

Supplementary Appendix

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Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria

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

Exclusion Criteria

- Unable to provide informed consent (e.g. impaired cognition or judgment)
- Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory, unable to speak and read English)
- Current participation in another clinical trial that, in the judgment of the principal investigator, will compromise the results of this study or the safety of the participant
- Current use of a non-FDA-approved closed-loop or hybrid closed-loop insulin delivery system
- Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the next 3-months, or sexually active without use of contraception. Participants must use acceptable contraception for the two weeks prior to the study, throughout the study and for the two weeks following the study. Acceptable contraception methods include:
 - Oral contraceptive pill (OCP)
 - Intrauterine Device (IUD, hormonal or copper)
 - Male condoms

- Female condoms
- Diaphragm or cervical cap with spermicide
- Contraceptive patch (such as OrthoEvra)
- Contraceptive implant (such as Implanon, Nexplanon)
- Vaginal ring (such as NuvaRing)
- Progestin shot (such as Depo-Provera)
- History of hypoglycemic seizures (grand-mal) or coma in the last year
- Unable to avoid hydroxyurea for duration of study (interferes with accuracy of Dexcom G6 CGM)
- Unable to avoid taking higher than the maximum dose of acetaminophen from all sources for the duration of the study (interferes with accuracy of Dexcom G6 CGM)
 - Adult: 1 g every 6 hours, up to 4 g every 24 hours
 - Pediatric: 75 mg/kg/day in up to 5 doses, not to exceed 4000 mg/day
- Have started or stopped a CFTR modulator in the past 4 weeks.
- Established history of allergy or severe reaction to adhesive or tape that must be used in the study
- Use of oral (e.g. thiazolidinediones, biguanides, sulfonylureas, glitinides, DPP-4 inhibitors, SGLT-2 inhibitors) or non-insulin injectable (GLP-1 agonists, amylin) anti-diabetic medications
- History of severe liver disease, including cirrhosis or portal hypertension
- Anticipated lung transplant (on transplant list)
- If the participant has already received a lung or liver transplant:
 - Hemoglobin A1c must be < 9% to be included
 - Doses of steroids and/or calcineurin inhibitors have been stable for one month prior to enrollment and are not expected to change significantly over the course of the study
- Acute pulmonary exacerbation or hospitalizations within the past 4 weeks or treatment with IV antibiotics in the past 4 weeks.
- History of a complete pancreatectomy
- Any factors that, in the opinion of the principal investigator would interfere with the safe completion of the study
- Presence of a medical condition or use of a medication that, in the judgment of the investigator, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following:
 - Current alcohol abuse (intake averaging >3 drinks daily in last 30 days) or other substance abuse (use within the last 6 months of controlled substances, other than marijuana, without a prescription)
 - Unwilling or unable to refrain from drinking more than 2 drinks in an hour or more than 4 drinks in a day during the trial
 - Unwilling or unable or to avoid use of drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study (use of beta blockers will be allowed as long as the dose is stable and the participant does not meet the criteria for hypoglycemia unawareness while taking that stable dose, but use of

benzodiazepines or narcotics, even if by prescription, may be excluded according to the judgment of the principal investigator) o

- Untreated or inadequately treated mental illness (indicators would include symptoms such as psychosis, hallucinations, mania, and any psychiatric hospitalization in the last year), or treatment with anti-psychotic medications that are known to affect glucose regulation.
- History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight
- Renal failure requiring dialysis
- Any known history of coronary artery disease including, but not limited to, history of myocardial infarction, stress test showing ischemia, history of angina, or history of intervention such as coronary artery bypass grafting, percutaneous coronary intervention, or enzymatic lysis of a presumed coronary occlusion)
- Congestive heart failure (established history of CHF, lower extremity edema, paroxysmal nocturnal dyspnea, or orthopnea)
- History of TIA or stroke
- Seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants
- History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment
- Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at a place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc); or having a first degree relative who is directly involved in conducting the trial

Supplementary Table S2. Bionic Pancreas User Opinion Survey (BPUOS)

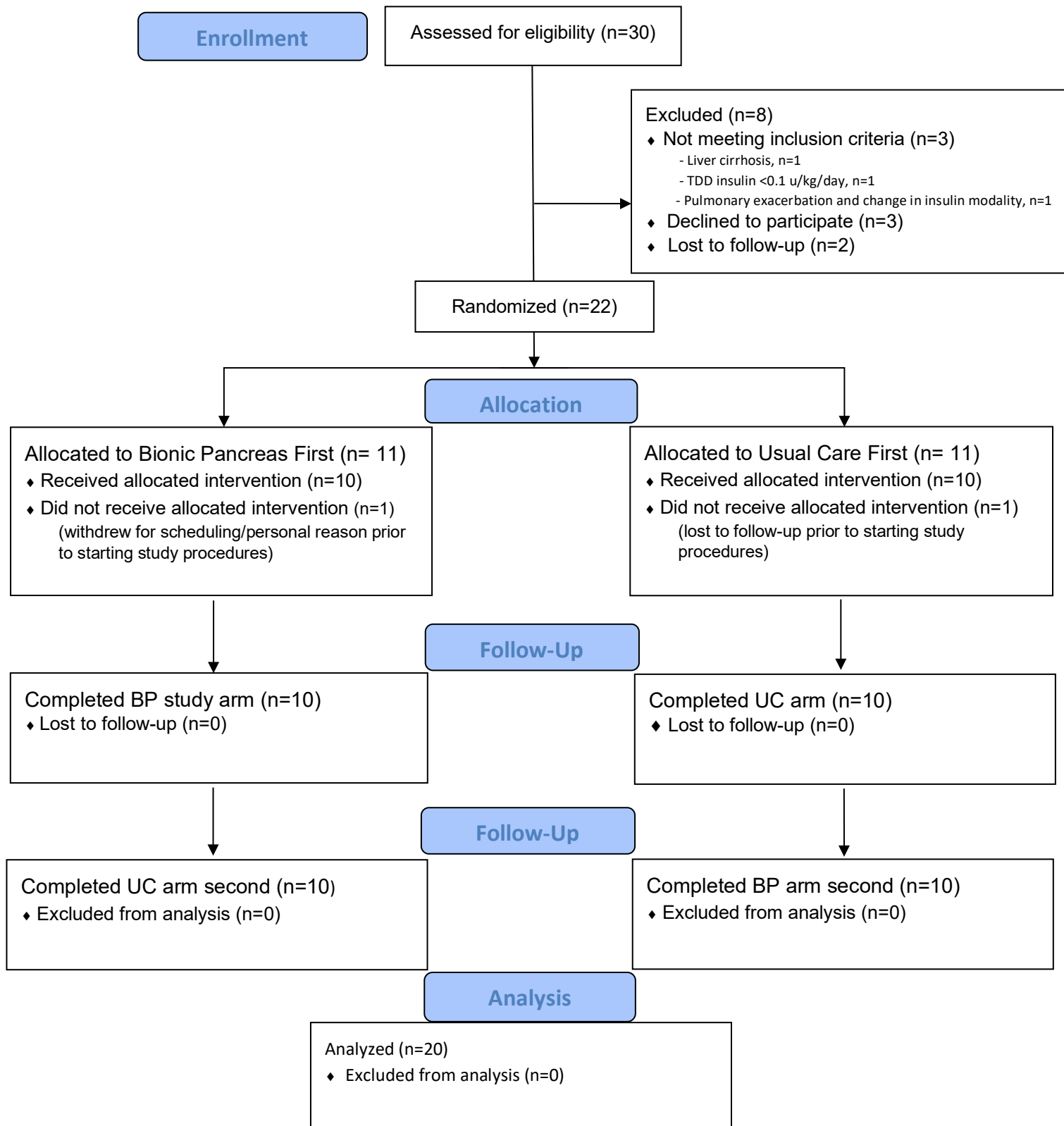
How do you feel about using the bionic pancreas?

Strongly Disagree=1, Somewhat Disagree=2, Neutral=3, Somewhat Agree=4, Strongly Agree=5

1. It caused me too many hassles in my daily life.
2. It was a big bother having to change sensors and pump sites.
3. I had a greater piece of mind while wearing the device.
4. I felt much freer with my food choices.
5. I felt freer to do the things I wanted to do.
6. I spent much less time thinking about my diabetes.
7. I was less worried about my blood sugars.
8. I was less worried about how my insulin was working.
9. I felt like I had more freedom to live my life.
10. The bionic pancreas was more intrusive than my typical method of diabetes care.
11. Feeling that my friends and family worry more about hypoglycemia than I want them to.
12. I was bothered by how long it took for the device to respond to low blood sugars.
13. I was bothered by how long it took the device to respond to high blood sugars.
14. I was never entirely comfortable with allowing the device to take over my diabetes care.
15. I found it hard to trust that the bionic pancreas could control my blood sugars.
16. I felt less burdened in managing diabetes while I was using it than I do when using my typical method of diabetes care.
17. I had trouble sleeping well while wearing it.
18. The device allowed me to have more time to devote to other areas of my life.
19. Wearing the device made me think about diabetes too much.
20. It taught me things about my diabetes that I didn't know before.
21. It helped to prevent low blood sugars from happening.
22. It had too many "glitches" and "bugs".
23. It helped me to relax, knowing that unwanted changes in blood sugar would be addressed automatically.
24. I found the device uncomfortable to wear.

25. Using the device was more trouble than it was worth.
26. It helped to prevent blood sugar problems from happening.
27. It helped me worry less about low blood sugars.
28. It helped me to worry less about high blood sugars.
29. When this study is over, I would very much like to keep using this device.
30. I often challenged the device with food and exercise to see how it would react.
31. I felt confident that the device would respond well to a high or low.
32. By the end of the study, I trusted the device to manage my blood glucose.
33. I would strongly recommend the bionic pancreas to everyone with type 1 diabetes.
34. I never stopped worrying about having a low while sleeping.
35. I found the alarms to be really annoying.
36. It would be hard to give up the device once the study is over.

Supplementary Figure S3: CONSORT diagram



Supplementary Table S4: CGM outcomes during the daytime and nighttime

	BP Arm		UC Arm	
CGM Outcomes	Daytime	Nighttime	Daytime	Nighttime
Percent time in range 70-180 mg/dL	74 (10)	77 (16)	63 (21)	62 (26)
Mean CGM glucose (mg/dl)	152 (17)	147 (28)	170 (41)	173 (56)
Percent time <54 mg/dL	0.3 (0, 0.7)	0.3 (0, 0.6)	0.4 (0, 0.7)	0.2 (0, 0.9)
Percent time <70 mg/dL	1.9 (0.7, 2.8)	1.2 (1.0, 2.7)	1.9 (0.2, 3.0)	1.3 (0, 3.3)
Percent time >180 mg/dL	22 (14, 33)	15 (9, 29)	30 (17, 53)	26 (12, 55)
Percent time >250 mg/dL	5.2 (2.0, 9.3)	3.2 (1.1, 7.8)	11 (3.5, 19.8)	7.6 (1.3, 26)
Standard Deviation	55 (15)	49 (17)	60 (15)	56 (20)
Coefficient of Variation	36 (6.0)	33 (6)	35 (5.1)	33 (9.4)

Data are reported as mean (SD) or median (range). Data correspond to days 3-14 of both the UC and BP arms. Daytime is defined as 7:00 AM to 11:00 PM and nighttime is defined as 11:00 PM to 7:00 AM.

CGM, continuous glucose monitor; BP, bionic pancreas; UC, usual care

Supplementary Table S5. Symptomatic hypoglycemia, insulin use, and number of CGM values during the UC and BP arms

	BP Arm	UC Arm	p-value
Median daily self-reported symptomatic hypoglycemia episodes	0.7 (0.4, 1.2)	0.4 (0,0.8)	0.01
Number of CGM values	3916 (3681, 3959)	3961 (3782, 4006)	0.07
Median insulin total daily dose (units/kg/day)	0.45 (0.31, 0.76)	0.45 (0.29, 0.56)	0.15
Median basal (units/kg/day)	0.17 (0.09, 0.30)	0.19 (0.12, 0.33)	0.14
Median bolus (units/kg/day)	0.28 (0.21, 0.50)	0.21 (0.16, 0.27)	0.004

Data are presented as median (IQR).

BP, bionic pancreas; UC, usual care; CGM, continuous glucose monitoring

Supplementary Table S6. Daily Survey Self-Reported Metrics: Carbohydrate Treatment, Exercise and Alcohol Consumption

	BP Arm	UC Arm
Daily average rapid-acting carbohydrates for treatment of hypoglycemia (grams)	13.7 (6.8,22)	4.3 (0,15)
Average carbohydrate consumed per hypoglycemia event	20 (13.6-29.2)	20.5 (14.2-23.6)
Days of reported exercise	1.5 (0,4.5)	0 (0,5)
Total exercise during study period (minutes)	55 (0,305)	0 (0,190)
Alcohol consumption (drinks/day)	0.04 (0-0.7)	0.3 (0-0.7)

Data presented as median (IQR)

BP, bionic pancreas; UC, usual care

Supplementary Table S7. Post-hoc analysis of subjects not achieving ADA target of $\geq 70\%$ time in target range 70-180 mg/dl during the usual care period (n=11)

CGM Outcomes	BP Arm	UC Arm	P-value
Percent time in range 70-180 mg/dL	67 (9)	47 (18)	0.002
Mean CGM glucose (mg/dl)	164 (16)	201 (41)	0.005
Percent time <54 mg/dL	0.14 (0.0-0.6)	0.28 (0,0.84)	0.93
Percent time <70 mg/dL	1.2 (0.23-2.1)	0.7 (0, 3.3)	0.64
Percent time >180 mg/dL	31 (27, 39)	52 (33-65)	0.003
Percent time >250 mg/dL	8.0 (4.8, 18)	20 (13-34)	0.002
Standard Deviation	62 (15)	72 (8.9)	0.02
Coefficient of Variation	38 (5.9)	37 (5.3)	0.71

Data are reported as mean (SD) or median (IQR range)

CGM, continuous glucose monitor; BP, bionic pancreas; UC, usual care

Supplementary Table S8: CGM outcomes by usual diabetes care modality

	Participants managed with MDI or non-automated insulin pump during usual diabetes care (n=12)		Participants managed with hybrid closed loop device during usual diabetes care (n=8)	
CGM Outcomes	BP Arm	UC Arm	BP Arm	UC Arm
Percent time in range 70-180 mg/dL	73 (12)	53 (24)	77 (10)	75 (10)
Mean CGM glucose (mg/dl)	153 (22)	187 (51)	145 (16)	147 (17)
Percent time <54 mg/dL	0.23 (0.0.72)	0.2 (0,0.9)	0.52 (0.16, 0.76)	0.48 (0.28,0.73)
Percent time <70 mg/dL	1.4 (0.68, 3.1)	1.8 (0.03,3.6)	1.8 (1.0-2.4)	1.3 (0.92, 3.3)
Percent time >180 mg/dL	23 (15, 35)	51 (18-63)	15 (14-30)	20 (15-32)
Percent time >250 mg/dL	4.5 (2.1, 12.3)	17 (4.5, 30.8)	2.7 (1.8, 9.7)	4.2 (1.1, 11.6)
Standard Deviation	55 (17)	68 (15)	51 (11)	52 (14)
Coefficient of Variation	35 (6)	36 (5)	35 (5)	35 (7)

Data are reported as mean (SD) or median (IQR range).

BP, bionic pancreas; UC, usual care; MDI, multiple daily injections; CGM, continuous glucose monitor; SD, standard deviation; IQR, interquartile range

Supplementary Table S9: CGM Data in the First 48 hours and Entire Study Period

CGM Outcomes	BP Arm		UC Arm	
	First 48 hours (Days 1-2)	Entire Study Period (Days 1-14)	First 48 hours (Days 1-2)	Entire Study Period (Days 1-14)
Percent time in range 70-180 mg/dL	71 (16)	74 (12)	65 (24)	63 (22)
Mean CGM glucose (mg/dl)	157 (37)	151 (21)	166 (48)	171 (44)
Percent time <54 mg/dL	0 (0, 0.7)	0.2 (0.1-0.8)	0 (0, 1.2)	0.5 (0-0.9)
Percent time <70 mg/dL	0.9 (0, 3.1)	1.6 (0.9-2.4)	1.8 (0-4.8)	1.7 (0.1, 3.5)
Percent time >180 mg/dL	24 (16, 35)	19 (15, 33)	24 (11, 49)	29 (16-52)
Percent time >250 mg/dL	4.2 (1.0, 11)	3.6 (2.1, 11)	4.7 (0.4, 21)	8.9 (2.4-22)
Standard Deviation	58 (21)	55 (16)	55 (20)	60 (16)
Coefficient of variation	36 (5.7)	36 (5.5)	33 (7.4)	36 (5.9)

Data are reported as mean (SD) or median (IQR range).

BP, bionic pancreas; UC, usual care; CGM, continuous glucose monitor; SD, standard deviation; IQR, interquartile range

Supplementary Table S10: Per-protocol analysis including participants adhering to the protocol, reflecting the time the BP was actively in use during the BP arm

CGM Outcomes	BP Arm	UC Arm	P-value
Percent time in range 70-180 mg/dL	73 (13)	62 (22)	0.003
Mean CGM glucose (mg/dl)	151 (23)	171 (45)	0.01
Percent time <54 mg/dL	0.27 (0.06-0.77)	0.36 (0, 0.82)	0.63
Percent time <70 mg/dL	1.8 (0.87-2.6)	1.5 (0.13, 3.5)	0.93
Percent time >180 mg/dL	18 (14-31)	31.2 (17, 52)	0.002
Percent time >250 mg/dL	3.2 (2.1-9.9)	10.3 (2.5, 22)	0.002
Standard Deviation	54 (16)	60 (16)	0.03
Coefficient of variation	35 (6)	35 (6)	0.86
Number of CGM values	3365 (359)	3354 (178)	0.91

Data are reported as mean (SD) or median (IQR range).

BP, bionic pancreas; UC, usual care; CGM, continuous glucose monitor; SD, standard deviation; IQR, interquartile range

Supplementary Table S11: Patient Reported Outcomes

Questionnaire	Baseline	Post-BP Arm	P-value
Diabetes Distress Scale (DDS)	1.3 (1.1-1.7)	1.3 (1.1-1.9)	0.60
DDS Subscale 1, Powerlessness	1.6 (1.3-2.1)	1.8 (1.2-2.5)	0.70
DDS Subscale 2, Management Distress	1.6 (1.3-2.6)	1.4 (1.1-1.9)	0.82
DDS Subscale 3, Hypoglycemia Distress	1.3 (1-2)	1.3 (1-2)	0.96
DDS Subscale 4, Negative Social Perceptions	1 (1-1)	1 (1-1)	0.50
DDS Subscale 5, Eating Distress	1.8 (1.3-2.2)	1.6 (1-2)	0.32
DDS Subscale 6, Physician Distress	1 (1-1)	1 (1-1)	1.00
DDS Subscale 7, Friend/Family Distress	1 (1-1)	1 (1-1)	0.85
Hypoglycemia Confidence Scale	3.6 (3-3.8)	3.5 (3-3.9)	0.97
Diabetes Technology Attitudes	25 (20.5-25)	25 (22-25)	0.71
Insulin delivery Systems: Perceptions, Ideas, Reflections and Expectation (INSPIRE)	87 (67-100)	67 (47-77)	0.003
Hypoglycemia Fear Survey (Total)	21.5 (9.5-29)	17 (10-32.5)	0.81
Hypoglycemia Fear Survey, Subscale: Behavior	11 (7.5-15.5)	11 (8-15)	0.98
Hypoglycemia Fear Survey, Subscale: Worry	10.5 (1-13.5)	6.5 (1.5-16)	0.67
Eq5d Health Today	74.5 (50-90)	77.5 (60-90)	0.41
WHO Well-Being Index (WHO-5)	64 (48-76)	72 (52-80)	0.385

Data are reported as median (IQR).

BP, bionic pancreas; IQR, interquartile range

Supplementary Table S12: Adverse Events

Table 3. Safety Outcomes during the Study Period

Event	BP Arm	UC Arm	During enrollment but not during either treatment arm
Any adverse event	7	5	7
Specific events			
Hyperglycemia without ketosis	6	0	0
Hyperglycemia with ketosis	0	2	0
Severe hypoglycemia	0	0	0
Diabetic ketoacidosis	0	0	0
Pulmonary exacerbation	0	2	5
Other AEs deemed unrelated	1	1	2

AE, adverse event; BP, bionic pancreas; UC, usual care

Supplementary Figure S13. Participant-level CGM and bionic pancreas insulin administration data

This supplement includes participant-level glycemic outcomes for each subject during both iLet bionic pancreas and usual care arms by week. A deidentified participant ID is indicated at the top of the panel.

In the bionic pancreas plot, the body mass (kg) used to initialize the algorithm is indicated. The first panel shows the 24 hour mean CGM glucose study week, and mean CGM glucose for each individual day. The glucose target set point of the algorithm (% time spent at each target) is also shown. The second panel denotes the CGM outcome for the nighttime period (11p-7am) for a one-week period and by each night individually. The third panel shows the CGM tracing over the study period as well as the time in the key CGM ranges. The fourth panel shows insulin dosing (as downward blue bars) administered by the bionic pancreas.

In the usual care plots, the first panel indicates the 24h mean CGM glucose by week as well as by each day of the study period. The second panel denotes the CGM outcome for the nighttime period (11p-7am) for a one-week period and by each night individually. The third panel shows the CGM tracing over the study period as well as the time in the key CGM ranges.