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The International Diabetes Closed Loop (iDCL) trial: A Randomized Crossover Comparison of Adaptive Model Predictive Control (MPC) Artificial Pancreas Versus Sensor Augmented Pump (SAP)/Predictive Low Glucose Suspend (PLGS) in the Outpatient Setting in Type 1 Diabetes (DCLP4)

Protocol Identifier: DCLP4

IND/IDE Sponsor: Sansum Diabetes Research Institute

Version Number: v6.0

14 DEC 2020

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The International Diabetes Closed Loop (iDCL) trial: A Randomized Crossover Comparison of Adaptive Model Predictive Control (MPC) Artificial Pancreas Versus Sensor Augmented Pump (SAP)/Predictive Low Glucose Suspend (PLGS) in the Outpatient Setting in Type 1 Diabetes (DCLP4)

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List of Abbreviations

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AID	Automated Insulin Delivery
AE	Adverse Event
AHCL	Advanced Hybrid Closed-Loop
AP	Artificial Pancreas
ATTD	Advanced Technologies & Treatments for Diabetes
AUC	Area Under the Curve
BG	Blood Glucose
BGM	Blood Glucose Meter
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FDR	False Discovery Rate
FWER	Familywise Error Rate
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed Loop
HMS	Health Monitoring System
iAPS	Interoperable Artificial Pancreas System
ID	Identification
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JCHR	Jaeb Center for Health Research
IRB	Institutional Review Board
MPC	Model Predictive Control
NIH	National Institutes of Health

ABBREVIATION	DEFINITION
PID	Proportional, Integral, and Derivative
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RCT	Randomized Controlled/Clinical Trial
RBM	Risk-Based Monitoring
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump
SD	Standard Deviation
SH	Severe Hypoglycemia
SMBG	Self-Monitoring of Blood Glucose
SUS	System Usability Scale Survey
T1D	Type 1 Diabetes
TDI	Total Daily Insulin
UADE	Unanticipated Adverse Device Effect
UI	User Interface

Site Principal Investigator Statement of Compliance

Protocol Title: The International Diabetes Closed Loop (iDCL) trial: A Randomized Crossover Comparison of Adaptive Model Predictive Control (MPC) Artificial Pancreas vs. Sensor Augmented Pump (SAP)/Predictive Low Glucose Suspend (PLGS) in the Outpatient Setting in Type 1 Diabetes (DCLP4)

Protocol Version/Date: v6.0/14 DEC 2020

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

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

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

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

Investigator's Name: _____

Site Name/Number: _____

Protocol Summary

Title	The International Diabetes Closed Loop (iDCL) trial: A Randomized Crossover Comparison of Adaptive Model Predictive Control (MPC) Artificial Pancreas Versus Sensor Augmented Pump (SAP)/Predictive Low Glucose Suspend (PLGS) in the Outpatient Setting in Type 1 Diabetes (DCLP4)
Précis	A randomized crossover trial will compare the efficacy and safety of an automated insulin delivery (AID) study system using an adaptive Model Predictive Control (MPC) algorithm versus SAP (which may or may not include PLGS; to be referred to as SAP) therapy in people with type 1 diabetes. A Pilot Phase involving at least 5 participants using the study system for 10-14 days will be conducted prior to the crossover trial.
Investigational Device	The AID study system is composed of a Tandem t:AP pump, a Dexcom G6 continuous glucose monitoring sensor, and a smart phone that contains the adaptive algorithm and communicates with the other devices.
Objectives	To compare the efficacy and safety of an AID system using an adaptive MPC algorithm versus SAP or PLGS therapy in people with type 1 diabetes.
Study Design	Randomized Crossover Trial with two 13-week periods, preceded by a CGM run-in phase.
Number of Sites	5-7 U.S. sites
Major Endpoints	Superiority for time in range 70-180 mg/dL and non-inferiority for time <54 mg/dL measured with CGM will be considered primary endpoints, analyzed using a hierarchical gatekeeping testing procedure Secondary outcomes will include HbA1c and the following CGM metrics • Mean glucose • Time >180 mg/dL • Time >250 mg/dL • Time <70 mg/dL • Time <54 mg/dL (superiority) • Coefficient of variation
Population	**Inclusion** • Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year • Using an insulin pump for at least 3 months (which may include use of automated features) • Familiarity and use of a carbohydrate ratio for meal boluses • Age ≥18.0 years old • For females, not currently known to be pregnant *If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.* • If using a personal CGM, willingness to use a Dexcom G6 CGM and discontinue personal CGM use during the study • Willing not to begin use of, or not to continue use of if currently using, a personal AID (closed loop control) system during the study; *note if the system offers an open-loop mode or can be switched to a PLGS mode that is compatible with the Dexcom G6, the system may be used during the study in these modes only* • Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study

	• Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial, and not to use Afrezza during the trial • Investigator believes that the participant can successfully and safely operate all study devices and is capable of adhering to the protocol **Exclusion Criteria** 1) Use of Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) unless participant is willing to discontinue during the trial. 2) Two or more episodes of DKA requiring an emergency room visit or hospitalization in the past 6 months 3) Two or more episodes of severe hypoglycemia with seizure or loss of consciousness in the last 6 months 4) Hemophilia or any other bleeding disorder 5) A medical or other condition that in the opinion of the investigator could create a safety concern for the participant or put the study at risk a. History of frequent severe hypoglycemia or history of frequent severe hyperglycemia and/or ketosis, without emergency room visit or hospitalization, due to poor diabetes self-management may be disqualifying per investigator judgment 6) Participation in another pharmaceutical or device trial at the time of enrollment or during the study
Sample Size	Up to 35 individuals randomized in the crossover trial with the goal of at least 32 completing the trial
Treatment Groups	Random assignment (1:1) to begin period 1 either with the AID study system or with SAP using home pump and then cross over to the other respective treatment in period 2
Participant Duration	6-7 months
Protocol Overview/ Synopsis	**Screening and Enrollment** • Informed consent will be signed, and eligibility will be assessed • Medical history and physical examination • HbA1c measurement using point-of-care device (if not available from prior 3 months) • Urine pregnancy test (if applicable) • Baseline questionnaires completed **Pilot Phase** The Pilot Phase will include 1-2 participants at each site, using a personal Dexcom G5/6 with use on at least 11 of the prior 14 days and the investigator believes that a CGM run-in is unnecessary. The Pilot Phase is intended to (1) test the functionality of all aspects of the study System and (2) train the clinical staff on the execution of the clinical protocol, including hands-on training with the device prior to initiating the RCT Period. Screening and study system start up procedures will be the same as for the Crossover Trial. Participants will use the study system for 10-14 days. After at least 5 total participants from at least 3 different sites have completed the Pilot Phase, the data will be reviewed for preset safety criteria before proceeding to the RCT. Assuming there are no significant safety or device issues that occur, the Crossover Trial will begin. **CGM Run-In (2-4 weeks)** Eligible participants using a personal Dexcom G5/G6 sensor, with use on at least 11 of the prior 14 days may skip the CGM run-in unless the investigator believes that there is a need to optimize insulin pump settings prior to randomization. Participants skipping the run-in can go directly to the randomization visit. Eligible participants not currently using a personal Dexcom G5/G6 sensor or using a Dexcom G5/G6 sensor with readings captured on less than 11 out of the prior 14 days will initiate a CGM run-in phase with a study Dexcom G6 sensor. • *Users of a sensor other than Dexcom G5/G6 (eg, Medtronic, Abbott) must be willing to discontinue use of that sensor for the duration of the study and users of an AID (closed loop*

	control) system must be willing to discontinue its use during the study (PLGS mode can be used during the study if feasible). Duration of the run-in will be 2-4 weeks at investigator discretion. During this time, Study Staff will review uploaded CGM data and may optimize insulin pump settings as needed by phone contact with subjects. Prior to each phone contact, the participant will be asked to upload the CGM and if possible pump data for study staff review. Successful completion of the run-in will require use of the sensor for at least 11 days during a final assessment period of 14 days. The run-in may be extended at investigator discretion if the investigator believes that additional training is needed or the participant should have another opportunity to achieve the 11 day use criterion. **Randomized Cross-Over Trial** Eligible participants will be randomly assigned to one of two treatment groups for 13 weeks each: 1. Group A: study system for period 1 for 13 weeks, then SAP for period 2 for 13 weeks 2. Group B: SAP for period 1 for 13 weeks, then study system for Period 2 for 13 weeks Study System Period: The participant will be trained regarding AID study system use including meal announcement, meal bolusing, correction doses, and exercise. Participants will be expected to use the study system at all times at home with the exception of times of illness. SAP Period: During the SAP period, participants will use their own insulin pump and a study-provided Dexcom G6 sensor. • *PLGS mode on the pump can be used if feasible but an AID system cannot be used.* **Study Flow** Period 1 will commence on the day of randomization with initiation of the study system or continued use of personal pump SAP. Both groups will have the same contact and visit schedule in both period 1 and period 2 • Visits at 2 weeks, 6 weeks, and 13 weeks • Phone contacts at 3 days, 4 weeks, and 9 weeks At randomization, and at each end of period visit, central lab HbA1c measurement will be made, a pregnancy test will be performed in applicable subjects, and quality of life and treatment satisfaction questionnaires will be completed. At the end of period 1 visit, the intervention will be switched to the study system or SAP for period 2. There will not be a washout period. Throughout the study, the occurrence of adverse events and device issues will be solicited and recorded.

Schematic of Study Design

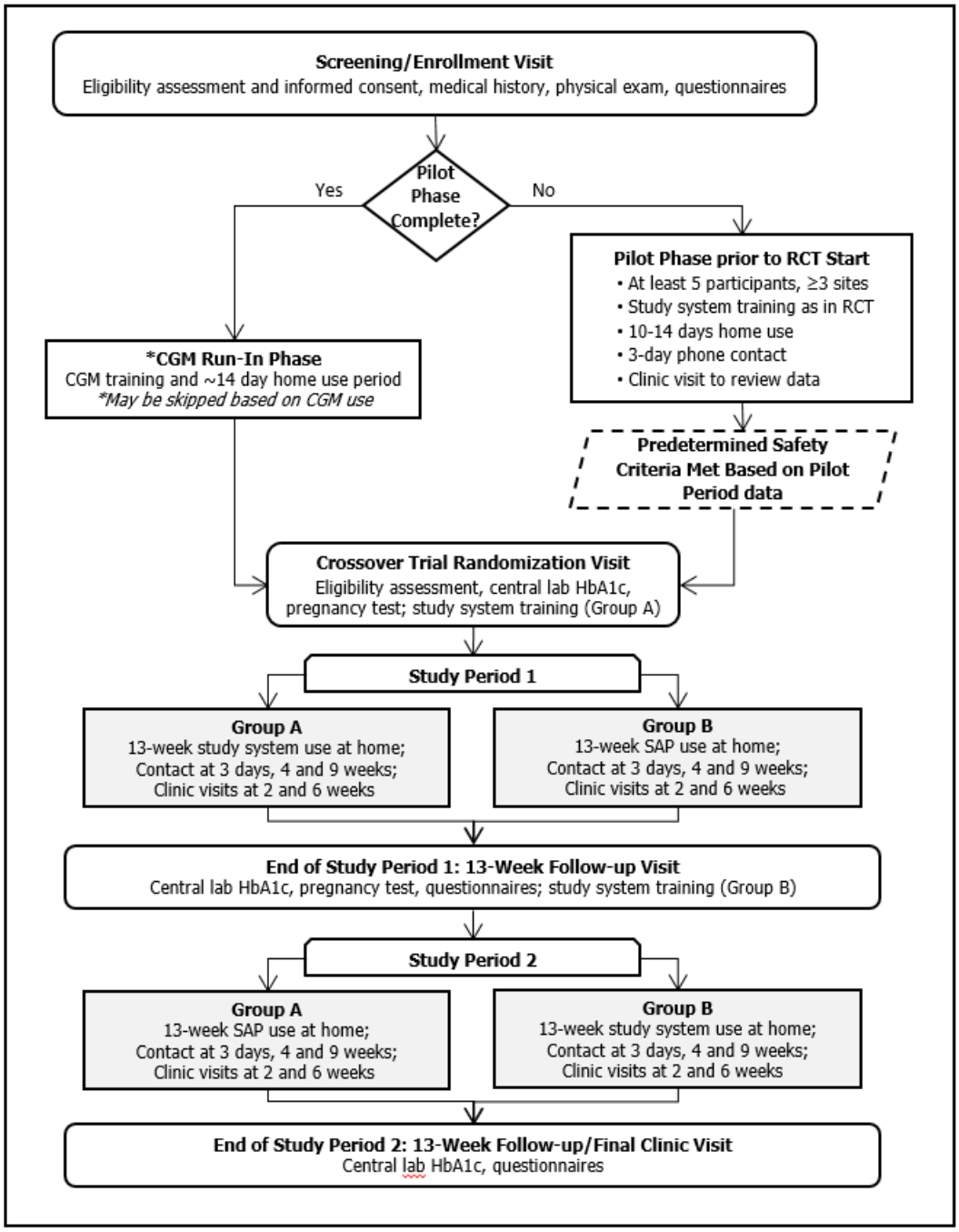

Figure 1. Schematic of Study Design; note clinic visits at 2, 6, and 13 weeks may be replaced by videoconferences at investigator discretion, as detailed in Chapter 7:.

Schedule of Study Visits and Procedures

Table 1. Schedule of Visits and Procedures During the Crossover Trial

	Screening Visit	CGM Run-in Visit	Randomization Visit	Days (d) or Weeks (w) from the Start of Each of Two 13-Week Study Periods[1]						
				0d[2]	3d	2w	4w	6w	9w	13w
Visit (V) or Contact (C)			V	V	C	V	C	V	C	V
Informed Consent	X									
Eligibility Assessment	X									
Medical history/ physical exam	X									
Height, weight, blood pressure and pulse	X									X
HbAlc (POC or local lab, if needed)	X									
HbA1c (Central lab)			X							X
C-peptide and blood glucose (Central Lab)			X							
Pregnancy test (females of child-bearing potential)	X		X	X[3]						
Questionnaires	X									X
Assessment of CGM use	X	X								
Study system training			X	X[4]						
AE Assessment		X	X		X	X	X	X	X	X
Upload device data from home					X		X		X	
Download device data at clinic visit		X				X		X		X

1. Two 13-Week treatment periods with no intervening washout
2. Will coincide with Randomization Visit for study period 1
3. For study period 2 only
4. For Group B participants (those assigned to use SAP during period 1) only

Chapter 1: Background Information

1.1 Introduction

Type 1 diabetes (T1D) causes autoimmune pancreatic beta cell destruction and lifelong dependency on exogenous insulin. Subsequently, patients with T1D are at risk for long-term life-threatening microvascular and macrovascular complications that can be abated by aiming to achieve near-normal blood glucose. However, this tight control is associated with a threefold increase in the risk of severe hypoglycemic events, one of the most feared and dangerous events for patients and their parents or caregivers (1). Therefore, the ultimate goal in diabetes care is to keep blood glucose in a narrow desired range with minimal hypoglycemic events. Over the past decade, the use of insulin pumps and sensors and their combination (sensor-augmented pumps) have shown advances towards improving glucose control (2-4). However, recent data from diabetes centers in Europe and the United States (US) indicate that the glycemic control achieved is still not satisfactory and is complicated by the risk of hypoglycemia (5,6), despite the use of the advanced technological tools now available (7). Some progress is being made with the introduction of the threshold suspend or predictive low-glucose suspend (PLGS) sensor and pump systems in the United States. We now need to combine predictive features with PLGS features to minimize hyperglycemia as well (8), without causing anxiety and burden for patients and caregivers due to the demand for continual attention to how well the systems cover meals, snacks and periods of illness. This is especially true in adolescents and some young adults whose compliance with treatment can be low, with 50% omitting or delaying insulin boluses needed for meals (9). Automated decision support systems, and ultimately, full automated management solutions, are strongly desired by patients with T1D and their caregivers to improve metabolic control and relieve them of the stress and burden of daily treatment of this chronic disease.

1.1.1 Prior Clinical Evaluations of the Proposed AP System

Several clinical studies using the novel zone MPC control framework which is the basis for the proposed research shows consistently that the Artificial Pancreas (AP) is able to improve glucose regulation in T1D. Dassau et al. (FDA IDE G090129) published in 2013 results of a pilot clinical trial conducted at Sansum Diabetes Research Institute (SDRI), evaluating individualized, fully automated (no premeal bolus) AP using commercial devices (1). Two trials (n= 22, n=17) were conducted using a multi parametric formulation of MPC and an insulin-on-board algorithm. Continuous glucose monitor (CGM) glucose was maintained in the near-normal range 70-180 mg/dL for an average of 70% of the trial time. These results showed the ability of a control algorithm tailored to an individual's physiology to successfully regulate glycemia, even when faced with unannounced meals or initial hyperglycemia. We (FDA IDE G110093) studied the safety and efficacy of a fully automated AP using zone MPC with the health monitoring system (HMS) during unannounced meals and overnight and exercise periods. A fully automated closed-loop AP was evaluated in 12 subjects with T1D and demonstrated 80% and 92% time in the 70–180 mg/dL range for the entire session and overnight, respectively. These results showed that the combination of the zone MPC controller and the HMS hypoglycemia prevention algorithm was able to safely regulate glucose in a tight range with no adverse events despite the challenges of unannounced meals and moderate exercise. The zone MPC algorithm was successfully used in 2015 (FDA IDE G130147), when Drs. Dassau and Doyle AP team, Mayo Clinic and SDRI, among other sites, showed in a randomized clinical trial of 32 subjects in a transitional environment (such as hotel) that algorithmic adjustment of individualized insulin dosing

parameters was safe and effective for AP use (2). As part of the DP3DK094331 research project, the fruitful collaboration among Drs. Dassau and Doyle AP team, UVA, Mayo Clinic, SDRI and other collaborators yielded a large outpatient clinical trial of the zone MPC and HMS system (FDA IDE G150063), where 30 adult subjects each used AP at home for three months (3). This study resulted in a statistically significant decrease in HbA1c (−0.3, 95% CI −0.5 to −0.2, p<0.001) and hypoglycemia during the day from 5.0 to 1.9% (−3.1, 95% CI −4.1 to −2.1, p<0.001) over the three months of AP use (Figure 2).

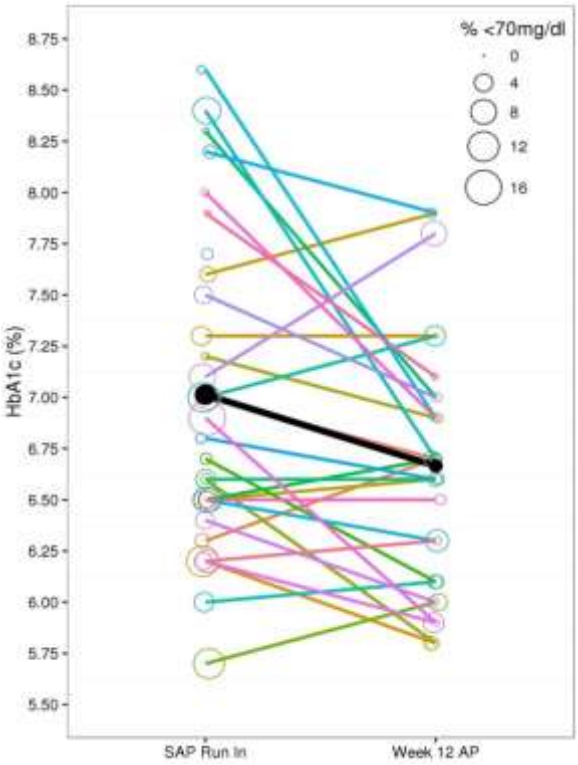

Figure 2. Change in HbA1c compared to percent time hypoglycemia in a three-month outpatient study comparing our zone MPC algorithm to SAP use in patients with T1D (3). Mean HbA1c change and reduction in percent time CGM glucose <70 mg/dL are shown by the black line and filled in black circles. Individual subjects are shown by the colored lines and colored circles.

The zone MPC controller has also been used for outpatient studies in adolescents (FDA IDE G150122), with unannounced exercise multiple times per day and large meals. Mean CGM glucose was significantly lower during AP vs. SAP use (150±19 vs 173±32, P = 0.042) (4). We also recently concluded a randomized-crossover study comparing glycemic control of the zone MPC AP system versus SAP therapy use at home in which insulin infusion set (IIS) and CGM failures were precipitated in 7 and 21 days of use, respectively, in which results were significantly better for zone MPC compared to SAP use (5). Our second generation target MPC AP system (enhanced MPC, or eMPC) (6) with the addition of a trust index that weights future insulin delivery based on past glucose predictions (7) was evaluated in 15 adult subjects studied for 48 hours in SDRI, and achieved 88% time in the target glucose range 70-180 mg/dL (8).

1.1.2 Next Generation Artificial Pancreas: Zone MPC and HMS on a Smartphone App

The zone MPC algorithm has been implemented on the interoperable Artificial Pancreas System (iAPS), a novel, user friendly smartphone application and the system was clinically evaluated in a feasibility study (FDA IDE G180011), where it achieved 83% time in glucose range 70-180 mg/dL and mean CGM of 136 mg/dL (9).

iAPS is a smartphone-based artificial pancreas platform which provides seamless integration with Dexcom G5 and G6 CGM, and two different insulin pumps: Tandem t:slim and Insulet Omnipod. The app is designed to be cross-platform (Android and iOS), can be used concurrently with typical apps in a smartphone, and is designed to be interoperable and compatible with leading devices for diabetes management. As the app resides in a smartphone and connects wirelessly to the CGM and the insulin pump, the complete system is very portable and user friendly.

In addition to the hardware integration, the iAPS app provides an interface to the algorithms for AP glucose regulation, namely the zone MPC and the HMS, which provides an audio-visual advisory alarm for hypoglycemia. The app has an intuitive user interface (UI) allowing the user to request an insulin bolus for meal/correction and providing ability to log various activities such as exercise (Figure 3). It also provides alarms for system malfunction, e.g. loss of connectivity with devices, including text-messages to the subject's care partners for alarm events such as impending hypoglycemia. A web-based remote monitoring facility complements the app running on the smartphone allowing the clinician to verify salient features of subjects' glycemic health.

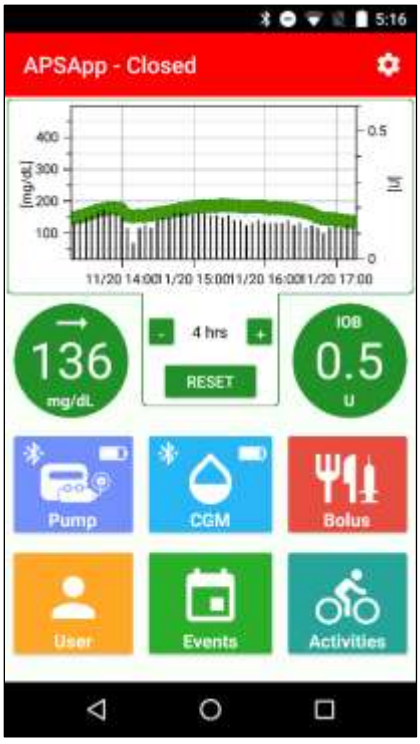

Figure 3. iAPS Interface

Our AP algorithms have been clinically evaluated in previous clinical studies (17 IDEs) with over 76,000 hours of human use as shown in Table 2.

Table 2. Summary of use of prior studies with the Artificial Pancreas System (APS) in different hardware configurations, as well as different variants of the Model Predictive Control (MPC) and Health Monitoring System (HMS) algorithms.

Study Year	IDE #	Components	Platform	Hours of Human Use	Location	PubMed Link
2019	G180011/S002	t:slim-Dexcom (ZMPC and HMS)	iAPS	>4,000 Hours 12 Subjects	Outpatient at Home	In Progress
2019	G180011/S001	t:slim-Dexcom (ZMPC and HMS)	iAPS	>3,500 Hours 10 Subjects	Outpatient at Home	In Progress
2018	G160279/S002	t:slim-Dexcom (ZMPC and HMS)	iAPS	800 Hours 18 Subjects	Supervised Outpatient	In Progress
2018	G180011	t:slim/OmniPod-Dexcom (ZMPC and HMS)	iAPS	300 Hours 6 Subjects	Supervised Outpatient	30547670
2017	G150063	Roche-Dexcom (ZMPC and HMS)	DiAs	>60,000 Hours 30 Subjects	Outpatient at Home	29030383
2017	G150122/S003	Roche-Dexcom (ZMPC and HMS)	DiAs	>6,000 Hours 19 Subjects	Outpatient at Home	28584075
2017	G160281	OmniPod-Dexcom (PBH algorithm)	pAPS	>50 Hours 10 Subjects	Supervised CRC	29355439
2017	G160281	OmniPod-Dexcom (Target eMPC and HMS)	pAPS	>700 Hours 15 Subjects	Supervised CRC	29958023
2016	G150122	Roche-Dexcom (ZMPC and HMS)	DiAs	>700 Hours 10 Subjects	Supervised Hotel	28459617
2016	G160169	OmniPod-Dexcom (Target eMPC and HMS)	pAPS	>1,950 Hours 54 Subjects	Supervised CRC	29431513
2015	G130147	Animas-Dexcom (ZMPC and HMS)	pAPS	>1,500 Hours 32 Subjects	Supervised CRC	26204135
2015	G130236	Animas-Dexcom (Target MPC/PID - HMS)	pAPS	>1,500 Hours 30 Subjects	Supervised CRC	27289127
2013	G110093/S006	Animas-Dexcom (ZMPC and HMS)	APS	36 Hours 4 Subjects	Supervised CRC	24351171
2013	G110093/S003	OmniPod-Dexcom (ZMPC/HMS, Inhaled Insulin)	APS	>200 Hours 9 Subjects	Supervised CRC	25901023
2012	G110093	Animas-Dexcom (Zone MPC and HMS)	APS	>275 Hours 12 Subjects	Supervised CRC	24471561
2012	G110069	Animas-Dexcom (ZMPC and HMS)	APS	>250 Hours 13 Subjects	Supervised CRC	24876535

1.2 Rationale

We aim to compare the efficacy and safety of an AID system using an adaptive MPC algorithm versus SAP (which may or may not include PLGS; to be referred to as SAP) in people with type 1 diabetes.

This study builds on the ideas presented in G150063 (3), where adaptation of insulin delivery settings occurred weekly to improve closed-loop function. In this study, adaptations of insulin

delivery settings occur weekly inside the study phone. These adaptations are posted on the study web monitoring website for complete visibility to study staff.

Current studies of Artificial Pancreas are initialized using fixed clinical inputs such as basal rate, insulin to carbohydrate ration and correction factors that are updated and managed by the clinical team, as well as fixed controller parameters. However, these settings frequently need adjustment over time. A major goal of this initiative is to reduce the burden of adapting these settings over time from the clinical team and the patient to move toward an automated system that gradually and continually optimizes these settings for the patient, as we believe this will aid controller function to improve time-in-range beyond what can be done today.

1.3 Automated Insulin Delivery System Description

The interoperable Artificial Pancreas System (iAPS) is an artificial pancreas system (as described in MAF-1625, Amendment #10), composed primarily of an insulin pump, a CGM, and a cellular phone device to connect the components. The portable AP device is intended to adjust insulin doses when glucose concentration is, or is predicted to be, outside the specified target range of 90-120 mg/dL. It includes a redundant safety control that will send warnings of impending hypoglycemia and recommend ingesting carbohydrates immediately to prevent hypoglycemia.

iAPS is described in MAF-1625, Amendment #10, and for this study will include:

- A cellular phone device to connect to the insulin pump and CGM transmitter.
  - Google Pixel 1, 2, 3 or 4 Cellular Phone. For subjects who agree, they may move their personal phone SIM card to the study phone and use the study phone as their personal phone during closed-loop.
- Dexcom G6® Sensor & Transmitter
- An insulin pump consisting of the Tandem t:AP insulin pump (San Diego, CA) (MAF 2032-A003)
- The same core control algorithm successfully used in IDE G180011/S002, G180011/S001 and G160279/S002 (Zone MPC with HMS).
- The same Health Monitoring System (HMS) algorithm used in G180011/S002, G180011/S001 and G160279/S002 which issues safety notifications to the subject and support personnel to prevent impending hypoglycemia.

A schematic of the iAPS system is shown in Figure 4.

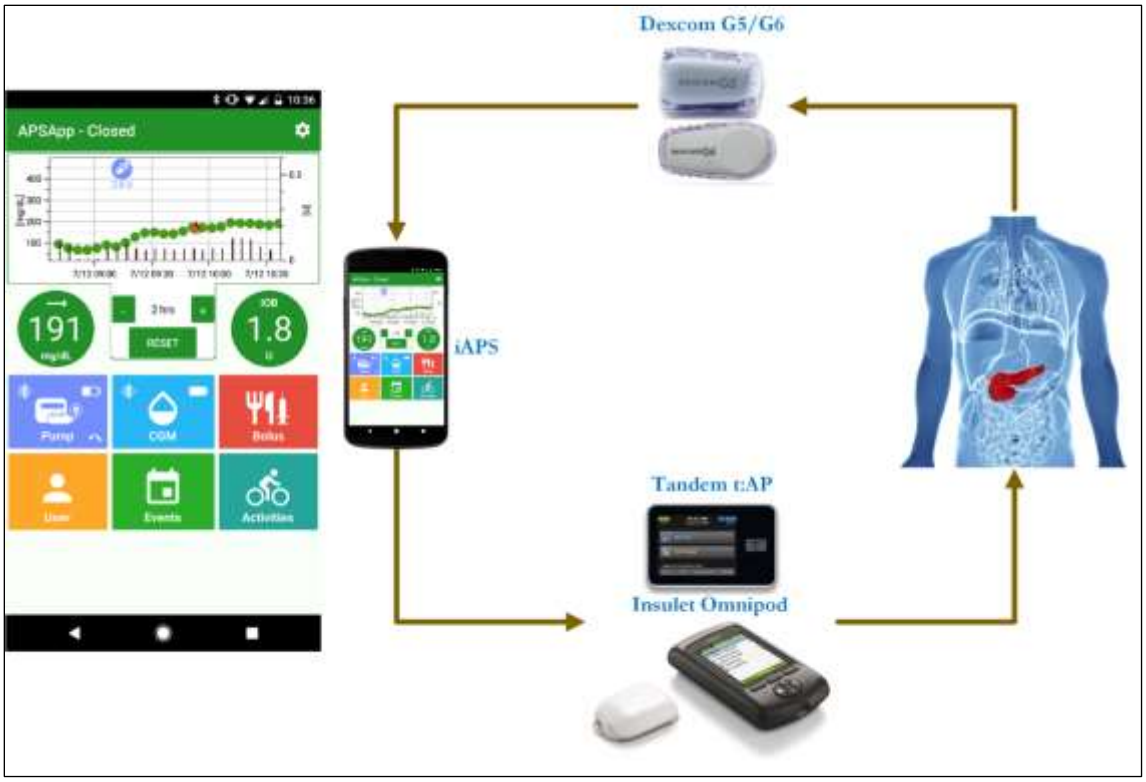

Figure 4. Schematic of the supported principal system hardware components of iAPS. For this study, only the Tandem t:AP pump and Dexcom G6 sensor will be used.

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

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

1.4.1 Known Potential Risks

1.4.1.1 Potential Risks and Benefits of the Investigational AID System

Even though the study system has been tested prior to this study, there is still a risk that parts of the system may not function properly. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery system;
- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin.

1.4.1.2 Risk of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of hypoglycemia. The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness,

and not feeling well. Severe hypoglycemia is possible with loss of consciousness or seizures. Recurrent hypoglycemia may reduce hypoglycemia awareness. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.4.1.3 Risk of Hyperglycemia

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

1.4.1.4 Insulin Infusion Risks

The pump infusion set is inserted under the skin. An infection can occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. Infusion set failure (clogs, kinks, accidental removal) may occur, leading to hyperglycemia or ketosis.

1.4.1.5 Venipuncture Risks

Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

1.4.1.6 Fingerstick Risks

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

1.4.1.7 Subcutaneous Catheter Risks (CGM)

Use of CGM has a low risk for developing a local skin infection at the site of the sensor needle placement. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

On rare occasions, the sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site.

1.4.1.8 Risks Associated with Device Reuse

In the study, we may reuse CGM receivers after careful cleaning. The CGM transmitters and sensors will not be reused.

In the study, the insulin pump may be reused after careful cleaning.

1.4.1.9 Questionnaire

As part of the study, participants will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires to be mildly

upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

1.4.1.10 Other Risks

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

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

1.4.2 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control the glucose level. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants who may learn how to better control their diabetes after the study ends and general benefit to others with diabetes.

1.4.3 Risk Assessment

The investigators believe that the risk of study participation is small over and above the daily risks of type 1 diabetes outside of a study, based on the facts that (1) people with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) although the study intervention involves periodic automated insulin dosing that may could increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may could increase the likelihood of hyperglycemia, it is more likely that the study intervention will decrease both hypoglycemia and hyperglycemia, and (3) mitigations are in place that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin.

1.5 General Considerations

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

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

The protocol is considered a significant risk device study, due to the fact that the AID study system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study in the US.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of at least 35 starting and 32 participants completing the crossover trial. A maximum of 60 individuals may be enrolled into screening (i.e., sign the informed consent form and initiate screening). Participants who have signed consent and started the screening process will be permitted to continue into the crossover trial, if eligible, even if the crossover trial randomization goal has been reached. All eligible participants will be included without regard to sex, gender, race, or ethnicity.

Study participants will be enrolled at approximately 5-7 clinical centers. All sites are experienced in type 1 diabetes and use of AID systems.

The recruitment goal for each site for the RCT is the same (approximately 5-7 participants per site); however, certain sites may recruit additional participants if necessary for the study to meet the overall recruitment goal. The maximum number to be enrolled into screening at a single site will be 15.

Potential eligibility may be assessed as part of a routine-care examination. Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read and will be given the opportunity to ask questions. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

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

A participant is considered enrolled when the informed consent form, and assent form if applicable, has been signed.

2.1.1 Pilot Phase

The Pilot Phase (details in Chapter 3) will include 1-2 participants at each site. All participants in the Pilot Phase must use CSII and a Dexcom G5/G6 sensor for their usual care. Participants in the Pilot Phase may subsequently participate in the Crossover Trial.

2.2 Participant Eligibility Criteria

2.2.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1) Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year

2) Using an insulin pump for at least 3 months (which may include use of automated features)

3) Familiarity and use of a carbohydrate ratio for meal boluses

4) Age ≥18.0 years old

5) For females, not currently known to be pregnant
   a. *If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.*

6) If using a personal CGM, willingness to use a Dexcom G6 CGM and discontinue personal CGM use during the study

7) Willing not to begin use of, or not to continue use of if currently using, a personal AID (closed loop control) system during the study; *note if the system offers an open-loop mode or can be switched to a PLGS mode that is compatible with the Dexcom G6, the system may be used during the study in these modes only*

8) Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study

9) Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial, and not to use Afrezza during the trial

10) Investigator believes that the participant can successfully and safely operate all study devices and is capable of adhering to the protocol

2.2.2 Exclusion Criteria

1) Use of Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) unless participant is willing to discontinue during the trial.

2) Two or more episodes of DKA requiring an emergency room visit or hospitalization in the past 6 months

3) Two or more episodes of severe hypoglycemia with seizure or loss of consciousness in the last 6 months

4) Hemophilia or any other bleeding disorder

5) A medical or other condition that in the opinion of the investigator could create a safety concern for the participant or put the study at risk

   a. History of frequent severe hypoglycemia or history of frequent severe hyperglycemia and/or ketosis, without emergency room visit or hospitalization, due to poor diabetes self-management may be disqualifying per investigator judgment

6) Participation in another pharmaceutical or device trial at the time of enrollment or during the study

2.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel, and local laboratory testing if needed to screen for exclusionary medical conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion. Individuals who do meet eligibility criteria will proceed to the Pilot Phase, CGM Run-In period, or Crossover Trial (as applicable, see below), which will be expected to start on the same day as screening, or up to 14 days thereafter.

2.3.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or qualified designee (e.g. a physician, fellow, nurse practitioner, or a physician assistant).

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Inclusion and exclusion criteria assessed
- Demographics (socioeconomic status, date of birth, sex, race, and ethnicity)
- Contact information (retained at the site and not entered into study database)
- Medical history
- Diabetes history
- Concomitant medications
- Physical examination to include:
  - Weight, height
  - Vital signs including measurement of blood pressure and pulse
- Blood draw or fingerstick for HbA1c level measured using the DCA Vantage or similar point-of-care device or local lab, if measurement not available from past 3 months
- Urine pregnancy test for all females of child-bearing potential
- The following questionnaires will be administered:
  - Diabetes Distress Scale
  - Glucose Monitoring Satisfaction Survey
  - Hypoglycemia Confidence
  - Diabetes Technology Attitudes
  - INSPIRE Survey

Screening procedures may last approximately 1-2 hours.

2.3.2 Screen Failures

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

Chapter 3: Pilot Phase

3.1 Description

The Pilot Phase will include 1-2 participants at each site, using a personal Dexcom G5/6, with use on at least 11 of the prior 14 days and for whom the investigator believes that a CGM run-in is unnecessary.

The Pilot Phase is intended to (1) test the functionality of all aspects of the study system and (2) train the clinical staff on the execution of the clinical protocol, including hands-on training with the device prior to initiating the RCT Period.

3.2 Enrollment and Screening Procedures

Participants in the Pilot Phase must meet all of the inclusion and none of the exclusion criteria listed in section 2.2. Additionally, they must be using a Dexcom G5/6 sensor and meet the criteria for skipping the CGM Run-In Phase. These participants will undergo the same screening procedures planned for the Crossover Trial as described in section 2.3.

Study system start up procedures will be the same as for the Crossover Trial.

3.3 Pilot Phase Visits and Procedures

The Pilot Phase will have one study start up visit that will follow the same procedures described in section 2.3 for the Screening Visit.

Participants will use the study system at home for 10-14 days and will follow all outpatient procedures described in Chapter 5 for use of the study system. Participants will have a phone call 3 days (+/- 1 days) after initiation of home use of the study system. Procedures will match those described in section 7.2.1.

Participants will have a follow up visit at the end of the home use period. Visit procedures will include the following:

- Assessment of adverse events, adverse device effects, and device issues
- Download of study system and CGM data
- Download of blood glucose meter and ketone meter
- Return of AID study system components (phone and insulin pump) and switch back to personal insulin pump
    - Participants interested in participating in the RCT may at the discretion of the investigator retain study CGM and meters for continued use until the Crossover Trial begins, at which time a Randomization Visit will occur as described in Chapter 5.

3.4 Safety Review of Pilot Phase Data

After at least 5 total participants from at least 3 different sites have completed the Pilot Phase, the data will be reviewed. If there are no significant safety, usability, or system functionality issues that occur as defined in the list of criteria below, the Crossover Trial may begin for sites who have completed at least 1 Pilot Phase participant. If any issues are identified, then the Pilot Phase may be repeated after the issues have been resolved and any associated approvals (IRB,

FDA, DSMB) have been obtained. If repeated, participants could have participated in the earlier pilot phase or could be new participants.

Specific criteria for proceeding to the main RCT include:

a) No serious adverse events related to use of the iAPS during the pilot phase.

b) All subjects have demonstrated an independent ability to initiate the iAPS system and operate it safely, as judged by the site investigators.

c) Investigators and engineering team are able to confirm that adaptation of clinical parameters is running successfully within the predefined bounds.

Chapter 4: CGM Run-in Phase

4.1 Introduction

Eligible participants using a personal Dexcom G5/G6 sensor, with use on at least 11 of the prior 14 days may skip the CGM run-in unless the investigator believes that a run-in is necessary prior to randomization. Participants skipping the run-in can go directly to the randomization visit.

Eligible participants not currently using a personal Dexcom G5/G6 sensor or using a Dexcom G5/G6 sensor with readings captured on less than 11 out of the previous 14 days will initiate a CGM run-in phase with a Dexcom G6 sensor.

- *Users of a sensor other than Dexcom G5/G6 (eg, Medtronic, Abbott) must be willing to discontinue use of that sensor for the duration of the study and users of an AID (closed loop control) system must be willing to discontinue its use during the study (PLGS mode can be used during the study if feasible).*

4.2 Initiation of CGM

The participant will be provided with sensors and a transmitter and a blood glucose meter, and instructed to use the study CGM on a daily basis. Training will be provided to participants not experienced with CGM use as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

- The participant will be given a CGM receiver (if desired) and trained on its use, or will be trained on the installation and use of the Dexcom phone-based mobile app
    - Participants may use available Dexcom software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose
- A study CGM training checklist will be used to document and facilitate the training process.

A physical or electronic copy of the study CGM user's guide will be provided for the participant to take home.

4.3 Assessment of Successful Completion of the CGM Run-in Phase

Enrolled participants will return approximately 14 days after the initiation of the run-in phase to assess progress or successful completion of the phase. If needed, one or more interim visits or phone contacts may occur to assist the participant with any system use issues and for pump settings optimization.

Visit procedures will include the following:

- Uploading of CGM data and assessment of amount of use of the CGM
- Assessment of skin reaction in areas where a CGM sensor was worn
- Assessment of eligibility to continue to the RCT phase of the study

To enter the randomized trial, participants must have obtained CGM readings on at least 11 out of the previous 14 days. If a participant fails to meet this criterion, or if it is determined that the participant will benefit from additional time with CGM use, the run-in period may be extended at the discretion of the investigator. One additional period may occur, with another clinic visit to assess results after the second period using the same criteria as above. The run-in duration will therefore vary from approximately 2 to 4 weeks, depending on the participant. Additional visits and phone contacts for further training are at investigator discretion.

Participants who are unable to meet the CGM compliance requirements will be withdrawn from the study, as will participants who no longer meet all of the inclusion and exclusion criteria.

Chapter 5: Randomization Visit

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until they are convinced that the participant is eligible and will accept assignment to either of the two treatment orders.

5.1 Visit Timing

The randomization visit is expected to begin on the same day the CGM Run-In period is completed (or it can be on the same day of screening if the run-in phase is skipped). If not on the same day, the randomization visit should occur within 14 days of the end of the run-in phase (or screening visit if run-in skipped).

Participants in the Pilot Phase will be on hold until the safety assessment of the Pilot Phase has been completed and the RCT begins. Once the RCT is initiated, Pilot Phase participants who will participate in the RCT will complete the consent process for the RCT and will then be able to complete the randomization visit.

If it has been more than 30 days since the Screening visit, changes in medications and medical conditions since screening will be solicited, and if necessary the standard physical exam described in section 2.3 will be repeated.

Eligibility criteria from screening will be reviewed again (if not the same day) to verify eligibility, and the study staff will evaluate whether the participant can safely use the study system. If the participant is no longer eligible based on these criteria, the participant will be dropped from the study.

5.2 Data Collection and Testing

The following procedures will be done at the randomization visit:

- Blood sample to send to the central laboratory for HbA1c; random, non-fasting C-peptide; and glucose
- Urine pregnancy test for all females of child-bearing potential (if not performed within the prior 6 days)

5.3 Randomization

Eligible participants will be randomly assigned, stratified by site, to one of two groups to determine treatment order during the 26-week study:

1. Group A: study system for period 1 for 13 weeks, then SAP for period 2 for 13 weeks
2. Group B: SAP for period 1 for 13 weeks, then study system for Period 2 for 13 weeks

Participant randomization assignment is determined after the Randomization Visit data are entered on the study website. The data from this visit and where applicable, prior visits, are assessed to verify eligibility prior to the randomization process being completed.

5.4 Device Training and Study Supplies

5.4.1 CGM System Training, Initiation, and Supplies

Participants who were eligible to skip the CGM Run-In phase will have the study CGM initiated at this time as described in section 4.2. At investigator discretion, applicable elements of the CGM system training may be completed as refresher training.

The participant will be provided with a supply of CGM sensors, a backup CGM transmitter, and blood glucose strips to last until the next study visit.

5.4.2 Blood Ketone Meter Training and Supplies

The participant will be provided with a study blood ketone meter and strips and instructed on the use of this device.

5.4.3 Home Glucagon Emergency Kit

Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

5.4.4 Study System Training and Device Use

Participants assigned to Group A will receive study system training prior to initiating period 1 of the crossover trial. These training sessions can occur on the same day as the randomization visit or extend to up to one additional session within the next 7 days if needed; participants will not take the study system home and initiate period 1 until training has been completed.

Participants assigned to Group B will receive study system training upon completion of period 1 (the SAP period). These participants will have the same option as above of completing training the same day as the period 1 13-Week Visit, or else within a 7-day period following that visit, prior to initiating home use of the study system.

Participants will receive study system training by the clinical center study team. The study system includes the Tandem t:AP insulin pump and Dexcom G6 CGM. The system also includes the study phone.

5.4.4.1 Pump Training

Pump training will include the following:

- The participant will be fully instructed on the study insulin pump. A member of the study research team will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.

- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.
- The appropriate study pump training checklist will be used to document and facilitate the training process; a physical or electronic copy of the pump user guide will be provided for the participant to take home.
- Participants will be provided with sufficient insulin infusion supplies to last until the subsequent visit.

5.4.4.2 Study Phone Training

Study phone training will include:

- The study team will confirm the subject's parameters are entered in the system (APS RM) with the study physician.
- How to switch the system between Pump mode (open-loop, preprogrammed basal insulin delivery) and Closed Loop mode depending on circumstances.
- How to calibrate the CGM unit during the study as per manufacturer's instructions and per clinical need.
- How to access the CGM trace from the sensor on the phone screen. Study staff will also explain the concept of "safe basal" to the subjects which can be activated after CGM connectivity is interrupted to the study phone.
- How to activate the meal bolus screen of the phone system any time insulin will be given with a meal or any time additional correction insulin is desired.
  - Specifically, study staff will follow inform the subject that:
    - The bolus screen correction calculation is based on the last CGM value.
    - They can add a fingerstick value into the bolus screen, and this will adjust the correction slider calculated correction dose. If there is any concern about the accuracy of the current CGM value, a fingerstick is generally more accurate and should be performed instead of relying on the current CGM value.
    - They can adjust the correction slider calculated correction dose.
    - They can use the total dose box to adjust the final dose to be delivered, regardless of what settings are entered into the other boxes (glucose value, carbohydrates, correction). The amount shown in this box will be delivered.
    - CGM trend information is not used in the meal bolus or correction bolus calculation.
    - Study staff will observe them using all buttons and boxes on the meal bolus screen to show us they understand how to use the meal bolus screen.
- How to inform the system of hypoglycemia treatment via a hypoglycemia treatment button on the phone UI after each hypoglycemic treatment is consumed.

- What to do when exercising while using the system.
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- How to perform blood ketone testing.
- Review of the iAPS App User Guide; a physical or electronic copy will be provided for the participant to take home.
- The study iAPS training checklist will be used to document and facilitate the training process.
- Review of the adaptation procedure, to inform subjects that the adapted closed-loop settings are internal to the system, and to ask study staff at any time if they have questions about ongoing adaptation.

For subjects who agree, they may move their personal phone SIM card to the study phone and use the study phone as their personal phone during closed-loop. Subjects will be assisted by study staff in this setup process. At the end of study system use, the study phone will be factory reset to remove any personal data from the study device.

5.4.4.3 General Usage Training and System Initiation

The participant will be instructed to use the system in closed-loop mode except 1) when no CGM sensor is available or 2) if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, participant will be instructed to turn off closed-loop mode for approximately four hours.

The participant will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

Participants will be specifically instructed:

1) Not to upgrade the phone operating system or the iAPS app will no longer allow closed-loop operation.
2) Not to plug headphones into the study phone or alerts will be silenced.
3) Not to put the phone on vibrate mode or alerts will be silenced.
4) Not to use any manufacturer provided (e.g. Dexcom G6 Mobile App) or third-party components for CGM connectivity and monitoring, as this will interfere with connectivity to the study phone.

After study system training has been completed, participants in Group A will proceed with home use of the study system. Participants may use the study pump and study phone without closed-loop and study CGM during periods of component disconnections or technical difficulties.

5.4.5 SAP Training and Device Use

During the SAP period, participants will use their own insulin pump and the study Dexcom G6 sensor. If a participant is using a home pump with PLGS capability compatible with the study sensor, he/she may keep the pump in PLGS mode; however, an AID system cannot be used.

All participants will have used a pump and sensor either prior to enrolling in the study or during the CGM run-in phase. Study staff will review use of pump and sensor therapy in diabetes self-management, uploading of device data as needed, and reviewing of data visualizations.

Participants may use available Dexcom software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

Chapter 6: Crossover Trial Home Procedures

6.1 Guidance on Clinical Staff Contact

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with any study-provided device. Questions relating to the study protocol will be dealt with by a study staff member on call. Participants will be referred to their own medical providers for issues not directly related to the study and to local Emergency Medical Services for medical emergencies

Study staff will discuss with the participant that routine contact is required and will make arrangements with the participant for the contacts. Participants who are not compliant with the arranged contacts may be discontinued at the discretion of the investigator.

6.2 Safety Measures

6.2.1 Drug and Alcohol Use

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

6.2.2 CGM Calibration

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labeling.

6.2.3 Study Pump Failure

In the event of a study pump failure, the participant will be instructed to use their personal insulin regimen until the problem can be resolved.

6.2.4 Insulin Dosing

During the Study System period of the Crossover Trial, all insulin dosing is supervised by the study system. Insulin injection for meal boluses must be performed using the pump bolus calculator.

During the SAP period, participants will dose insulin in accordance with manufacturer labeling of their insulin pumps and the study CGM system.

6.2.5 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings is not allowed during the study. Insulin pump settings may be adjusted for safety concerns only if the study participant contacts the study physician due to concerns about pump settings due to recurring hypo- or hyperglycemia, or if the study physician has overriding concerns for safety.

During the AID period, if there is a safety concern necessitating a pump settings change, this will force a reset of the stored adaptation of pump parameters. In this case, the investigator will contact the protocol chairs to review the need for safety adjustments, who will then help the

study site reset the APS RM pump parameters, assure those settings match the settings on the study pump, and then reset the adaption on the APS RM website.

In the SAP arm, if there is a safety concern necessitating a pump settings change, the site investigator may make the adjustments and document this on the appropriate study CRF. However, the goal of the study is not to have physicians perform data-driven optimizations of pump settings, but instead to try to limit changes to safety concerns only.

6.2.6 Hypoglycemia Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app (as applicable), but will be instructed to choose a value no less than 60 mg/dL.

If a participant receives a CGM hypoglycemia threshold or predictive alarm or notes that the CGM glucose is below the hypoglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling and the participant will be instructed to treat hypoglycemia with ~15 grams of fast-acting oral glucose.

6.2.7 Hyperglycemia Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app (as applicable), but will be instructed to choose a value no greater than 300 mg/dL.

If a participant receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is above the hyperglycemia threshold alarm value, confirmatory fingerstick testing will be performed if required by CGM labeling.

If a participant's CGM reading is >300 mg/dL for over 2 hours or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is >0.6 mmol/L, take correction insulin, change insulin (pump) infusion site and contact study staff.
- If a participant administers correction insulin via insulin syringe, participants will be instructed to disable closed-loop control for approximately four hours.

6.2.8 Device Data Uploads

The study system phones will include a study-supplied SIM card (if personal SIM card is not being used) to ensure near continuous automatic upload of data to the remote monitoring system.

During the SAP study period, participants will be asked to upload CGM data (and pump data, if possible) prior to each scheduled phone call or clinic visit.

6.2.9 Remote Monitoring

During the 2-week Pilot Phase, subjects will have real-time event-based remote monitoring alerts present from the study phone to notify study staff of prolonged periods of hypoglycemia (>30

minutes <70 mg/dL) or hyperglycemia (>2 hours above 300 mg/dL, or greater than 400 mg/dL at any time). On-call clinic staff will contact the participant following these alerts to evaluate the situation and provide guidance with respect to device use and management of the hypo- or hyperglycemia.

During the 2-week pilot phase, study clinicians at each site will review the weekly adaptation changes no later than 6 hours from time of adaptation and log that the review occurred. If there is a safety concern about the adaptation, site clinicians will follow the procedures in Section 6.2.5 - Optimization of Insulin Pump Settings to contact the protocol chairs and discuss if reset of adaptation parameters is needed.

During the RCT, remote real time alerts for participants using the study system will not be enabled unless requested or deemed to be useful by study staff and participants for troubleshooting connectivity issues. Instead, study staff will review the data from all subjects using the study system on the web interface for iAPS at least once a week so they can evaluate ongoing data and adaptations, and will contact participants if there are ongoing issues related to connectivity or other areas. Study staff may contact the subjects at any time for concerns arising from remote monitoring data.

Chapter 7: RCT Follow-up Study Visits

7.1 Timing of Visits

7.1.1 Visit and Phone Contact Schedule during Study Periods 1 and 2

During each of the two 13-Week study periods, visits and contacts will be scheduled as outlined in Table 3 below:

Table 3. Visit and Phone Contact Schedule

Target Day/Week	Type	Target/Allowable Window (around Target Day/Week)
3 days*	Phone	+/- 2 days
2 weeks	Visit**	+/- 4 days
4 weeks	Phone	+/- 7 days
6 weeks	Visit**	+/- 7 days
9 weeks	Phone	+/- 7 days
13 weeks	Visit**	+/- 7 days

** During the study system use period, this 3 days will be with respect to the start of home use of the study system, rather than with respect to the start of the period*

*** Videoconferences may be performed instead of in-person visits at investigator discretion, for example in case of local restrictions on in-clinic visits or participant-specific quarantine/isolation requirements; 13-Week visits involving iAPS system training/initiation must be in-clinic unless formal permission is obtained from clinical Protocol Chair to perform the visit remotely*

Additional contacts or visits may occur as needed.

7.2 Procedures at Phone Contacts and Follow-up Visits

7.2.1 Phone Contacts

Prior to each phone contact, the participant will be asked to upload device data as described in section 6.2.8 for study staff review. During the phone call, study staff will:

- Assess compliance with study device use
- Answer questions about using the study system
- Assess adverse events, adverse device effects, and device issues
- Review glycemic control

Phone contacts may be performed via videoconference at investigator discretion.

7.2.2 Procedures Performed During Each Follow-up Visit

The following procedures will be done at all visits in both periods, unless otherwise stated

- Assessment of compliance with study device use
- Retraining on system use as needed

- Assessment of adverse events, adverse device effects, and device issues
- Download of CGM data (when available), blood glucose meter data, and blood ketone meter data (for videoconferences, participant upload of any devices that supports cloud upload, and subsequent download by clinic staff)
- During clinic visits, QC test blood glucose meter with the available concentration(s) of control solution if the meter is brought to the visit (except for 13-week visit of period 2)

In addition, the following will be done at the 13-week visit in each period, unless otherwise stated:

- Urine pregnancy test for females of child-bearing potential (period 1 only); for videoconferences, test can be performed at home with a study-provided kit and verbal report of test result
- Participant weight, height, and blood pressure and pulse; for videoconferences, a verbal report of the participant's weight and height will be acceptable
- Collection of a blood sample to send to the central laboratory for HbA1c determination; for videoconferences, a capillary sample may be obtained at home with a study-provided kit and mailed to the central laboratory
- Completion of the following questionnaires:
  - Diabetes Distress Scale
  - Glucose Monitoring Satisfaction Survey
  - Hypoglycemia Confidence
  - Diabetes Technology Attitudes
  - INSPIRE Survey (following study system period only)
  - System Usability Scale Survey (SUS) (following study system period only)
- Return study devices as appropriate
- Initiate period 2 devices (end of period 1 only)
- Place back on pre-study insulin delivery method and glucose monitoring method at 13-week visit (end of period 2 only).

7.2.3 Early Termination Visit

If a participant discontinues the study early, an attempt will be made to have a clinic visit or videoconference to return study devices and supplies, to record any adverse events or device issues that have occurred, complete final questionnaires, and collect a final HbA1c.

7.2.4 Unscheduled Visits

An Unscheduled Visit form will be completed for any contact the participant has with the site for significant protocol-related issues/questions outside the visit schedule.

Chapter 8: Study Devices

8.1 Description of the Study Devices

8.1.1 AID Study System

The study system is composed of a Tandem t:AP pump, a Dexcom G6 continuous glucose monitoring sensor, and a smart phone that contains the adaptive algorithm and communicates with the other devices.

8.1.2 Insulin Pumps

During the study system period, participants will use a Tandem t:AP pump. During the SAP period, participants will use their personal pump.

8.1.3 Continuous Glucose Monitoring

Participants in both arms will use a Dexcom G6 sensor, identical to the commercially available G6 sensor. A transcutaneous glucose sensor for the Dexcom G6 CGM will be inserted in the subcutaneous tissue and will provide input to the controller. The CGM sensor will be replaced at least once every 10 days. Only approved insertion sites will be used (abdomen).

8.1.4 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the study-assigned blood glucose meter (glucometer) and the CGM device will be calibrated if needed using the study glucometer and strips in accordance with the manufacturer's labeling.

8.1.5 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra (or equivalent meter, such as the Optium Neo) meter and strips in accordance with manufacturer labeling. Any blood glucose meter component of ketone meters will not be used.

8.2 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

8.3 Participant Access to Study Device at Study Closure

Participants will be permitted to keep the blood glucometer and blood ketone meter at the end of the study, but will need to return all other devices, including study phone, insulin pump, and CGM components and related supplies.

Chapter 9: Laboratory Testing and Questionnaires

9.1 Laboratory Testing

HbA1c:

- HbA1c level measured using the DCA2000 or comparable point of care device or local lab at the Screening visit, if no measurement is available from the past 3 months
- A blood sample will be obtained for central lab analysis at Randomization and at the conclusion of each 13-Week Crossover Trial period. Final HbA1c also may be collected from participants who withdraw from the study.

Random C-Peptide and Glucose:

- Collected at Randomization for central lab analysis

Urine Pregnancy:

- Performed locally for females of child-bearing potential at Screening, randomization (if not performed within the prior 6 days) and at the beginning of the second study period during the crossover trial. This test may also be performed at any time pregnancy is suspected.

9.2 Questionnaires

The following questionnaires will be completed at Screening and at the end of each 13-week periods during the crossover trial (except for the SUS survey, which will only be administered after the AID period, and the INSPIRE survey, which will only be administered at Screening and after the AID period). Final questionnaires also may be collected for participants who withdraw from the study.

Each questionnaire is described briefly in Table 4 below. The procedures for administration are described in the study procedures manual.

Table 4. Questionnaires

Measure	Construct Measured/Relevant Points
Diabetes Distress Scale	Gold standard measure for understanding distress symptoms related to diabetes. A recently validated version for adults with T1D, but will also be administered to adolescents (17 items; 6 min)
Glucose Monitoring Satisfaction Survey	This recently validated survey is an outgrowth of DirecNet and JDRF CGM surveys; evaluates treatment satisfaction and burden. Administered to all participants (15 items; 4 min)
Hypoglycemia Confidence	Includes 8 different common situations where hypoglycemia occurs (e.g., physical activity, driving) and evaluates level of confidence in those situations (8 items; 3 min)

Measure	Construct Measured/Relevant Points
Diabetes Technology Attitudes	Subjective questions about attitudes related to diabetes technologies and devices (5 items; 3 min)
INSPIRE Survey	Measures the psychological side of automated insulin delivery. Adult survey has 22 items; adolescent version 17 items. (6-8 mins)
System Usability Scale (SUS)	A 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic.

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Chapter 10: Adverse Events, Device Issues, and Stopping Rules

10.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Additionally, unanticipated problems must be reported to the JCHR IRB within 7 calendar days of recognition.

For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

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

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as the central laboratory.

10.2 Adverse Events

10.2.1 Definitions

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

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

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

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

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which a study device may have caused or to which the device may have contributed (note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in). *An event that occurs solely due to participant (i.e., user) error in which the device functions properly generally will not be considered an ADE unless it is determined that the instructions on the screen of the device or user manual (or similar training materials) may have contributed to the event (note: the event may still meet criteria for reporting as an adverse event).*

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). *Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.*

10.2.2 Reportable Adverse Events

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

- An SAE
- An ADE as defined in section 10.2.1, unless excluded from reporting in section 10.3
- An AE as defined in 10.2.1 occurring in association with a study procedure
- An AE as defined in 10.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
- An AE as defined in 10.2.1 that affects the participant's ability to complete any study procedures
- An AE as defined in 10.2.1 for which a visit is made to a hospital emergency department
- Hypoglycemia meeting the definition of severe hypoglycemia as defined below
- Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, hyperglycemia or ketosis event meeting the criteria defined below

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

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

10.2.3 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

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

10.2.4 Hyperglycemia/Ketosis Events

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 3 criteria is met:

- The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- Blood ketone level ≥1.0 mmol/L, even if there was no communication with a health care provider at the time of the event

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO2) <15; and
- Treatment provided in a health care facility.

When a hyperglycemia/ketotic event meets the above reporting requirements, a Hyperglycemia/ DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA criteria are considered to be serious adverse events with respect to reporting requirements.

Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in section 10.2.1 is met.

10.2.5 Relationship of Adverse Event to Study Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device.

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

Yes

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

No

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

10.2.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

10.2.7 Expectedness

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

10.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

10.2.9 Outcome of Adverse Events

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

- RECOVERED/RESOLVED: The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE: The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL: A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING): An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.

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

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

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

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

10.3 Reportable Device Issues

All UADEs and ADEs as defined in section 10.2.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment. As noted in section 10.2.1, events that occur due to participant (user) error generally will not require completion of a device issue form. Such 'errors' could include improper use of an insulin pump or using a pump infusion set or CGM sensor for a period of time longer than its labeling.

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

- CGM sensor lasting fewer days than expected per manufacturer
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

10.4 Timing of Event Reporting

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

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee. The JCHR IRB must be informed of all UADEs within seven calendar days.

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

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

10.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within 24 hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review

compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB).

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

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

10.6 Stopping Criteria

10.6.1 Participant Discontinuation of Study Device

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

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

- The investigator believes it is unsafe for the participant to continue on the intervention. *This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety*
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA as defined in 10.2.4
- Two distinct severe hypoglycemia events as defined in section 10.2.3
- One episode of DKA as defined in section 10.2.4 and one severe hypoglycemia event as defined in section 10.2.3

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

An additional requirement for continued [study device] use following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor and DSMB concur. If either the Medical Monitor or DSMB determines that the

occurrence of the event indicates that it is not safe for the participant to continue to use the BP system, use will be discontinued.

10.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in 10.6.1, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). In addition to suspension of device use due to a UADE, the study will be suspended for 2 severe hypoglycemia and/or DKA related events related to device function. The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

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

Chapter 11: Miscellaneous Considerations

11.1 Drugs Used as Part of the Protocol

U-100 rapid acting insulin analogues, Aspart or Lispro, will be used during the study since these are the only insulins approved for the study pump.

11.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

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

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

11.3 Prohibited Medications, Treatments, and Procedures

Participants are not permitted to use Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).

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

11.4 Rescue Medications

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

11.5 Pregnancy Reporting

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

11.6 Participant Compensation

Participant compensation will be specified in the informed consent form.

11.7 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal. An early termination visit may be completed to collect final study data.

If participants wish to discontinue using the study device without withdrawing, participants will be encouraged to remain in the study through the final study visit.

11.8 Confidentiality

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

Chapter 12: Statistical Considerations

12.1 Statistical and Analytical Plans

The outcome metrics and the statistical analyses are summarized below. A detailed Statistical Analysis Plan will be written and finalized prior to the first tabulation of data by treatment group (i.e., for DSMB review).

12.2 Statistical Hypotheses

The primary outcome for this study is CGM-measured % in range 70-180 mg/dL over 12 weeks in each one of the two crossover periods. The intervention will be considered effective if time in range during the CLC period is superior to the SAP period using a statistical significance of α=0.05 and the model specified below (section 12.6).

The null/alternative hypotheses are:

a. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180 mg/dL over 12 weeks between SAP and CLC periods

b. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 12 weeks is different for SAP and CLC periods.

12.3 Sample Size

Sample size has been computed for the primary outcome (CGM-measured % in range 70-180 mg/dL). Data from the SAP group in DCLP3 (The International Diabetes Closed Loop Protocol 3 Pivotal Trial of t:slim X2 with Control-IQ Technology) were used to calculate sample size specific to ≥18 years age group. For the SAP group, the standard deviation for time in range 70-180 mg/dL over the course of the first 3 months was 12% (95% CI 10% to 16%) and the correlation between the first 3 months and last 3 months was 0.92.

A total sample size was computed to be N=31 for the following assumptions: (1) two 3-month periods [CLC:SAP] crossover randomization, (2) 90% power, (3) a 8% absolute increase in % time in range 70-180 mg/dL, (4) a SD of 17%, (5) a correlation between the two periods of 0.70, and (6) 2-sided type 1 error of 0.05.

The total sample size has been increased to N=35 to account for potential dropouts.

12.4 Outcome Measures

12.4.1 Primary Efficacy Endpoint

CGM-measured % in range 70-180 mg/dL

12.4.2 Secondary Efficacy Endpoints

12.4.2.1 Secondary Efficacy Endpoint Included in Hierarchical Analysis

CGM-measured % below 54 mg/dL (non-inferiority outcome with a non-inferiority limit of 1.0%) will be tested in a hierarchical fashion as described in section 12.7.1. This is the only non-inferiority outcome in the study; all others are superiority.

12.4.2.2 Other Secondary Efficacy Endpoints

The following endpoints are considered exploratory.

CGM-Measured:

- % in range 70-140 mg/dL
- mean glucose
- glucose variability measured with the coefficient of variation (CV)
- glucose variability measured with the standard deviation (SD)
- % <70 mg/dL
- % <60 mg/dL
- % <54 mg/dL
- low blood glucose index
- hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- % >180 mg/dL
- % >250 mg/dL
- % >300 mg/dL
- high blood glucose index
- CGM metrics by time of day. Calculate all CGM metrics listed above (including the primary outcome) for:
  - All 24 hours of the day
  - Daytime only (06:00AM to 00:00AM)
  - Nighttime only (00:00AM to 06:00AM)

HbA1c:

- HbA1c at 13 weeks
- HbA1c <7.0% at 13 weeks
- HbA1c <7.5% at 13 weeks
- HbA1c improvement from baseline to 13 weeks >0.5%
- HbA1c improvement from baseline to 13 weeks >1.0%
- HbA1c relative improvement from baseline to 13 weeks >10%

Questionnaires:

- Diabetes Distress Scale at 13 weeks – total score and 4 subscales:
  - Emotional burden

- Physician-related distress
- Regimen-related distress
- Interpersonal distress

- Glucose Monitoring Satisfaction Survey – satisfaction, burden, and total scores
- Hypoglycemia Confidence Scale
- Diabetes Technology Attitudes survey
- INSPIRE survey scores - following study system period only
- SUS survey scores - following study system period and at 13 weeks only

Other:

- Insulin at 13 weeks
  - Total daily insulin (units/kg)
  - Basal: bolus insulin ratio
- Weight and Body Mass Index (BMI) at 13 weeks

12.4.3 CGM Metrics Calculations

The last 2 weeks of personal CGM data or last 2 weeks of CGM run-in data will serve as baseline. Since participants will receive up to 7 days of training before taking the CLC system home, the first 7 days in the SAP and CLC periods will not be included in the CGM analyses. CGM data starting from day 8 following randomization visit through the 13-week visit for first period and from day 8 following treatment reassignment through the second 13-week visit for the second crossover period will be included in the calculation of CGM metrics. At least 72hr of CGM data at baseline and in each one of the two periods are needed in order for the metrics to be calculated.

12.5 Analysis Datasets and Sensitivity Analyses

All analyses comparing the CLC period with SAP period will follow the intention-to-treat (ITT) principle with each period and participant analyzed according to the randomization. All randomized periods with at least 72hr of CGM data will be included in the primary and secondary hierarchical analyses.

Safety outcomes will be reported for all enrolled participants, irrespective of whether the participant was randomized or the study was completed.

12.5.1 Per Protocol Analyses

- If more than 10% of participants in a treatment period have fewer than 168 hours of CGM data, the primary analysis will be replicated excluding such subjects.
- The primary analysis will be replicated only with participants who used the system in CL mode for >80% during the CLC period and used the sensor for >80% during the SAP period.

12.5.2 Sensitivity Analyses

12.5.2.1 Missing Data

It is worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used. To that end, sensitivity analyses will be performed to explore whether results are similar for primary analysis when using different methods. The following methods will be applied:

- Available cases only (≥72hr in at least one of the two cross-over periods, primary analysis described below)
- Rubin's multiple imputation

12.5.2.2 Carry-over Effect

A model will be run for the primary outcome to test for any carry-over effects, by adding a treatment by period interaction term.

12.6 Analysis of the Primary Efficacy Endpoint

Summary statistics [mean ± SD or median (IQR)] will be reported for the CGM-measured % in range 70-180 mg/dL and for baseline and two randomized cross-over periods.

A repeated measures linear regression model will be fit for CGM-measured % in range 70-180 mg/dL. The model will include pre-randomization baseline, the two cross-over periods, and will adjust for period and site (as random effect). Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. It is expected that the residual values for CGM-measured % in range 70-180 mg/dL will follow an approximate normal distribution.

12.7 Analysis of the Secondary Endpoints

Point estimates and confidence intervals for the treatment period differences will be presented for all secondary metrics. Models similar with the one described above will be implemented.

12.7.1 Hierarchical Analyses

To preserve the overall type 1 error for CGM-measured % below 54 mg/dL, a hierarchical testing procedure will be used. A formal statistical assessment of non-inferiority (limit 1%) for time below 54 mg/dl will only be performed if the primary analysis for time in range described above results in a statistically significant result ($p < 0.05$).

Regardless of the results for the primary outcome, summary statistics appropriate to the distribution will be tabulated by treatment period for CGM-measured non-inferiority % below 54 mg/dL. However, the reported one-sided 95% confidence interval for CGM-measured % below 54 mg/dL that excludes the non-inferiority limit of 1.0% will not be considered a statistically significant result if the primary outcome failed to reach statistical significance.

12.7.2 Other Endpoint Analyses

CGM-Measured Outcomes

The analyses for the secondary CGM-measured outcomes will parallel those mentioned above for the primary outcome.

HbA1c

Summary statistics [mean ± SD or median (IQR)] will be reported for the central lab HbA1c at randomization and 13 weeks in each treatment period.

Lab HbA1c values at 13 weeks will be compared between the two treatment periods using a linear model while adjusting for period, site (random effect), and baseline value.

For the binary HbA1c outcomes listed above, risk-adjusted percentages by treatment period will be computed from a logistic regression model. The logistic regression will adjust for the same factors mentioned above for the analysis with HbA1c as a continuous factor (i.e., period, site, and baseline value).

Questionnaires and Other Outcomes

For questionnaires administered during both randomization periods, comparisons will be made using similar linear models as described above for the primary outcomes. Separate models will be run for the total score and each of the subscales listed above.

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

12.8 Safety Analyses

All enrolled participants will be included in these analyses and all their safety events will be reported.

The circumstances of all reportable cases of the following will be summarized and tabulated by treatment period:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Ketone events defined as day with ketone level ≥1.5 mmol/L
- CGM-measured hypoglycemic events (≥15 minutes with glucose concentration <54 mg/dL)
- CGM-measured hyperglycemic events (≥15 minutes with glucose concentration >300 mg/dL)
- Worsening of HbA1c from start of the period to 13 weeks by >0.5%
- Other serious adverse events (SAE) and serious adverse device events (SADE)
- Adverse device effects (ADE)
- Unanticipated adverse device effects (UADE)

Statistical analyses to compare rates of severe hypoglycemia and rates of diabetic ketoacidosis between treatment arms will only be performed if there are at least 10 events after randomization. If yes, the numbers will be compared between the two treatment periods using a robust Poisson regression. The amount of follow up will be included as an offset covariate to compare the rates.

Comparison of safety outcomes between the two treatment periods only include those events occurring on or after randomization until the final 13 week visit.

Any pre-randomization adverse events will be tabulated separately and will include participants who were never randomized.

12.9 Intervention Adherence and Adaptation

The following tabulations and analyses will be performed by treatment period to assess intervention adherence for the study:

- Sensor use –percent time of use, overall and by 4-weekly
- The overall daily frequency of downloaded BGM use
- For CLC period only, the following will be tabulated:
  - Percent time in different operational modes - overall and by month
  - Percent change of clinical and controller adaptation parameters throughout closed-loop use

12.10 Adherence and Retention Analyses

The following tabulations and analyses will be performed by treatment period to assess protocol adherence for the study:

- Number of protocol and procedural deviations per participant along with the number and percentage of participants with each number of deviations
- Number of protocol and procedural deviations by severity with brief descriptions listed
- Flow chart accounting for all participants at all scheduled visits and phone contacts post treatment initiation to assess visit and phone completion rates
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment and reasons

12.11 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized using summary statistics appropriate to the distribution of each variable.

12.12 Device Issues

Reported Device malfunctions and other reported device issues will be tabulated.

12.13 Planned Interim Analyses

The DSMB will review all cases of severe hypoglycemia and diabetic ketoacidosis irrespective of device relationship, all device-related SAEs, and all UADEs at the time that they occur during the study and will review compiled safety data at periodic intervals. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary.

12.14 Subgroup Analyses

In exploratory analyses, the primary outcome will be assessed separately with tests of interaction in various subgroups and for continuous variables according to the baseline value, which will be described in the Statistical Analysis Plan.

12.15 Multiple Comparison/Multiplicity

Hierarchical testing will be done to control the type 1 error for the time in range and time below 54 mg/dl outcomes as described above in Section 12.7.1.

No multiplicity adjustment will be done for safety analyses. For all other secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

Chapter 13: Data Collection and Monitoring

13.1 Case Report Forms and Device Data

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

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

13.2 Study Records Retention

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

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Quality Assurance and Monitoring

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

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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

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

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

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

Chapter 14: Ethics/Protection of Human Participants

14.1 Ethical Standard

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

14.2 Institutional Review Board (IRB) (or Ethics Committee (EC))

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

14.3 Informed Consent Process

14.3.1 Consent Procedures and Documentation

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

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

14.3.2 Participant and Data Confidentiality

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

The study monitor, other authorized representatives of the Coordinating Center, representatives of the IRB/EC or device company supplying study product may inspect all documents and

records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional/national regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored either at the Jaeb Center for Health Research (JCHR) in Tampa, FL, USA or at Harvard University in Cambridge, MA, USA. Harvard uses a cloud-based provider for storage of the closed-loop system data. These data will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the JCHR research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the JCHR in Tampa, FL. Permission to transmit data will be included in the informed consent.

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

Chapter 15: References

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