collection or study-specific procedures. If a volunteer is a patient of one of the study MDs or NPs, another staff MD or NP will answer questions and administer consent. A licensed physician investigator will be available to speak with the participants during the consent process in the event of a non-physician administering consent. The site principal investigators will be responsible for assuring that the informed consent process is properly followed and that each study participant is well informed about the study and the participant's responsibilities. Consent will be documented with either electronic or wet ink signatures. Electronic consent will be obtained via REDCap.

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 participation at any time.

5 Study Procedures

5.1 Study Design

This study will assess delivery of the insulin-only iLet bionic pancreas by primary care providers and endocrinologists, as well as delivery of the iLet bionic pancreas via in-person training and support vs telehealth training and support. It will employ a two-center, random-order, two-arm cross-over trial design in a home-use setting in 40 adult participants (18-85 years of age) with type 1 diabetes. This number is based on 10 participants per arm, per site, which has been successfully implemented in previous iLet studies and which has yielded highly significant results in those studies. The two centers will be community-based primary care and academic medical center-based endocrinology. Study participants will be managed by appropriate site-specific study team clinicians: endocrinology providers at MGH, or primary care providers at CU.

The two 14-day study arms will occur in a random-order cross-over design. One arm will involve using the insulin-only iLet bionic pancreas and the other arm will involve insulin delivery via the participants' usual care (multiple daily injections or insulin pump, depending on the study site). Half of the participants will receive care via in-person visits, and the other half will receive care exclusively via telehealth visits. This will result in four study cohorts overall [endocrinology in-person (EN-IP), endocrinology telehealth (EN-TH), primary care in-person (PC-IP), primary care telehealth (PC-TH)].

5.2 Screening Data

- Age
- Sex
- Race and ethnicity
- Basic demographic information
- Date of last menstrual period in pre-menopausal participants
- Approximate date of diabetes diagnosis
- Medical, surgical, and social history, allergies and review of systems relevant to inclusion and exclusion criteria
    - Medical history relevant to T1D diagnosis will also be assessed for information supporting a clinical diagnosis of T1D, which may include: prior diagnosis of T1D, age at diagnosis, symptoms at diagnosis (e.g. DKA), presence of autoimmune markers, family history of

diabetes without type 2 features (e.g. obesity or high-risk ethnicity), body habitus at time of diagnosis, the presence of other autoimmune disorders, low C-peptide levels, as well as any other relevant data in the medical history.

- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump and CGM use, if applicable
- Type of insulin(s) currently used
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio for pump and if known for MDI; otherwise doses and schedule for MDI, sliding scale/correction if applicable)
- Average total daily dose of insulin in the last 30 days
- Usage of CGM (type of CGM, days per month worn, usage of data, whether insulin dosing is based on CGM alone, alarm settings), if applicable
- Height and weight
- Urine HCG (post-menarchal, pre-menopausal participants)

5.3 Drugs

The study involves subcutaneous administration of **insulin lispro** (Humalog, Lilly) or **insulin aspart** (Novolog, Novo Nordisk). Humalog and Novolog are commercially available by prescription and are indicated for patients with diabetes but are not indicated for use in the iLet bionic pancreas. No participants will use insulin Fiasp during the bionic pancreas arm. Participants using insulin Fiasp as part of their usual care will use insulin aspart with the iLet.

Participants randomized to the UC arm will follow their standard diabetes regimen with the insulin prescribed by their health care provider. During the iLet arm, participants will fill the Ready-to-Fill insulin cartridge with whichever insulin (lispro or aspart) they were using during their usual care, unless using insulin other than lispro or aspart for UC, in which case they will be provided with lispro or aspart for the iLet arm.

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

5.4 Devices

5.4.1 *Infusion sets*

Participants in the iLet arm will be provided with infusion sets for use with 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. This will be done in person for EN-IP and PC-IP, and through HIPAA compliant video conferencing software for EN-TH and PC-TH. Participants will be instructed to replace their infusion sets as needed when it fails (or is suspected of failing), falls out, or at least every 3 days. Participants will be given contact information of the study team in the case that they wish to complete the infusion set changes on HIPAA compliant video conferencing software for Healthcare. The number of participants choosing to do this will be tracked.

5.4.2 *Continuous glucose monitor (CGM) Sensor*

One transcutaneous glucose sensor for the Dexcom G6 CGM will be inserted in the SC tissue and will provide input to the controller. The sensor is powered by the battery within the transmitter that clips to

the sensor. The whole assembly is held to the skin with an adhesive patch and communicates wirelessly via Bluetooth Low Energy with the Dexcom G6 system built into the bionic pancreas. If the G6 sensor fails for any reason during the experiment it will be replaced promptly. The G6 sensor will be replaced at least every 10 days. In the PC group, if the participant is not a CGM user the CGM will be blinded.

5.4.3 *iLet Bionic Pancreas*

The iLet bionic pancreas has an integrated graphical user interface (GUI) and touchscreen display that displays the current CGM glucose, a graphical history of the CGM glucose, and doses of insulin delivered by the control algorithm. The GUI can also be used to input meal announcements, designating qualitatively the meal carb content as "Usual for me", "More", or "Less" than usual. This will trigger a partial meal-priming bolus, the size of which will adapt during the course of the trial in accordance with the insulin needs for that size and mealtime (e.g. a portion of the mealtime insulin need).

The target BG for the insulin-only BP is 120 mg/dl by default ("Usual"), but the user may designate a lower default target (of 110 mg/dl, "Lower") or a higher default target (of 130 mg/dl, "Higher"). Participants transitioning to the BP from an MDI regimen or those who have a very low insulin TDD at baseline may be set to start the study period at the higher glucose target at the discretion of the site investigator. Participants who have a high HbA1c at screening and who may have symptoms of hypoglycemia in the normoglycemic range may be set to start the study period at a higher target at the discretion of the site investigator. Participants will be able to edit their glucose target in all BP arms, but they will be instructed to contact study staff prior to changing their target.

The GUI can also be used to manage meal boluses and correction boluses during periods when the CGM is offline, such as the period after a sensor is replaced and before the new sensor has been calibrated. During these times, the control algorithm will determine and direct the administration of insulin basal rates either based on the participant's weight in the first 24 hours of the experiment, or on the average of adaptively determined basal rates for that time of day once sufficient experience has been accumulated (i.e. 24 hours or more) by the control algorithm. The controller also will administer insulin or decrease basal insulin as appropriate, in response to any entered BG values, just as if the BG values were CGM values.

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

Study teams will be trained by Beta Bionics on the use and implementation of the iLet. A delegation log reflecting training completion for study team members will be signed and maintained onsite.

5.4.4 *Ascensia Diabetes Care Contour Next One Glucose Meter system*

The Contour Next One glucometer is FDA approved and commercially available. Participants will be asked to use this meter and its proprietary test strips for all blood glucose measurements during the study.

5.4.5 *Precision Xtra Ketone Meter system*

The Precision Xtra ketone meter is FDA approved and commercially available. Participants will be asked to use this meter and its proprietary test strips for all blood ketone measurements during the study.

5.5 Screening and Randomization

5.5.1 *Screening Visit (Visit 1)*

At the screening visit, the following procedures will be performed:

- Informed consent
- Assessment of eligibility, including review of medications and medical history
- Recording of height and weight
- Urine pregnancy test for all post-menarche and premenopausal people who are not surgically sterile

A study MD or NP will review the case report form to determine eligibility. If participants are not eligible to continue in the study, the study MD or NP will explain why. Participants who have been screened and are eligible can participate without having to be re-screened for a period of 3 months. The study staff should verbally confirm that there have been no health events that would make them ineligible at every study visit and rescreen participants for eligibility if it has been greater than three months.

5.5.2 *Prior to Randomization*

- Psychosocial questionnaires (including quality of life, fear of hypoglycemia, diabetes distress).
- HbA1c assessment using a validated method (a value within 2 weeks prior to enrollment is acceptable)

5.5.3 *Randomization of Study Arm Sequence*

Participants will be recruited specifically into the in-person or telehealth cohorts, based on their circumstances. Once the participant has been enrolled and eligibility has been established, participants within each of these cohorts will be randomized to one of two possible study arm sequences.

5.6 Study Visit Procedures

5.6.1 *Visit Procedures for in-person (IP) visits*

5.6.1.1 Day 1 Visit (Visit 2):

- The body weight of the participant will be documented.
- A urine pregnancy test will be performed in participants of child-bearing potential at the start of the first arm. If the test is positive, the participant will be informed of the result and the visit will be ended. The date of the last menstrual period will also be documented. .
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.

5.6.1.1.1 Participants randomized to usual care:

- Study staff will provide supplies and review the study procedures.
- Participants will be trained how to insert, maintain and use the Dexcom G6 (in blinded mode if they are not a CGM user).
- The participants will wear a Dexcom G6 sensor and study staff will confirm they are doing it properly.

5.6.1.1.2 Participants randomized to bionic pancreas:

- Study staff will provide supplies and review the study procedures.
- Participants will be trained how to insert, maintain and use the Dexcom G6 CGM.
- The participants will wear a Dexcom G6 sensor and study staff will confirm they are doing it

properly.

- Participants will be trained to use the iLet, including navigating the GUI, filling and installing cartridges and inserting infusion sets.
- Participants will set up the iLet and insert the infusion set and study staff will confirm they are doing it properly.
- The control algorithm will be initialized with the participant's weight.
- If using an insulin pump (EN group), their own insulin infusion pump will be stopped and disconnected if applicable, and its infusion set will be removed
- If using MDI therapy (PC group), they will be instructed not to take any additional insulin injections once the bionic pancreas is started, unless instructed to do so by study staff
    - Participants on multiple daily injections (MDI) may be started on the iLet without a need for adjustment of their long-acting insulin dose. The new equilibrium will not be reached until all the long-acting insulin has completely cleared their system, which may take 48 hours or more. Participants must be advised that they may see escalating dosing by the iLet during this period.
    - Investigators may consider starting MDI users at the "higher" glucose target setting. If the "higher" setting is used, wait ~2 days before moving down to the default target.
- Participants will complete Clarke's Instrument for Impaired Awareness of Hypoglycemia.
    - Participants with a score > 4 will be instructed to check BG at 2am for the first 2 nights using the iLet

5.6.1.2 Mid-period Follow Ups (Visits 3, 4, 6, and 7):

- Study staff may supervise the first site change via a video visit, as needed or requested based on participant's prior experience and comfort level
- All participants will have a virtual phone visit on Day 2 and Day 5 (+/-2 days) to assess device adaptation, glucose control, and to answer any questions the participant may have
- Study staff will query the participant for any adverse events and assess the participant's ability to follow protocol and, if applicable, use the device at this time.

5.6.1.2.1 BP arm

- Participants on the BP will be asked about their glucose control and study staff will educate as needed. The study staff may suggest a change to the permanent glucose target if indicated.

5.6.1.2.2 UC arm

- No modifications will be made to dosing regimens for participants in the usual care arm.
- Study staff will confirm the participant is wearing the study CGM, and answer any questions the participant may have about the CGM. They will remind the participant to replace the study CGM after 10 days.

5.6.1.3 Crossover Visit (Visit 5):

- At the end of the first study period (Day 14 [+2]), participants will return to the clinic and answer the post questionnaires for the study arm.
- A urine pregnancy test will be performed in participants of child-bearing potential. If the test is positive, the participant will be informed of the result and the next planned study arm will not proceed. The date of the last menstrual period will also be documented.
- Any changes to medications or medical history and any adverse events that may have occurred since the last study visit will be documented.

- All study devices applicable to the arm just completed will be downloaded
    - BP arm: iLet and study glucometer and ketone meter
    - UC arm: Dexcom G6 and study glucometer
- Participants will repeat psychosocial questionnaires (including quality of life, fear of hypoglycemia, diabetes distress).
    - Participants coming off of the BP arm will be asked to complete the Bionic Pancreas User Opinion Survey
- Participants will then start over with Day 1 procedures for the arm they are randomized to next. This may occur immediately, or within 14 days after the completion of the first arm.
    - If the participant is switching from usual care to bionic pancreas:
        - If using an insulin pump (EN group), their own insulin infusion pump will be stopped and disconnected if applicable, and its infusion set will be removed
        - If using MDI therapy (PC group), they will be instructed not to take any additional insulin injections once the bionic pancreas is started, unless instructed to do so by study staff
    - If the participant is switching from bionic pancreas to usual care, a provider (MD or NP) will review the last several hours of insulin dosing and assist the participant in resuming their usual care.
        - For participants whose usual care is MDI therapy:
            - If normal long-acting dose time is MORNING:
                - Morning study visit – take full dose at visit, take next day dose at usual time
                - Afternoon study visit – three quarters of normal dose at visit, take next day dose at usual time
            - If normal long-acting dose time is EVENING:
                - Morning study visit – take half of full dose at visit (acts as loading dose), take full dose at normal time that same evening
                - Afternoon study visit – take one fourth of full dose at visit (acts as loading dose), take full dose at normal time that same evening
        - Investigators may use a different approach according to their judgment.

5.6.1.4 Final Visit (Visit 8):

- Any changes to medications or medical history and any adverse events that may have occurred since the last study visit will be documented.
- The Dexcom CGM sensor and all bionic pancreas infusion sites will be removed, as necessary.
- All study devices, including the iLet, Dexcom G6, and the study glucose and ketone meters will be downloaded.
- If the participant is coming off of the bionic pancreas, a provider (MD or NP) will review the last several hours of insulin dosing and assist the participant in resuming their usual care.
        - For participants whose usual care is MDI therapy:
            - If normal long-acting dose time is MORNING:
                - Morning study visit – take full dose at visit, take next day dose at usual time
                - Afternoon study visit – three quarters of normal dose at visit, take next day dose at usual time

- If normal long-acting dose time is EVENING:
    - Morning study visit – take half of full dose at visit (acts as loading dose), take full dose at normal time that same evening
    - Afternoon study visit – take one fourth of full dose at visit (acts as loading dose), take full dose at normal time that same evening
- Investigators may use a different approach according to their judgment.

- Participants will be explicitly instructed to resume their usual, pre-study glucose monitoring and to contact their usual diabetes care provider in case any questions or concerns arise about their usual diabetes care following completion of the study.
- All collected equipment will be cleaned using the validated cleaning and disinfecting procedures.
- Participants will be reminded to bring their own pump (EN group) or MDI supplies (PC group), and all other appropriate supplies and insulin to this visit.
- Participants will repeat psychosocial questionnaires (including quality of life, fear of hypoglycemia, diabetes distress).
    - Participants coming off of the BP arm will be asked to complete the Bionic Pancreas User Opinion Survey

5.6.2 *Visit Procedures for telehealth visits*

- Supplies will be shipped to the participant in advance of the scheduled study start visit (Day 1 Visit immediately below). They will be instructed not to unpack any study materials until the scheduled telehealth visit. This will include a scale for measurement of weight, a home pregnancy testing kit, and supplies required for the study.
- All TH study visits will be completed using HIPAA compliant videoconferencing software.

5.6.2.1 Day 1 Visit (Visit 2):

- The body weight of the participant will be verbally self-reported by the participants, who will be instructed to use the scale provided.
- A urine pregnancy test in participants of child-bearing potential will be completed at home using the study-provided pregnancy test at the start of the first arm. Participants will be instructed to complete the pregnancy test during the virtual visit and to show result to study staff. If the test is positive, the participant will be informed of the result and the visit will be ended. The date of the last menstrual period will also be documented.
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.

5.6.2.1.1 Participants randomized to usual care:

- Study staff will review supplies provided and the study procedures.
- Participants will be trained how to insert, maintain and use the Dexcom G6.
- The participants will wear a Dexcom G6 sensor and study staff will confirm they are doing it properly.

5.6.2.1.2 Participants randomized to bionic pancreas:

- Study staff will review supplies provided and the study procedures.
- Participants will be trained how to insert, maintain and use the Dexcom G6 CGM.
- The participants will wear a Dexcom G6 sensor and study staff will confirm they are doing it properly.
- Participants will be trained to use the iLet, including navigating the GUI, filling and installing

cartridges and inserting infusion sets.

- Participants will set up the iLet and insert the infusion set and study staff will confirm they are doing it properly.
- The control algorithm will be initialized with the participant's weight.
- If using an insulin pump (EN group), their own insulin infusion pump will be stopped and disconnected if applicable, and its infusion set will be removed.
- If using MDI therapy (PC group), they will be instructed not to take any basal insulin starting the morning of this study visit, and no additional insulin injections once the bionic pancreas is started, unless instructed to do so by study staff
    - Participants on multiple daily injections (MDI) may be started on the iLet without a need for adjustment of their long-acting insulin dose. The new equilibrium will not be reached until all the long-acting insulin has completely cleared their system, which may take 48 hours or more. Participants must be advised that they may see escalating dosing by the iLet during this period.
    - Investigators may consider starting MDI users at the "higher" glucose target setting. If the "higher" setting is used, wait ~2 days before moving down to the default target.
- Participants will complete Clarke's Instrument for Impaired Awareness of Hypoglycemia.
    - Participants with a score > 4 will be instructed to check BG at 2am for the first 2 nights using the iLet

5.6.2.2 Mid-period Follow Ups (Visits 3, 4, 6, and 7):

- Participants may complete a virtually supervised site change, as needed or requested based on participant's prior experience and comfort level.
- All participants will have a virtual phone visit on Day 2 and Day 5 (+/-2 days) to assess device adaptation, glucose control, and to answer any questions the participant may have.
- Study staff will query the participant for any adverse events and assess the participant's ability to follow protocol and, if applicable, use the device at this time.

5.6.2.2.1 BP arm:

- Participants on the BP will be asked about their glucose control and study staff will educate as needed. The study staff may suggest a change to the permanent glucose target if indicated.

5.6.2.2.2 UC arm

- No modifications will be made to dosing regimens for participants in the usual care arm.
- Study staff will confirm the participant is wearing the study CGM, and answer any questions the participant may have about the study CGM. They will remind the participant to replace the study CGM after 10 days.

5.6.2.3 Crossover Visits (Visit 5):

- At the end of the first study period (Day 14 [+2]), participants will have a virtual study visit and answer the post questionnaires for the study arm.
- Study staff will review any changes in the participant's medical history or medications to ensure continued eligibility, and any adverse events that may have occurred since their screening visit.
- A urine pregnancy test will be performed in participants of child-bearing potential. Participants will be instructed to complete the pregnancy test during the virtual visit and to show result to study staff. If the test is positive, the participant will be informed of the result and the next planned study arm will not proceed. The date of the last menstrual period will also be

documented.

- They will start over with Day 1 procedures for the arm they are randomized to next. This may occur on the same day, or within 14 days of the final visit of the first arm.
    - If the participant is switching from usual care to bionic pancreas:
        - If using an insulin pump (EN group), their own insulin infusion pump will be stopped and disconnected if applicable, and its infusion set will be removed.
        - If using MDI therapy (PC group), they will be instructed not to take any basal insulin starting the morning of this study visit, and no additional insulin injections once the bionic pancreas is started, unless instructed to do so by study staff
    - If the participant is switching from bionic pancreas to usual care, a provider (MD or NP) will review the last several hours of insulin dosing and assist the participant in resuming their usual care.
        - For participants whose usual care is MDI therapy:
            - If normal long-acting dose time is MORNING:
                - Morning study visit – take full dose at visit, take next day dose at usual time
                - Afternoon study visit – three quarters of normal dose at visit, take next day dose at usual time
            - If normal long-acting dose time is EVENING:
                - Morning study visit – take half of full dose at visit (acts as loading dose), take full dose at normal time that same evening
                - Afternoon study visit – take one fourth of full dose at visit (acts as loading dose), take full dose at normal time that same evening
- Investigators may use a different approach according to their judgment.
- Participants will repeat psychosocial questionnaires (including quality of life, fear of hypoglycemia, diabetes distress).
    - Participants coming off of the BP arm will be asked to complete the Bionic Pancreas User Opinion Survey

5.6.2.4 Final Visit (Visit 8):

- The body weight of the participant will be documented using the scale provided.
- Any changes to medications or medical history and any adverse events that may have occurred since the last study visit will be documented.
- The Dexcom CGM sensor and all bionic pancreas infusion sites will be removed, as necessary.
- Participants will be reminded to have available their own pump (EN group) or MDI supplies (PC group), and all other appropriate supplies and insulin at this visit.
- If the participant is coming off of the bionic pancreas, a provider (MD or NP) will review the last several hours of insulin dosing and assist the participant in resuming their usual care.
        - For participants whose usual care is MDI therapy:
            - If normal long-acting dose time is MORNING:
                - Morning study visit – take full dose at visit, take next day dose at usual time
                - Afternoon study visit – three quarters of normal dose at visit, take next day dose at usual time
            - If normal long-acting dose time is EVENING:
                - Morning study visit – take half of full dose at visit (acts as loading

dose), take full dose at normal time that same evening
        - Afternoon study visit – take one fourth of full dose at visit (acts as loading dose), take full dose at normal time that same evening
    - Investigators may use a different approach according to their judgment.
- Participants will be explicitly instructed to resume their usual, pre-study glucose monitoring and to contact their usual diabetes care provider in case any questions or concerns arise about their usual diabetes care following completion of the study.
- All study devices, including the iLet, Dexcom G6, and the study glucose and ketone meters will be packaged by participants into supplied packing and shipping materials, and returned to the study site using supplied prepaid shipping label/box.
    - Upon receipt of the materials at the site, equipment will be cleaned and disinfected by the study team using validated procedures.
    - The iLet, Dexcom G6, and study glucose and ketone meters will be downloaded.
- Participants will repeat psychosocial questionnaires (including quality of life, fear of hypoglycemia, diabetes distress).
    - Participants coming off of the BP arm will be asked to complete the Bionic Pancreas User Opinion Survey

5.7 General Study Policies for all Study Arms

- Participants will be advised not to use alcohol or other drugs in sufficient quantity to reduce sensitivity to symptoms of hypoglycemia or hinder appropriate decision-making.
- Any medical advice needed by the participants during their participation that is not directly related to the study protocol should be obtained in the usual manner with their own physician. 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.
- There are no restrictions of any kind on diet, exercise, or other activities.
- Participants will be asked to complete a daily survey in all study arms including questions about hypoglycemia and carbohydrate interventions and diabetes tasks that occurred in the prior 24 hours. Participants on the BP arm will also be asked about time disconnected from the iLet.
- Study participants will be instructed to keep fast-acting carbohydrates and a glucagon emergency kit (supplied by the study) easily accessible in case they are needed.
- Participants will be instructed to keep fast-acting insulin with them in case of a hyperglycemic emergency.
- Participants will be instructed to carry an extra sensor with them at all times. They will be taught to replace the sensor if it falls out, or after 10 days.

5.7.1 *Policies for the Usual Care Arm*

- Participants may be contacted between visits if needed, per the discretion of either the participant, a healthcare provider, or a member of the study team.
- The UC arm will continue its pre-study diabetes management, including approach to insulin delivery and management. Diabetes management will be handled by the participant's usual diabetes health care provider. *No adjustments to the diabetes care plan will be made by the study team.*

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

5.7.2 *Policies for the Bionic Pancreas Arms*

- Participants may be contacted between visits if needed, per the discretion of either the participant, a healthcare provider, or a member of the study team.
- Participants using the iLet will not be allowed to travel outside the United States or its territories for the entire time the system is in use.
- Participants may perform calibrations of the Dexcom G6 CGM if it is inaccurate relative to a BG measurement, per the device manufacturer's instructions.
- The iLet will have CGM glucose alarm settings available to the participants. Study staff will work with participants to configure the alarm settings in a way that will be most appropriate for each individual.
    - Study staff will recommend a low CGM glucose alarm be set for 75 mg/dl and a high CGM glucose alarm be set for > 300 mg/dl for 90 minutes.
- If participants receive a high or low CGM glucose alarm, they will be trained to verify the CGM glucose with a fingerstick glucose value using the Contour Next One glucometer.
    - The participant will be trained to treat hypoglycemia with rapid acting carbohydrates, in case the glucometer confirms hypoglycemia. This may be done according to their usual practice or with less carbohydrate than their usual practice since the BP system will typically have suspended insulin delivery prior to the occurrence of hypoglycemia. They will be trained to continue to monitor their glucose levels until they return to normoglycemia.
    - Participants will be trained to assess their infusion set and tubing for patency, the insulin reservoir for sufficient insulin supply, the iLet for sufficient battery power, proper functioning, and insulin delivery, in case the glucometer confirms hyperglycemia. In case hyperglycemia > 300 mg/dl persists for more than 90 minutes, they will be trained to check their blood ketone level using the Precision Xtra blood ketone meter.
        - In case ketones are ≥0.6 mmol/l, they will be trained to replace their infusion set and to inform study staff. They will be trained to continue to monitor their glucose and blood ketone levels until they return to normoglycemia and ketones are < 0.6 mmol/l.
        - If ketones are <0.6 mmol/l, they will be advised to continue to monitor their glucose until it returns to normoglycemia and to repeat the ketone measurement in 90 minutes if necessary
    - If the glucometer reading is not consistent with the CGM glucose reading, participants will be trained to look for possible scenarios that could lead to an inaccurate CGM reading.
        - They will be educated about the lag between interstitial and capillary glucose readings, and to delay a calibration in times of rapid changes in glucose. They will also be trained about the standard difference between CGM and capillary glucose readings, and to consider the CGM inaccurate if it is >20% different than their glucometer reading. If their CGM glucose is not changing rapidly and is >20% different from their capillary glucose reading, they will be instructed to calibrate

their CGM if possible.
        - A compression artifact at the site of the sensor may cause false hypoglycemic readings. This should resolve by removing the compression of the sensor.
- If there is a technical fault with the iLet, the participant will be instructed to call the clinical site immediately.
    - All contacts from a study participant will be documented. The site will be responsible for all reporting of device issues and adverse events.
    - If necessary, a staff member will meet the participant to assist with troubleshooting. This meeting may be delayed until morning if the problem occurs overnight —in this case, the participant will use their own pump or use injectable insulin until a meeting is possible. A member of the study staff (within their scope of practice and under the supervision of the site principal investigator) may advise them on how to manage their diabetes in the interim. If necessary, the iLet device may be replaced. This may require shipping a new device to the participant. For participants in the telehealth arm, a new device will either be sent via express delivery or driven to the participant if feasible. Participants will be instructed to revert to usual care until they get the iLet.
- If there is a complete failure of the iLet operation and it is anticipated that restarting it will take more than an hour, or there is physical disconnection from the iLet that lasts longer than one hour, participants may revert to usual care using their own insulin pump or with insulin injections until the iLet can be brought back online with the help of study staff. In addition, frequent BG checks (every 2 hours and before meals) will be advised for any participant not receiving CGM data in this circumstance. Every effort should be made to correct the problem as soon as possible, which should almost always be within 24 hours
- Participants will be instructed to call the study team immediately, at any time of day or night, under any of the following circumstances:
    - They have questions or concerns
    - They want assistance troubleshooting the device
    - They have unexplained glucose over 300 mg/dL for greater than 90 minutes
    - They have ketones greater than 2.5 mmol/L (Large)
    - They have ketones greater than 0.6 mmol/L for more than 90 minutes
- If the sensor fails, it should be replaced. If the sensor is offline, participants will be instructed to self-check blood glucose at least every two hours and before meals.
    - If the sensor is offline for more than 4 hours, the sensor alerts as failed and should be replaced.
    - When the CGM is offline, the iLet will continue giving basal doses based on the latest basal dosing that it had learned, allow the user to make meal announcements in exactly the same way as when the CGM was online, and automatically respond to user-entered BG values by issuing a correction dose of insulin when applicable. If the CGM sensor is not reading glucose levels, the system will provide basal insulin based on past requirements and will allow announcement of meals and entry of fingerstick BG measurements, which will be treated as CGM data and may result in administration of insulin or temporary suspension of basal insulin. The system will alarm and request a BG measurement every 2 hours when the CGM signal is not available. Participants will be trained in various ways to bring their study CGM sensor back online. This may involve replacement of the Dexcom G6 CGM sensor. If instructed by the iLet to do so, the

participant will start a new CGM sensor. If the sensor is offline for more than 3 hours, the participant will start a new sensor. The closed loop system may be used without CGM input for a maximum of 6 hours. Normal (online) BP control will resume automatically when the CGM sensor is reporting glucose values again.
    - Study staff will contact Beta Bionics for additional troubleshooting as necessary.
- Participants will be instructed to announce up to three major meals a day to the iLet. The meal announcement will consist of choosing the size of the meal relative to usual meals for that participant at that time of day (Usual for me, Less, More). Participants will be trained not to announce snacks that occur between major meals.
- Participants will be trained on the interface to change the glucose targets. They will be asked to consult with study staff before making any changes to the permanent target or to setting a daily/night recurring target alteration schedule.
- Participants will be asked to change their infusion set at least every 3 days.
- The insulin cartridge and tubing will be replaced as needed, but no less often than every 3 days.
- A new Dexcom CGM sensor will be placed every 10 days if no replacement was required before this time. The iLet will generate an alarm when replacement is required.
- Participants will be asked to charge their iLet routinely (preferably at least once daily, such as when they are bathing) and whenever they notice the battery level is low. The iLet will alarm at low battery thresholds.
- Participants will not tamper with or alter the iLet device in any way.
- The iLet is water resistant but participants will be instructed to remove it for showering and swimming and to keep it dry during exercise.
- Participants will be trained to take appropriate precautions when they are disconnected from the iLet, including frequent BG checks using the study Contour Next One glucometer if they are not monitoring CGM glucose by another method (e.g. their phone) and to have carbohydrate readily available. They are urged to limit the amount of time they are disconnected from the iLet to ensure optimal glucose control.
- If a participant develops an illness during the study, they can seek medical care as usual. If the participant is unable to eat for a period exceeding one day, they must notify study staff so that the medical staff can assess the safety of continuing to use the iLet. Use of the iLet may be temporarily discontinued if study staff believe this is warranted.
- If a participant discontinues use of the iLet either due to investigator judgment that it is not safe for the participant to continue to use the iLet or the participant's choice, the participant will return to their pre-study insulin delivery and glucose monitoring method and will be instructed to contact their usual diabetes care provider in case any questions or concerns arise about their usual diabetes care following cessation of study activities.

5.7.3 *Alarm Settings and Response to Hypoglycemia and Hyperglycemia*

All alarm settings will be the same during both BP arms. The blinded CGM will not have any alarms. Participants using their personal CGM as part of their usual care will be instructed to follow the alarm settings prescribed by their diabetes care provider.

- Alarms will sound and a visual alert will appear on the screen of iLet when the CGM glucose is ≤ 55 mg/dl. There is an optional additional hypoglycemia alarm at 75 mg/dl. Study staff will recommend participants use this alarm as well.
    - Participants will be trained to test their BG with the study glucometer in response to such

an alarm and take any necessary measures to treat hypoglycemia as described in section 5.7.2.

- An optional alarm will sound, and a visual alert will appear on the iLet if CGM glucose is > 300 mg/dl for 90 minutes. Study staff will recommend participants use this alarm.
    - Participants will be trained to test their BG with the study glucometer in response to such an alarm and take any necessary measures to treat hypoglycemia as described in section 5.7.2.

5.7.4 *Supervision by study staff*

A study provider (MD or NP) will be on call at all times during the course of the study to answer questions and address any issues that arise. The Beta Bionics technical support center will be readily available by phone consultation at all times to assist with any needed troubleshooting.

A study provider (MD or NP) will respond to calls regarding ketosis concerning for DKA or severe hypoglycemia requiring assistance from another person. In such circumstances, the study MD or NP will speak directly to the participant (or to the person assisting them). The Site PI must be informed within one hour if they are not already aware of the event. If the site PI will not be available, then the site PI will designate another investigator for the period during which they will not be available so that it is clear who has this responsibility.

If based on their experience and judgment study staff believes that the participant needs emergency care, they should recommend to the participant that the participant 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 the participant arrived. If the study staff calls 911, they should remain on the telephone with the participant (or the person assisting 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 a study staff member should attempt to speak with a member of the medical staff (e.g., physician, PA, NP, nurse) at the emergency department to confirm arrival and provide information about the reason for referral to the ED.

If there is serious concern for the well-being of the participant and the participant cannot be reached within 15 minutes in the case of glucose <55mg/dL or 90 minutes in the case of glucose >300mg/dL, then study staff should attempt to reach close contacts. If no contacts are available or their contacts do not succeed in reaching them, then 911 should be called immediately and a well-being check should be requested. Study staff must follow up on and document the results of the well-being check.

6 Biostatistical Analysis

6.1 Data Collected

6.1.1 *Prior to the start of the experiment:*

- Age
- Sex
- Race and ethnicity

- Basic demographic information
- Date of last menstrual period in pre-menopausal participants
- Approximate date of diabetes diagnosis
- Medical, surgical, and social history, allergies and review of systems relevant to inclusion and exclusion criteria
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump and CGM use, if applicable
- Type of insulin(s) currently used
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio for pump and if known for MDI; otherwise doses and schedule for MDI, sliding scale/correction if applicable)
- Average total daily dose of insulin in the last 30 days from pump data and/or self-reported estimate from MDI patient report
- Usage of CGM (type of CGM, days per month worn, usage of data, whether insulin dosing is based on CGM alone, alarm settings), if applicable
- Height and weight (height will be self-reported for TH participants)
- Urine HCG (pre-menopausal participants)
- Hemoglobin A1c

6.1.2 *During study arms*

- CGMG (CGM glucose) every five minutes from the Dexcom CGM
- All fingerstick BG measurements taken by the participant (meter download)
- Average glucose target used
- Insulin total daily dose from bionic pancreas download
- Timing of meal announcements and size of meals announced from bionic pancreas download
- Time participants were not under bionic pancreas control
- Information collected from the daily survey:
    - Number of reported hypoglycemic events requiring carbohydrate intervention
    - Total grams of carbohydrates taken to prevent or treat hypoglycemia
    - Number of severe hypoglycemic events (defined as participant required assistance to treat)
    - Number of unscheduled insulin cartridge/infusion set changes
    - Time disconnected from the iLet (for participants on the BP arm)
- Data from questionnaires about quality of life, attitudes and expectations regarding the bionic pancreas at baseline and on day 14 of each arm.
- Number of and reasons for unscheduled visits and phone calls
- Device malfunctions requiring study team contact and other reported device issues
- Type of automation used, if any, by participants in the EN group

6.2 Primary endpoint

- Percentage of individuals with mean CGM glucose <183 mg/dL (corresponding to an estimated HbA1c of <8.0%) on days 3-14, by group.

6.3 Secondary endpoints

- Mean CGM glucose on days 3-14

- Percentage of time with CGM glucose <54 mg/dl on days 3-14
- Percentage of time with CGM glucose in the 70-180 mg/dl range on days 3-14
- Percentage of individuals with mean CGM glucose <154 mg/dL (corresponding to an estimated HbA1c of <7.0%) on days 3-14, by group.

6.4 Safety endpoints

- Frequency of adverse events
- Frequency of severe hypoglycemia
- Frequency of diabetic ketoacidosis, as defined within this protocol in Section 9.2.

6.5 Other endpoints

- The percentage of time that valid CGM glucose readings are captured by the iLet
- The percentage of the time that the insulin pump channel of the iLet is available
- Percentage of time across days 3-14 within each of the following CGM glucose ranges:
    - < 70 mg/dl
    - > 180 mg/dl
    - > 250 mg/dl
- Percentage of time participants were disconnected from the iLet
- Number of episodes of symptomatic hypoglycemia (reported daily by participants)
- Percentage of participants with mean Dexcom CGMG <154 mg/dl (estimated average glucose corresponding to an A1c of <7.0%) on days 3-14
- Mean total daily dose of insulin in the iLet arms and in the usual care arms of the EN groups (from pump download) on days 3-14
- Mean daily basal insulin dose in the iLet arms and in the EN groups' usual care arms (from pump download) on days 3-14
- Mean daily bolus insulin dose in the iLet arms and in the EN groups' usual care arms (from pump download) on days 3-14
- Mean number of daily meal announcements in the iLet arms and meal boluses in the EN groups' usual care arms (from pump download) on days 3-14
- Glucose variability measured with coefficient of variation (CV) and with mean of daily difference (MODD) on days 3-14
- Number of unscheduled insulin cartridge/infusion set changes in the iLet arms
- Mean glucose target in the iLet arms
- Scores from psychosocial questionnaires (including quality of life, fear of hypoglycemia, and diabetes distress). These surveys will be collected at baseline and after each arm. Post-BP measurements, including the bionic pancreas user opinion survey, will be given only after the BP arm.

6.6 Sample Size Determination

No formal statistical power or sample size calculations have been done for this study. This study is primarily intended to be a feasibility trial to verify that the iLet can be managed by both primary care physicians, endocrinologists, and delivered through telehealth.

6.7 Statistical Analyses

An intention-to-treat analysis will be performed. Descriptive statistics will be used to summarize patient characteristics and assessments. We will estimate the percentage of participants who have a mean sensor glucose <183 mg/dl in the iLet arms of all four groups (PC-IP, PC-TH, EN-IP, EN-TH), along with confidence intervals using the Clopper-Pearson method. The hypothesis is that there is no difference in the percentage of each group that meet this metric.

The primary analysis of the designated endpoints will be calculated on an intention-to-treat basis. In cases where an arm was not completed, we will use the available data from that arm in the data analysis. We will calculate percentages, means, standard deviations (and medians and interquartile ranges as appropriate), and ranges in descriptive analyses. Unless otherwise specified, continuous data will be summarized by presenting the number of non-missing observations, mean and standard deviation (SD) or median, minimum, and maximum. Categorical data will be summarized by presenting the number of patients and percentage for each category. We will use the t-test for comparisons of means for normally distributed outcomes and the Mann-Whitney U test for comparisons of medians on non-normally distributed outcomes between groups (PC-IP, PC-TH, EN-IP, EN-TH). We will use the paired t-test for comparison of means for normally distributed outcomes and the Wilcoxon Signed Rank test for comparisons of medians on non-normally distributed outcomes when comparing between iLet and usual care within groups. There will be no adjustments for multiple comparisons.

We may, in exploratory analyses, also stratify subjects for secondary analyses of the pre-specified endpoints by the following characteristics: sex, age, usual care insulin total daily dose, body mass index, baseline A1c, and use of CGM in usual care.

P-values can be displayed to aid interpretation, not for inference. Tables, figures and listings of all primary, secondary and safety endpoints will be created.

Data from periods when the bionic pancreas was not in use will be included, if available (Dexcom CGM data may not be available in some failure modes).

All questionnaire data (including quality of life data) for patients who have completed a minimum of 4 days with a device will be included. Results will be compared by Wilcoxon signed-rank test.

6.7.1 *Safety Analyses*

No inferential tests of safety data will be performed. Descriptive summaries of safety data will be presented. Treatment-emergent AEs are defined as AEs with onset date on or after the first day of exposure to randomized treatment.

6.7.2 *Baseline Descriptive Statistics*

The number and percentage of patients who were screened, randomized, discontinued (with reason for discontinuation), and completed the trial will be summarized descriptively for all screened patients. Baseline and demographic data will be summarized using descriptive statistics. All comparisons will be between treatments within patients. Listings of de-identified individual patient data will be presented.

6.7.3 *Tabulation of Individual participant Data*

Listings of de-identified individual patient data will be presented.

6.7.4 *Exploratory Analyses*

The performance of the iLet in each period can be compared with historical data from previous bionic pancreas trials. If the performance of the iLet in this study is comparable to our previous data, that will support the hypothesis that the iLet can be safely used in primary care settings and via telehealth. All participants with at least 24 hours of CGM data during days 3-14 of any treatment periods will be included in these analyses.

7 Risks and Discomforts

Participants may experience mild discomfort associated with the insertion of infusion sets and the Dexcom CGM sensor into the SC tissues. The risk of discomfort due to insertion of infusion sets and sensors may be greater than in their lives outside the trial because more infusion sets and sensors are required than are used in usual care, and some participants will have only used MDI.

There is a risk of hypoglycemia. 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. All of our previous studies have shown that hypoglycemia is reduced in all configurations of the bionic pancreas when compared with usual care.

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

8 Potential Benefits

It is expected that this protocol will yield increased knowledge about the safety and efficacy of the iLet bionic pancreas managed in care models previously untested (PCP in-person, PCP via telemedicine, and endocrinology via telemedicine). The individual participant may not benefit from study participation.

Based on evidence from previous trials of the bionic pancreas and the design of this trial, participants enrolled in the study may benefit from a reduction in risk of hypoglycemia and hyperglycemia and a closer to physiologic mean glucose than they typically achieve with their usual care.

Participants will be financially compensated for participating in the study.

9 Data and Safety Monitoring

9.1 Monitoring of Source Data

During the experiment, CGM data and insulin dosing data will be automatically stored in the bionic pancreas device (from which it will be downloaded at intervals). All of the data will be combined in a single database that will be compared against the primary data files for integrity. The computer database will be backed up at least monthly and the backup media stored in a secure location.

Study staff will be encouraged to raise any concerns they may have or problems they have identified at any time. The site PIs, in consultation with the co-investigators, will decide a course of corrective action, and resolution or progress will be assessed regularly.

An audit of procedures, regulatory documentation, and a sample of participant files will be performed by a member of the University of Colorado or the Diabetes Research Center, as applicable, 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.

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 store in password protected and user-limited electronic files. 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.

The study data will be shared with collaborators at Beta Bionics, Inc., but only in a form in which all personally identifiable information has been removed (e.g. combined database including BG values, record of insulin delivered by the device, and blood insulin levels). Shared data will be in the form of a database in which only a number identifies participants.

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

9.2 Safety Monitoring

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

Use of the bionic pancreas system by a participant in the study will be discontinued if any of the following occur:

- A participant experiences an episode of diabetic ketoacidosis (DKA) requiring hospitalization in the iLet arm.
    - Hyperglycemic events will be classified as DKA if all of the following are present:
        - Symptoms including but not limited to polyuria, polydipsia, nausea or vomiting
        - Serum ketones > 1.5 mmol/L or large/moderate urine ketones
        - Arterial blood pH <7.30 or venous blood pH < 7.24 or serum bicarbonate < 15
        - Treatment provided in a healthcare facility
- A participant experiences an episode of severe hypoglycemia in the iLet arm. Severe hypoglycemia is defined as requiring the assistance of another person due to altered consciousness, and requiring another person to actively administer carbohydrate, glucagon or other resuscitative

actions. This means the participant was impaired cognitively to the point that they were unable to treat themselves, were unable to verbalize their needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is sufficient evidence that the event was induced by a low plasma glucose concentration.

- The investigator believes it is unsafe for the participant to continue in the study
- A participant becomes pregnant
- The participant requests that the study be stopped
- If more than 1 participant must have their bionic pancreas use stopped for severe hypoglycemia or DKA during the bionic pancreas arm that is not due to deliberate inappropriate use of the iLet (i.e., any two participants with a single event each), study randomization will stop and a vote of the DSMB will be required to restart. All serious and unexpected events will be reported to the DSMB within 72 hours.

Study participation is voluntary, and participants may withdraw at any time. The investigator may withdraw a participant who is not complying with the protocol. For participants who withdraw, their data will be used up until the time of withdrawal. For participants using the iLet who withdraw, a study provider will help them transition to their own therapy safely.

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

9.3 Adverse Event Reporting Guidelines

9.3.1 *Definitions*

An **adverse event** 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).

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

Hyperglycemic events are recorded as Adverse Events (severe hyperglycemic event) if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or in the

absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis.

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

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

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

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

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

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

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

Serious adverse event means any event temporally associated with the 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).

9.3.2 *Reporting Guidelines*

Any serious adverse events or unexpected but related or possibly related adverse events will be communicated to the PIs as soon as possible and within 48 hours of the time they are detected. Adverse events will be reported promptly to the IRB, the DSMB, and Beta Bionics. Beta Bionics is the sponsor of the Investigational Device Exception (IDE) for the bionic pancreas to be used in this trial. Reports of adverse events will be made to the FDA in compliance with the terms of IDE.

10 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 per the following schedule.

		Cross over: Usual Care			**Cross over: Bionic Pancreas**			
	Screening	Day 1	Mid Period Follow-up		Crossover/Day 1	Mid Period Follow-up		Final Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Screening	$25							
Visit Stipend		$50			$50			$50
Mid-period follow-up			$20	$20		$20	$20	
Questionnaire Completion		$25			$25			$25

The total compensation for a participant who completed all study visits and questionnaires would be $330.

Parking/transportation expenses will be paid for up to $30 per participant for each visit.

Participants who are unable to complete the study or choose to stop participation will receive prorated compensation for the portion of the study visits that they complete.

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12 Appendices

12.1 Appendix A: Prior Bionic Pancreas Studies

Prior studies utilizing the Bionic Pancreas are summarized herein. Relevant citations are included in a reference list at the end of the document.

12.1.1 *iPhone-Based BP Outpatient Studies*

Subsequent to our past preclinical studies (2005–2009) at BU that used a diabetic swine model and our inpatient clinical trials (2008–2012) in the Clinical Research Center at MGH, we began our outpatient clinical studies using the iPhone-based BP.

12.1.2 *The Beacon Hill Study, the 2013 and 2014 Summer Camp Studies, and the Bionic Pancreas Multi-Center Study*

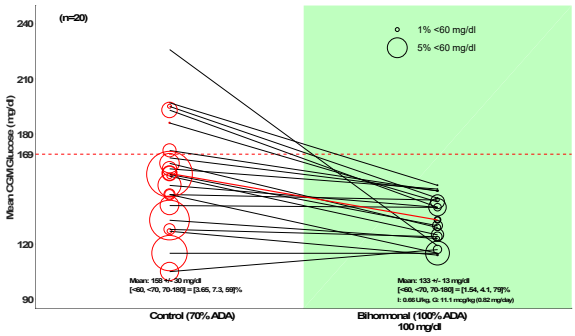
In 2013, we conducted our first outpatient study, which we refer to as the Beacon Hill Study (2013), and which followed a random-order cross-over design in which 20 adults (≥21 y) with T1D, with 5 days on the BP and 5 days of usual care. In the usual-care control arm, participants used insulin pump therapy (and their CGM if applicable), 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 freely at restaurants and exercised at will with access to two gyms. Analysis was pre-specified to 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 of Figure 2. Results of the Beacon Hill Study were included in a 2014 article published in the *New England Journal of Medicine*.

In parallel, we conducted the 2013 Summer Camp Study, which followed a random-order cross-over design in which 32 adolescents with T1D participated, with 5 days on the BP and 5 days of supervised camp care in the control arm. In the control arm, participants used conventional insulin pump therapy (and their CGM if applicable) and wore the BP without pumps (to enable remote monitoring). All participants were monitored remotely for CGM glucose < 70 mg/dl lasting more than 15 minutes, which prompted potential treatment by the study staff. 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 of Figure 2. Results of the 2013 Summer Camp Study were included in a 2014 article published in the *New England Journal of Medicine*.

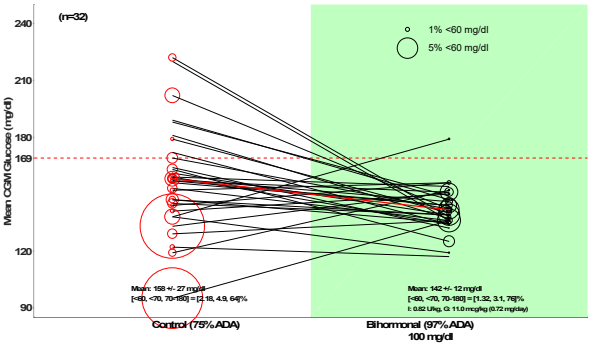
In 2014, we conducted our 2014 Summer Camp Study, in pre-adolescents 6–11 years old with T1D. The study was of similar in design to our 2013 Summer Camp Study. Results are summarized in the plots of Figure 2. Results of the 2014 Summer Camp Study were published in 2016 in *The Lancet Diabetes & Endocrinology.*

Also in 2014, we conducted our first home-use study, testing the BP in adults (≥18 y) with T1D. The study is referred to as the Bionic Pancreas Multi-Center study and followed a random-order cross-over design in which 39 adults participated in 11 days on the BP and 11 days of usual care. Participants went to work as usual, and lived and slept at home, all without clinical supervision. There were no restrictions placed on diet or exercise. The study included four medical centers (10 participants per center), namely MGH, the University of Massachusetts Medical School, Stanford University, and the University of North Carolina at Chapel Hill. Results are summarized in the plots of Figure 2. Results of the Multi-Center were published in 2016 in *The Lancet*.

<u>Beacon Hill Study</u>



<u>2013 Summer Camp Study</u>



<u>2014 Summer Camp Study</u>

<u>BP Multi-Center Study</u>

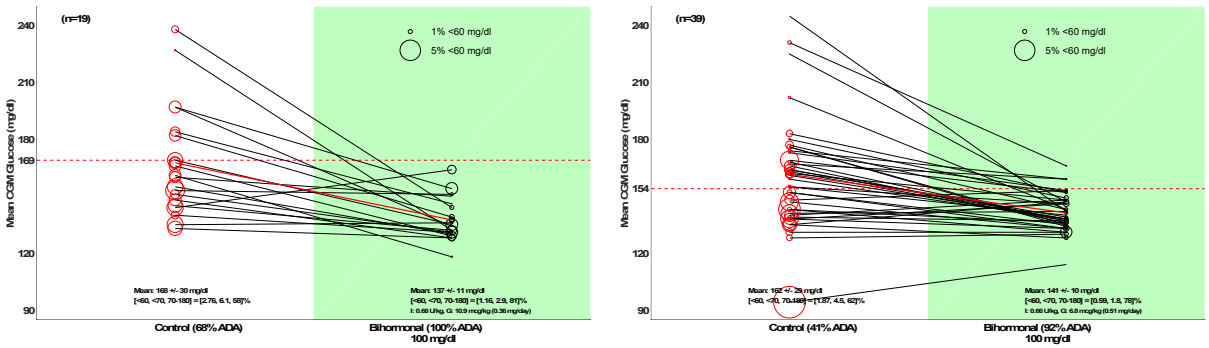


Figure 2. *Outpatient summary results of mean CGM glucose levels and hypoglycemia in the bihormonal BP and control arms from the Beacon Hill Study, 2013 and 2014 Summer Camp Studies, and the Bionic Pancreas Multi-Center Study. Mean CGM level for each participant under usual care (red circle on the left) is connected with their mean CGM level on the BP (black circle on the right). The circle diameter is proportional to % CGM values <60 mg/dl. The bold circles and lines represent group means. The horizontal red dashed line refers to the glucose level corresponding to the ADA therapy goal for that age group at that time, which corresponds to 154 mg/dl (HbA1c < 7%) for adults and 169 mg/dl (HbA1c < 7.5%) for children (the ADA target has since been unified to be HbA1c < 7% (mean glucose <154 mg/dl) for all age groups).*

12.1.3 *The Bionic Pancreas Set Point Study*

In 2015, we conducted our MGH Set-point Study, where we tested the BP at different static glucose targets ("set-points") in both the bihormonal and insulin-only configurations. Twenty 20 adults participated in 7 study arms, each lasting 3 days. Unlike preceding studies where the target glucose for the bihormonal BP was set to 100 mg/dl, glucose targets of 100, 110, 130 mg/dl were studied in the bihormonal configuration and 110, 120, 130, and 145 mg/dl were studied in the insulin-only. configuration. Results are summarized in Figure 3. Based on the study results, we determined that a default glucose target of 110 mg/dl for the bihormonal configuration and 120 mg/dl for the insulin-only configuration strike optimal balance between minimizing mean glucose and hypoglycemia while maximizing patient satisfaction.

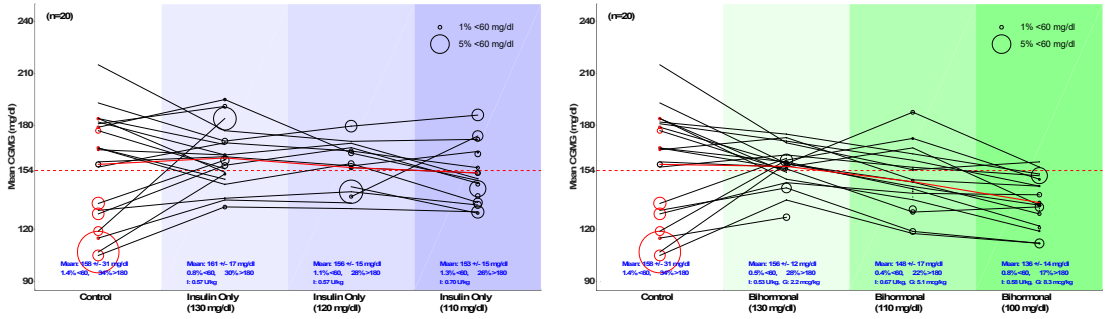


Figure 3. *Summary results from the Bionic Pancreas Set-Point Study. Left: Outpatient results summarizing the distribution of mean CGM levels and hypoglycemia in the insulin-only BP arms (with set-points 130, 120, and 110 mg/dl) and usual-care arm (control). Right: Outpatient results summarizing the 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). Mean CGM levels for each participant in each study arm (red circles) are connected by black lines. The circle diameter is proportional to % of CGM values < 60 mg/dl. The heavy circles and lines represent the group means. The horizontal red dashed line refers to the ADA therapy goal, which corresponds to 154 mg/dl (HbA1c <7%) for adults with T1D ≥ 18 years old.*

12.1.4 *The Stanford Insulin-Only Study*

In 2015, we conducted the Stanford Insulin-Only Study, where 16 adults participated in a week of usual care followed by a week on the insulin-only BP, where a target glucose of 130 mg/dl was initiated and potentially lowered to 115 mg/dl if certain criteria were met. Participants were monitored remotely for CGM glucose <50 mg/dl lasting more than 15 minutes, which prompted a call by the study staff. Results of the study are summarized in Figure 5.

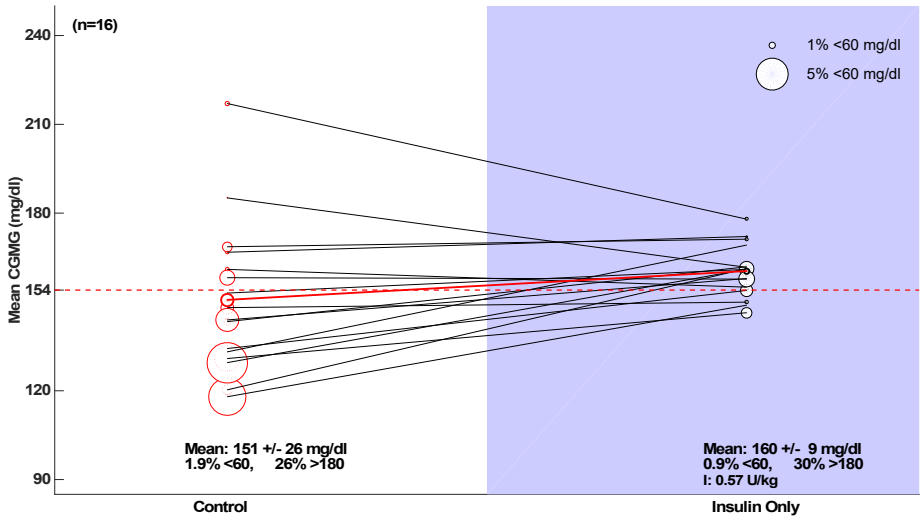


Figure 4. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Stanford Insulin-Only Study. Mean CGM levels for each participant in each study arm (red circles) are connected by black lines. The circle diameter is proportional to % of CGM values < 60 mg/dl. The heavy circles and lines represent the group means. The horizontal red dashed line refers to the ADA therapy goal, which corresponds to 154 mg/dl (HbA1c <7%) for adults with T1D ≥ 18 years old.*

12.1.5 *The Bionic Pancreas Monitoring Study*

In 2016, we conducted the Monitoring Study, where we tested the prospects of removing remote telemetric monitoring for severe biochemical hypoglycemia by testing the bihormonal BP at a target of 100 mg/dl, the insulin-only BP at a target 110 mg/dl, and usual care, each two 7-day arms, one with and the other without remote telemetric monitoring for hypoglycemia (total of 6 study arms). The results are summarized in Figure 6. There was more hypoglycemia without monitoring relative to with monitoring in the two usual-care arms (1.95 versus 1.32%, p=0.02), but 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. We concluded that remote telemetric monitoring had no effect on hypoglycemia with the BP. and could be safely omitted from future studies.

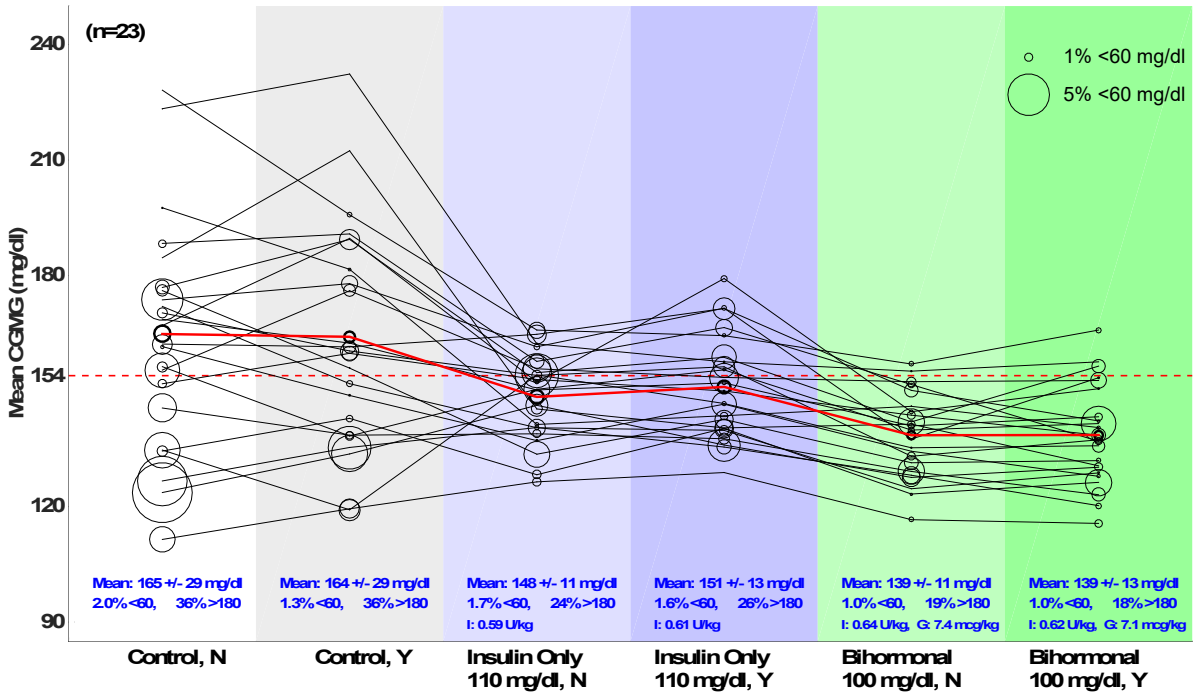


Figure 5. *Outpatient results summarizing the distribution of mean CGM glucose levels and hypoglycemia in the insulin-only BP and control arms from the Bionic Pancreas Monitoring Study. Mean CGM levels for each participant in each study arm (red circles) are connected by black lines. The circle diameter is proportional to % of CGM values < 60 mg/dl. The heavy circles and lines represent the group means. The horizontal red dashed line refers to the ADA therapy goal, which corresponds to 154 mg/dl (HbA1c <7%) for adults with T1D ≥ 18 years old.*

12.1.6 *iPhone BP System Studies*

Year	Name of Study	Setting, Date span	Cohort studied	Duration & device exposure*	Configuration & Set Points	Medications used	Protocol Description, Outcome, if applicable.	Result: Mean CGM, % CGM < 60 mg/dl
2013	Beacon Hill IDE: G120255 11-2012	Supervised hotel stay Start–End: 02-2013–09-2013	20 adults aged ≥21	5 days 2,400 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at home Direct supervision	BP: 133±13 mg/dl, 1.5% UC: 158±30 mg/dl, 3.7%
2013	2013 Summer Camp IDE: G130065 04-2013	Supervised summer setting Start–End: 07-2013–08-2013	32 adolescents aged 12–18	5 days 3,840 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at camp Remote telemetric monitoring	BP: 142±12 mg/dl, 1.3% UC: 158±27 mg/dl, 2.2%
2014	2014 Summer Camp IDE: G130065 04-2013	Supervised camp setting Start–End: 07-2014–08-2014	19 pre-adolescents aged 6–11	5 days 2,280 hours	Bihormonal 100 mg/dl iPhone + two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Glucagon (Eli Lilly)	RCT with usual care at camp Remote telemetric monitoring	BP: 137±11 mg/dl, 1.2% UC: 168±30 mg/dl, 2.8%
2014	BP Multi-center IDE: G140045 04-2014	Outpatient, home, 4 study sites Start–End: 05-2014–03-2015	39 adults aged ≥18	11 days 10,296 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with usual care Remote telemetric monitoring	BP: 141±10 mg/dl, 0.6% UC: 162±29 mg/dl, 1.9%
2015 - 2016	BP Set Point IDE: G150130 JUL-2015	Outpatient, unsupervised at home Start–End: 08-2015–12-2016	20 adults aged ≥18	8 arms, 4 days each 15,360 hours	Bihormonal and Insulin-only Bihormonal: 100, 110, 115, 130 mg/dl Insulin-only: 110, 120, 130, 145 mg/dl iPhone and one or two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with usual care and 8 different BP configurations testing different glucose target set points in addition to insulin only for the first time Both configurations at 110 mg/dl and 130 mg/dl included an exercise challenge to induce hypoglycemia under direct observation in the clinic Results helped identify the glucose target settings that will be used in future studies. These were set to range from 110 mg/dl to 130 mg/dl, with a default of 120 mg/dl in the insulin-only configuration, and set to range from 100 mg/dl to 120 mg/dl, with a default of 110 mg/dl in the bihormonal	Bihormonal: 100 mg/dl: 136±14 mg/dl, 0.8% 110 mg/dl: 148±17 mg/dl, 0.4% 115 mg/dl: 146±15 mg/dl, 0.9% 130 mg/dl: 156±12 mg/dl, 0.5% Insulin-only 110 mg/dl: 153±15 mg/dl, 1.3% 120 mg/dl: 156±15 mg/dl, 1.1% 130 mg/dl: 161±17 mg/dl, 0.8% 145 mg/dl: 174±23 mg/dl, 1.0% UC: 158±31 mg/dl, 1.4%

							configuration Remote telemetric monitoring	
2015 - 2016	Stanford Insulin-only IDE: G150142 JUL-2015	Outpatient, unsupervised at home Start–End: 10-2015–01-2016	16 adults aged ≥18	2 arms, 7 days each 5,376 hours	Insulin-only 115 to 130 mg/dl iPhone and one Tandem t:slim pump	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk)	RCT with usual care Results helped identify the glucose target settings that will be used in future studies Remote telemetric monitoring	BP: 160±9 mg/dl, 0.9% UC: 151±26 mg/dl, 1.9%
2017	Monitoring IDE: G150130 JUL-2015	Outpatient, unsupervised at home Start–End: APR-2017–MAY-2017	23 adults aged ≥18	4 arms, 7 days each 15,456 hours	Bihormonal and Insulin-only Bihormonal: 100 mg/dl Insulin-only: 110 mg/dl iPhone and one or two Tandem t:slim pumps	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Glucagon (Eli Lilly)	RCT with one usual care arm and two BP arms, each repeated with and without remote monitoring Each arm repeated with and without remote telemetric monitoring Results confirmed that the insulin-only and bihormonal BP set at their lowest targets (110 and 100 mg/dl, respectively) are safe to be used in outpatient setting without remote monitoring for hypoglycemia	With monitoring: Insulin-only: 151±13 mg/dl, 1.6% Bihormonal: 139±13 mg/dl, 1.0% UC: 164±29 mg/dl, 1.3% Without monitoring: Insulin-only: 148±11 mg/dl, 1.7% Bihormonal: 139±11 mg/dl, 1.0% UC: 165±29 mg/dl, 2.0%
2016 - 2017	Zealand Feasibility Study IDE: G160012 FEB-2016	Supervised, in clinic Start–End: 12-2016–03-2017	10 adults aged ≥18	2 arms, 8 hours each 160 hours	Bihormonal 100 mg/dl iPhone and two Tandem t:slim pumps	Insulin lispro (Lilly) Insulin aspart (Novo Nordisk) Glucagon, 1 mg/ml (Lilly) Dasiglucagon, 1 mg/ml (Zealand)	RCT comparing Eli Lilly glucagon with dasiglucagon in clinic setting BP was challenged with participants wearing their own insulin pump in addition to the BP insulin dosing, with up to two times their normal basal running and a full meal bolus via their own pump. There was an exercise challenge in the late post-prandial period Direct supervision	Dasiglucagon: 110±29 mg/dl, 13% Lilly glucagon: 99±22 mg/dl, 20%

*Total device exposure is calculated based on cohort size used in the final study analysis

12.1.7 *iLet Outpatient Studies*

The studies described below used the Gen 3 iLet and either the G5 Dexcom CGM or Senseonics Eversense CGM. The Insulin-Only Bionic Pancreas Pivotal Trial will use the Gen 4 iLet with the G6 Dexcom CGM.

12.1.8 *The iLet Insulin-Only Bionic Pancreas Bridging Study*

In 2018, the Adult RCT phase of the iLet Insulin-only Bridging Study was conducted as a random-order,

cross-over, home-use trial that compared the insulin-only iLet using lispro or aspart to the insulin-only iLet using Fiasp to usual care (UC) for 7 days each. The study enrolled 12 subjects who used MDI therapy and 22 subjects who used insulin pump for their UC. Participants at MGH (n = 17) used the Senseonics Eversense CGM while those at Stanford (n = 17) used the G5 Dexcom CGM as the input CGM to the iLet. This is the only automated insulin delivery study to test (1) two CGM devices, (2) an ultra-rapid insulin analog, and (3) a cohort including MDI and insulin pump users. Since only body weight is required to initialize the iLet, and no information is required about either insulin therapy regimen, the iLet is the only device that undergo this test without a run-in period to first determine a baseline pump therapy regimen. The iLet is ideally suited for use in underserved or insulin-pump-naïve populations, as well as in populations where endocrinologists and diabetologists are not available or are in short supply. The iLet performed equally well on MDI and insulin pump therapy subjects. Results are summarized in Figure 7.

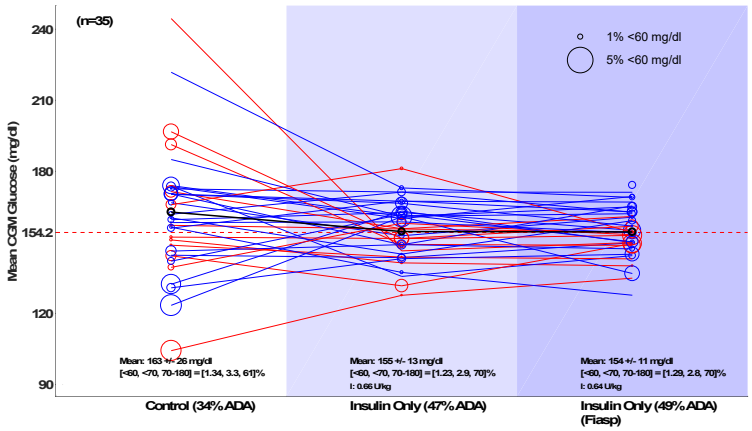


Figure 6. *Distribution of mean glucose and hypoglycemia in the Insulin-Only Bionic Pancreas Bridging Study. Mean CGM glucose level for each subject is shown over Days 3–7 under usual care, on the insulin-only iLet in using lispro or aspart, and on the insulin-only iLet using Fiasp. The mean CGM glucose and % CGM values <60 mg/dl were respectively 163 ± 26 mg/dl and 1.3% under usual care, 155 ± 13 mg/dl and 1.2% with the iLet using lispro or aspart, and 154 ± 11 mg/dl and 1.3% with the iLet using Fiasp. Red lines and circles correspond MDI subjects and blue lines and circles correspond to insulin-pump therapy users.*

12.1.9 *The iLet Day-Camp Transitional Study in Pediatrics*

Also in 2018, the Pediatric Transitional Study was conducted as a random-order, cross-over, outpatient trial comparing the insulin-only iLet (using lispro or aspart) to usual care (UC) for 5 days each in 20 pediatric subjects (6–17 y) with T1D and who used insulin-pump therapy for their UC (n = 6 at Nemours Children's Health System, n = 6 at Barbara Davis Center at the University of Colorado, and n = 8 at Stanford University). Results are summarized in Figure 7.

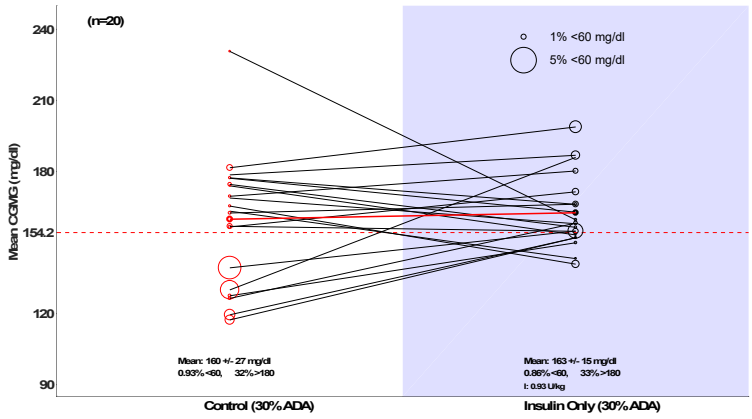


Figure 7. *Distribution of mean glucose and hypoglycemia in the Pediatric Day-Camp Transitional Study. Mean CGM glucose levels for each subject is shown over Days 2–5 in the control arm connected with the corresponding mean CGM glucose level on the iLet. The mean CGM glucose and % CGM values <60 respectively were 163 ± 15 mg/dl and 0.9% on the insulin-only iLet and 160 ± 27 mg/dl and 0.9% under usual care.*

12.1.10 *The iLet Bihormonal Cross-Over Study*

In 2019, the Bihormonal Cross-Over Study was conducted at MGH as a random-order, cross-over, home-use trial that compared the insulin only iLet using lispro or aspart to the bihormonal iLet using lispro or aspart and dasiglucagon (4 mg/ml) for 7 days each in 10 adults (≥ 18 y) with T1D and who used an insulin pump for their usual care. Results are summarized in Figure 9.

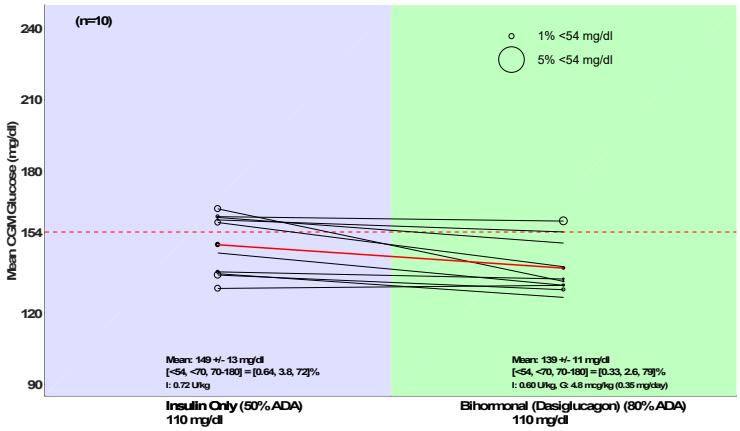
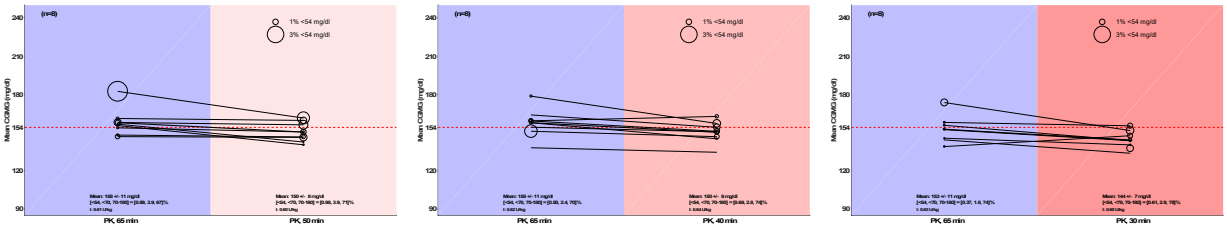


Figure 8. *Distribution of mean glucose and hypoglycemia in the Bihormonal Cross-Over Study. Mean CGM glucose level for each subject is shown over Days 2–7 in the insulin-only iLet arm, as a black circle on the left side, connected with the corresponding mean CGM glucose level on the bihormonal iLet with dasiglucagon, as a black circle on the right. The diameter of each circle is proportional to the % 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.*

12.1.11 *The iLet Fiasp Exploratory Study*

We conducted another trial in 2019 which we believe is indicative of future development and partnership

opportunities available to us which will extend the pervasiveness of iLet use. In this trial, we evaluated use of the ultra-rapid-acting insulin Fiasp at three different pharmacokinetic settings compared to the default setting in three separate, eight-patient, cohorts over a seven-day period. The intent of this trial was to assess glycemic control impacts with Fiasp that would result from decreasing the Tmax setting, which governs the time the algorithm assumes it takes for insulin concentration to peak in blood following subcutaneous insulin dosing.



	Tmax = 65 min	Tmax = 50 min	Tmax = 65 min	Tmax = 40 min	Tmax = 65 min	Tmax = 30 min
CGM	158 ± 11 mg/dl	150 ± 8 mg/dl	158 ± 11 mg/dl	150 ± 8 mg/d	153 ± 11 mg/dl	144 ± 7 mg/dl
% <54:	0.89%	0.98%	0.50%	0.69%	0.37%	0.61%
% <70:	3.9%	3.9%	2.4%	2.8%	1.8%	2.9%
% 70–180:	67%	71%	70%	74%	74%	78%

A statistically significant reduction in mean glucose levels was observed between the default Tmax value of 65 minutes and two of the three evaluated Tmax values. Across all three cohorts studied, the average percent of time that blood glucose levels were less than 54 mg/dl, indicative of hypoglycemia, was less than one percent. The trial showed the potential value of optimizing the Tmax setting of the iLet in terms of maximizing the potential benefits that Fiasp, or other new insulin therapies in general, might offer to patients. Future wider-scale studies are planned to rigorously investigate such potentials for Fiasp and other fast-acting insulins.

12.1.12 *iLet BP System Studies*

Year	Name of Study	Setting, Date span	Cohort studied	Duration & device exposure[1]	Configuration & Set Points	Medications used	Protocol Description, Outcome, if applicable.	Result: Mean CGM, % CGM < 60 mg/dl
2018	Adult Bridging study IDE: G180083 MAY-2018	Outpatient, unsupervised at home, 2 centers Start–End: MAY-2018–OCT-2018	34 adults aged ≥18 completed all three arms (36 started)	3 arms, 7 days each 11,424 hours	Insulin-only 120 mg/dl Gen 3 iLet MGH used Senseonics Eversense CGM, Stanford used Dexcom G5 CGM	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Fiasp PumpCart (Novo Nordisk)	RCT with one usual care arm and 2 BP arms, where one BP arm used insulin lispro/aspart, the other BP arm used Fiasp. The BP was set at the default glucose target of 120 and tmax setting of 65 minutes for both arms Remote telemetric monitoring Remote telemetric monitoring. Results demonstrated that the insulin-only iLet BP was safe and effective using both Fiasp or lispro/aspart at the default PK settings, consistent with results of the iPhone BP studies, paving the path for a larger & longer study with	BP: 155±13 mg/dl, 1.2% BP with Fiasp: 154±11 mg/dl, 1.3% UC: 163±26 mg/dl, 1.3%

							same device settings and insulins	
2018	Day-camp Transitional Study IDE: G180083 MAY-2018	Supervised day camp, followed by unsupervised home nightly, 2 centers Start–End: JUL-2018–AUG-2018	20 children aged 6-17	5 days 2,400 hours	Insulin-only 120 mg/dl Gen 3 iLet	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk)	RCT comparing usual care with BP Remote telemetric monitoring Results demonstrated that under stressful conditions, the inuslin-only iLet BP was safe and effective to use in adolescents and pre-adolescents, preparing the path for a larger and longer study using the same device settings in this age group	BP: 163±15 mg/dl, 0.9% UC: 160±27 mg/dl, 0.9%
2019	Fiasp Exploratory Study IDE: G180150 JUL-2018	48 hour supervised hotel stay, followed by unsupervised home, 5 days Start–End: MAR-2018–MAY-2018	24 adults aged ≥18, 8, Tmax=65, 8, Tmax=50 8, Tmax=40	3 cohorts, 8 subjects ≥18 each. 2 arms, 7 days each 8,064 hours	Insulin-only 120 mg/dl Gen 3 iLet	Fiasp PumpCart (Novo Nordisk)	RCT to compare default insulin PK settings (tmax = 65 minutes) with faster PK settings (tmax = 50, 40 and 30 minutes). Faster PK setting was escalated over three cohorts of 8 subjects Remote telemetric monitoring	Cohort #1, Tmax=65 157.7 mg/dl, 0.89% Cohort #1, Tmax=50 150.3 mg/dl, 0.98% Cohort #2, Tmax=65 157.6 mg/dl, 0.50% Cohort #2, Tmax=40 150.1 mg/dl, 0.69% Cohort #3, Tmax=65 152.5 mg/dl, 0.37% Cohort #3, Tmax=30 144.1 mg/dl, 0.61%
2019	Bihormonal Crossover Study IDE: G190028 FEB-2019	Outpatient, unsupervised at home Start–End: MAY-2019–JUN-2019	10 adults aged ≥18	2 arms, 7 days each 3,360 hours	Bihormonal and Insulin-only Bihormonal: 110 mg/dl Insulin-only: 110 mg/dl Gen 3 iLet	Insulin lispro (Eli Lilly) Insulin aspart (Novo Nordisk) Dasiglucagon, 4 mg/ml (Zealand Pharma)	RCT to compare insulin-only with bihormonal using dasiglucagon, testing bihormonal iLet for the first time Remote telemetric monitoring	Bihormonal: 139±11 mg/dl, 0.69% Insulin-only: 149±13 mg/dl, 1.38%

*Total device exposure is calculated based on cohort size used in the final study analysis

12.1.13 *Pediatric (6–<18 yr) iPhone-based and iLet BP studies – insulin-only and bihormonal*

Year	Name of Study	Setting, Population, Device exposure	Configuration & Set Points	Protocol Description	Results: Mean CGM, % time CGM < 60	Conclusions
2013	2013 Summer Camp Study IDE: G130065	Supervised summer camp setting 32 adolescents aged 12 to 20 5 days 3,840 hours	Bihormonal iPhone BP with two Tandem t:slim pumps and Dexcom G4 AP CGM Glucose target: 100 mg/dl Insulin lispro (Eli Lilly) & Glucagon (Eli Lilly)	RCT comparing bihormonal iPhone BP with usual care at camp Remote telemetric monitoring	BP: 142±12 mg/dl, 1.3% UC: 158±27 mg/dl, 2.2%	The results of this study demonstrated that under stressful conditions, the bihormonal BP was safe and effective to use in adolescent children.
2014	2014 Summer Camp Study IDE: G130065	Supervised summer camp setting 19 pre-adolescents aged 6 to 11 5 days 2,280 hours	Bihormonal iPhone BP with two Tandem t:slim pumps and Dexcom G4 AP CGM Glucose target: 100 mg/dl Insulin lispro (Eli Lilly) & Glucagon (Eli Lilly)	RCT comparing bihormonal iPhone BP with usual care at camp Remote telemetric monitoring	BP: 137±11 mg/dl, 1.2% UC: 168±30 mg/dl, 2.8%	The results of this study demonstrated that under stressful conditions, the bihormonal BP was safe and effective to use in pre-adolescent children
2018	Day-camp Transitional Study IDE: G180083 MAY-2018	Supervised day camp, followed by unsupervised home nightly, 2 centers 20 children aged 6-17 5 days, 2,400 hours Start–End: JUL-2018–AUG-2018	Insulin-only 120 mg/dl Gen 3 iLet	RCT comparing usual care with BP Remote telemetric monitoring	BP: 163±15 mg/dl, 0.4% UC: 159±27 mg/dl, 0.1%	Results demonstrated that under stressful conditions, the inuslin-only iLet BP was safe and effective to use in adolescents and pre-adolescents, preparing the path for a larger and longer study using the same device settings in this age group