Signature Page

The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of AI Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children with Type 1 Diabetes

Protocol Identifying Number: PEDAP-AI

IDE Sponsor: University of Virginia

Version Number: 5.0

14FEBRUARY 2024

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The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of AI Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children with Type 1 Diabetes

IDE Sponsor
University of Virginia
Center for Diabetes Technology
IDE# G230127

Funded by:
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

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Version Number: v5.0
14 FEBRUARY 2024

KEY ROLES

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	J. Lum	M. Breton, P. Wadwa	25 APR 2023	Initial protocol draft
2.0	D. Rojas J. Lum	M. Breton, P. Wadwa	15 MAY 2023	Reorganize Chapter 4, add new section 4.2 Add certificate of confidentiality language in section 10.3.2 Address FDA questions during IDE review, including time period for pump training, requirement not to change pump settings without discussion with study team, and logistics associated with occasional stoppage of closed-loop delivery related to exogenous insulin delivery Fix typos, spacing errors
3.0	D. Rojas J. Lum	M. Breton, P. Wadwa	13 JUNE 2023	Revisions to address IRB requests, including: • clarified language in exclusion criterion 8 • minor edits, added footnotes to Table 1 • clarified eConsent process in Section 2.1.1 • specified timing of procedures at screening and pump initiation visits in Section 2.4 • specified method of delivery for scale in Section 2.4.1 • specified eConsent is repeated at rescreening in Section 2.5 • removed reference to randomization in Section 7.3 • added reference to study pump data collection in Section 9.1 • specified device materials language in Section 10.3.1 • indicated no genetic testing in Section 10.3.2 Minor clerical edits throughout Fix typos
*4.0	Z. Reed	M. Breton, P. Wadwa	28 AUG 2023	Revisions to Statistical Considerations chapter: • Both primary safety outcomes (hypoglycemia and hyperglycemia) will be tested for non-inferiority • Restructured safety endpoints section to specify the pair of hierarchical CGM-measured primary safety endpoints plus additional safety endpoints • Restructured efficacy endpoints to specify a set of hierarchical CGM-measured efficacy endpoints plus additional secondary and exploratory efficacy endpoints

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
				• Revised material describing analysis details for various outcomes • Added section on insulin metrics • Expanded description of comparison with PEDAP historical control Revised Endpoints row of Protocol Summary table to match Stats chapter changes. Revisions based on JCHR QA review
5.0	J. Lum	M. Breton, P. Wadwa	14 FEB 2024	• Relaxed eligibility criteria to allow enrollment sooner after T1D diagnosis and allow current pump users • Corrected "Error" text in several TOC entries by fixing text style in section 6.2 • Revised Protocol Overview section of Protocol Summary table to make 3 Day Visit procedures identical to subsequent visit procedures, consistent with remainder of document • Clarified insulin data needed for system initialization in section 3.2.1 • Revised section 3.3.4 to allow off-cycle optimization of pump settings • Revised section 4.2.1 to describe use of either Dexcom G6 or G7 CGM components, making this section consistent with the rest of the document

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring System
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
LGS	Low Glucose Suspend
NGSP	National Glycohemoglobin Standardization Program
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
RCT	Randomized Control Trial
SC	Standard of Care group
SD	Standard Deviation
TDD	Total Daily Dose
UI	User Interface

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: **The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of AI Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children with Type 1 Diabetes**

Protocol Version/Date: 5.0 / 14 February 2024

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

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

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

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

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

Investigator's Name: _____

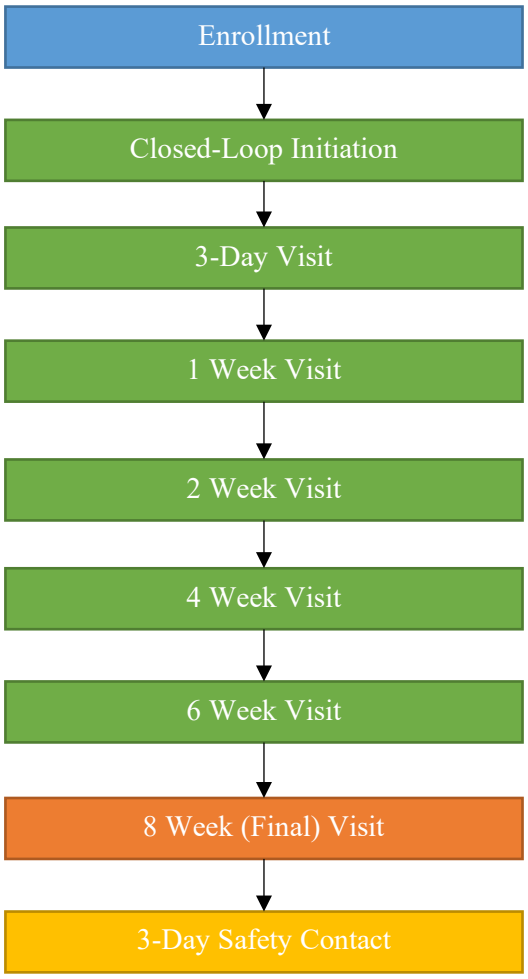
Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	The Pediatric Artificial Pancreas Automated Initialization trial (PEDAP-AI): A Pilot Study of AI Advisor-Driven Pump Initiation and Parameter Adaptation in Young Children with Type 1 Diabetes
Précis	A single-arm pilot study of AI Advisor-driven at-home closed loop system initiation and parameter adaptation in youth age 2 to <6 years old.
Investigational Device	Tandem t:slim X2 with Control-IQ and t:connect mobile application and Dexcom G6 or G7 system, connected to UVA cloud-based Physician Dashboard
Objectives	The objective of the study is to obtain safety data and exploratory glycemic control data with initiation and use of a closed loop control (CLC) system (t:slim X2 with Control-IQ Technology) in young children with initial selection of pump parameters and subsequent periodic parameter adjustment driven by an AI-based Advisor system over a 8-week period.
Study Design	In this single-arm intervention trial, all participants will use the study system (pump and CGM) in closed-loop mode for 8 weeks.
Number of Sites	~3 US clinical centers
Endpoints	**Safety** The key safety outcomes are adverse events related to hypoglycemia and hyperglycemia, CGM-measured time spent below 54mg/dL, and CGM-measured time spent above 250mg/dL. CGM-measured endpoints will be tested against baseline for non-inferiority. **Efficacy** Glycemic outcomes including time in target range 70-180 mg/dL (TIR) and various other CGM measures of hypo- and hyperglycemia will be assessed and tested for superiority against baseline and a matched historical control population from the prior PEDAP study that did not involve the use of any AI-driven pump parameters.
Population	**Key Inclusion Criteria** 1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 1 month 2. Familiarity and use of a carbohydrate ratio for meal boluses 3. Age ≥2 and <6 years old 4. Using a Dexcom CGM at the time of enrollment, with use on at least 21 out of the prior 28 days 5. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 6. Parent/guardian has a phone that can run the Tandem t:connect Mobile App (typically Android 10 or above or iOS 15 or above) 7. Willingness to use the t:connect Mobile App as needed during the study and ensure connectivity for a data upload at least once per day 8. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol 9. 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 for participants using a study-provided Tandem pump during the study. 10. Total daily insulin dose (TDD) at least 5 U/day 11. Body weight at least 20 lbs 12. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 13. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff 14. Parent/guardian proficient in reading and writing English

PARTICIPANT AREA	DESCRIPTION
	15. Live in the United States, with no plans to move outside the United States during the study period **Key Exclusion Criteria** 1. Concurrent use of any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) 2. Hemophilia or any other bleeding disorder 3. History of >1 severe hypoglycemic event with seizure or loss of consciousness in the last 3 months 4. History of >1 DKA event in the last 6 months not related to illness, infusion set failure, or initial diagnosis 5. History of chronic renal disease or currently on hemodialysis 6. History of adrenal insufficiency 7. Hypothyroidism that is not adequately treated in the opinion of the investigator 8. Use of oral or injectable steroids within the last 8 weeks 9. Known, ongoing adhesive intolerance 10. Plans to receive blood transfusions or erythropoietin injections during the course of the study 11. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk 12. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 13. Having immediate family members employed by Tandem Diabetes Care, Inc. or Dexcom, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
Sample Size	Up to 45 screened participants with the goal of at least 30 participants completing the study pump use period
Intervention	t:slim X2 with Control-IQ Technology and t:connect mobile application with mobile bolus capabilities and Study CGM
Participant Duration	~8 weeks
Study Duration (planned)	~8 months from first enrollment until last participant visit
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants will proceed to the main study described below. Initial pump parameter settings will be reviewed by clinical site staff after uploading baseline personal CGM and insulin data to a web-based AI-driven Advisor interface. The Advisor will suggest pump parameter settings that the study investigator may either accept unchanged or else override based on clinical judgment if there are any safety concerns. A study pump will be configured with the resulting parameter values, the participant will be provided with the study pump and study CGM and other supplies, and the participant will begin home use of the pump. Visits* will occur at 3 days and at 1, 2, 4, and 6 weeks, with each visit including site upload of pump/CGM data to the Advisor interface to obtain recommended adjustments to pump parameters. As before, the study investigator may either accept unchanged or else override based on clinical judgment if there are any safety concerns. A final study visit will occur at 8 weeks, at which time the study participant will be transitioned back to preferred post-study insulin therapy. A follow-up safety visit will occur 3 days after the final visit to confirm successful transition to post-study insulin therapy. ** All study visits may be conducted either remotely via teleconference, or else in person at the clinical site*

SCHEMATIC OF STUDY DESIGN



Initial configuration of AI-driven pump parameters

Initial adjustment of AI-driven pump parameters

AI-driven pump parameter adjustment

AI-driven pump parameter adjustment

AI-driven pump parameter adjustment

AI-driven pump parameter adjustment

Return of study supplies; transition to post-study insulin therapy

Confirm successful transition to post-study insulin therapy

SCHEDULE OF STUDY VISITS AND PROCEDURES

Table 1. Schedule of Study Visits and Procedures

	Screening Visit*	Baseline-Pump Initiation**	3d	1w	2w	4w	6w	8w	8w +3d
Informed Consent	X								
Eligibility Assessment	X								
Medical history/ height/weight	X								
Central lab HbA1c		X							
Study pump training		X							
Upload device data from home			X	X	X	X	X	X	
Review diabetes management, AEs, and medications		X	X	X	X	X	X	X	X
Manual pump parameter adjustment only if safety issue			Any scheduled or unscheduled visit						
AI-driven pump parameter initiation/adjustment		X	X	X	X	X	X		

* All screening visit procedures must be completed within 28 days of eConsent.

** All Pump initiation visit procedures must be completed within 10 days of screening visit procedure completion.

Chapter 1: Background Information

1.1 Introduction

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system (TypeZero Technologies, Inc.).

The system has received FDA approval for use in individuals ≥6 years old following a series of pivotal trials that demonstrated the system's safety and efficacy, first in participants ≥14 years old (1) then in participants ≥6 years old (2), and finally in participants ≥2 years old (3).

Closed-Loop Control System

The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is described in Master File MAF-2032/A008. Control-IQ Technology is derived from inControl previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is an "artificial pancreas" (AP) application that uses advanced closed loop control algorithms to automatically manage blood glucose (BG) levels for people with Type 1 Diabetes. The system modulates insulin to keep BG in a targeted range. The system components include the t:slim X2 with Control-IQ Technology, t:connect Mobile App, and Dexcom G6 or G7 system, connected to UVA cloud-based Physician Dashboard.

1.2 Rationale

The objective of this trial is to obtain safety data and exploratory glycemic control data with initiation and use of a closed loop control (CLC) system (t:slim X2 with Control-IQ Technology) in young children with initial selection of pump parameters and subsequent weekly parameter adjustment driven by an AI-based Advisor system over a 8-week period.

1.3 Potential Risks and Benefits of the Investigational Device

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 these events.

1.3.1 Known Potential Risks

1.3.1.1 Potential Risks and Benefits of the CLC 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.

1.3.1.2 Risk of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the

participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

1.3.1.3 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.

1.3.1.4 Fingerstick Risks

At various times several drops of blood will be removed by fingerstick. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

1.3.1.5 Subcutaneous Catheter Risks (CGM)

Participants using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours, it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The participant should be further instructed to notify the study coordinator immediately if this occurs.

1.3.1.6 Risk of Device Reuse

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The receiver, if used, is a hand-held device. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin. Participants will be informed that FDA or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e., Hepatitis B) may be spread through the use of multiple users.

The study insulin pump is labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.) Participants will be informed that FDA or relevant national authorities typically approve the insulin pump device for single use and that by using them among multiple patients, bloodborne pathogens (i.e., Hepatitis B) may be spread through the use of multiple users.

The study BG meter and blood ketone meter are labeled for single-patient use.

During the study, only one person can use each device as there are rare risks that bloodborne pathogens (i.e., Hepatitis B) may be spread through the use of multiple users.

1.3.1.7 Other Risks

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

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

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

1.3.2 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about the feasibility of using an AI-driven algorithm to adjust pump therapy parameters for an automated closed-loop system to control the glucose level. The individual participant may not benefit from study participation.

1.3.3 Risk Assessment

Based on the facts that (1) children with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may reduce the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may reduce the likelihood of hyperglycemia, (3) if any, hypo and/or hyperglycemia occur, mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 45 CFR 46.405 and 21 CFR 50.52 as a clinical investigation involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. In addition, it is the belief of the investigators that this study also presents prospect of general benefit to others with diabetes.

1.4 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).

The protocol is considered a significant risk device study, due to the fact that the closed loop system is experimental in the population under study and the AI-driven pump parameter adjustment algorithm—though all adjustments are reviewed and approved by study physicians—is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having 30 completing the study pump use period. A maximum of 45 individuals may be enrolled into screening for the study in order to achieve this goal.

Study participants will be recruited at ~3 clinical centers in the United States without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each clinical center toward the overall recruitment goal.

The study team will make every effort to have the following minimum numbers of participants complete the trial in the specified subgroups at the time of enrollment:

- At least 50% of the participants with most recent available HbA1c ≥ 7.5%

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

A parent/legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions either via phone/videoconference or by mail or email. If the parent is interested in the study, the investigator will schedule a virtual or in-person visit to discuss study, and if the parent agrees to participation, the Informed Consent Form will be electronically signed through the JCHR website. A copy of the electronically signed consent form can be printed by the parent and another copy will be printed by the site to add to the participant's study record. This process is referred to as eConsent.

As part of the eConsent process, each parent will be asked to electronically sign an authorization for release of the participant's personal information (i.e., HIPAA Authorization). The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the parent, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the eConsent has been signed by the parent and the investigator.

The participants are not being asked to provide assent as (1) they will be less than 7 years of age, (2) it is not expected that they would have the capacity to understand, and (3) their wear of the devices will be similar to the wear of these devices outside of the study.

2.2 Participant 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 1 month
2. Familiarity and use of a carbohydrate ratio for meal boluses
3. Age ≥2 and <6 years old
4. Using a Dexcom CGM at the time of enrollment, with use on at least 21 out of the prior 28 days
5. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff

6. Parent/guardian has a phone that can run the Tandem t:connect Mobile App (typically Android 10 or above or iOS 15 or above)
7. Willingness to use the t:connect Mobile App as needed during the study and ensure connectivity for a data upload at least once per day
8. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol
9. 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 for participants using a study-provided Tandem pump during the study
10. Total daily insulin dose (TDD) at least 5 U/day
11. Body weight at least 20 lbs
12. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial
13. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff
14. Parent/guardian proficient in reading and writing English
15. Live in the United States, with no plans to move outside the United States during the study period

2.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Concurrent use of any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas)
2. Hemophilia or any other bleeding disorder
3. History of >1 severe hypoglycemic event with seizure or loss of consciousness in the last 3 months
4. History of >1 DKA event in the last 6 months not related to illness, infusion set failure, or initial diagnosis
5. History of chronic renal disease or currently on hemodialysis
6. History of adrenal insufficiency
7. Hypothyroidism that is not adequately treated in the opinion of the investigator
8. Use of oral or injectable steroids within the last 8 weeks
9. Known, ongoing adhesive intolerance
10. Plans to receive blood transfusions or erythropoietin injections during the course of the study
11. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk
12. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
13. Having immediate family members employed by Tandem Diabetes Care, Inc. or Dexcom, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

2.4 Screening Procedures

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

The screening visit and subsequent scheduled study visits may be conducted virtually via videoconference at the discretion of the study investigator, for example due to institutional restrictions or the participant or investigator's preference for a remote visit. Study staff will discuss the feasibility of conducting virtual visits with each participant and provide support as needed to ensure adequate access. All screening procedures must be completed within 28 days of participant enrollment (i.e., eConsent). All pump initiation visit procedures must be completed within 10 days of completion of screening.

2.4.1 Data Collection and Testing

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

The following procedures will be performed at the screening visit:

- Informed consent process
- Assessment of eligibility
- Contact information (retained at the clinical center and not entered into study database)
- Demographics (date of birth, sex, race and ethnicity)
- Measurement of height/weight
    - If the visit is conducted virtually, a verbal report of the participant's weight and verbal report of height will be acceptable. A scale will be mailed to participants who do not already have access to one.
- Determination of most recent HbA1c level from medical records or verbal report

Screening procedures will last approximately 1-2 hours.

2.5 Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion. They will be asked to complete eConsent again.

Chapter 3: Main Phase

3.1 Visit and Contact Schedule

Visits and contacts will be scheduled as outlined below:

Table 4-1. Study Visits

Target Day/Week	Contact Type[1]	Target/Allowable Window (around Target Day/Week)
3 days	VC/V	± 1 day
1 week	VC/V	± 2 days
2 weeks	VC/V	± 2 days
4 weeks	VC/V	± 4 days
6 weeks	VC/V	± 4 days
8 weeks	VC/V	± 4 days
3-day post-study safety contact	VC/P	± 1 day

[1] Contact Types are defined as Clinic Visit (V), Videoconference (VC), or Phone call (P); Phone calls may be replaced by Videoconferences or Clinic Visits and Videoconferences may be replaced by Clinic Visits at investigator discretion

Additional office visits may occur as needed.

3.1 Blood Glucose Testing, Ketone Testing, and Glucagon

Participants will receive supplies, training, and instructions for blood glucose and ketone testing as described in section 4.3.

Participants will be required to have glucagon at home. Participants who currently do not have one will be given a prescription for glucagon (either emergency kit or nasal glucagon per investigator discretion for participants over 4 years of age).

3.2 Study Pump Procedures and Training

The study pump, study CGM, study blood glucose and ketone meters and associated supplies will be provided to participants within 3 days of completion of the Screening visit once eligibility to continue in the study has been confirmed. Dispensation of supplies may occur either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

Training on use of the study pump will be completed within 10 days of completion of the Screening visit, and closed-loop system use will begin at that time. Pump training may be delivered in one or more sessions (in-person or virtual), as needed. During the training window, participants will be permitted to use the study CGM and to use the study pump in open-loop mode if desired by the investigator.

Parents of participants will receive study pump training by a qualified trainer and will be fully instructed on the study insulin pump. The trainer will discuss topics such as: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc. The participating child will participate in training sessions to the degree judged appropriate by the parent and trainer.

Parents will be instructed to change the study insulin pump infusion set at least once every 3 days or per manufacturer guidelines, whichever is shorter.

Parents will be trained to use the bolus calculator following the standard t:slim X2 training.

- The study team will assist the parent in study pump infusion site initiation and will start the participant on the study pump.
- The parent will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The parent will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.
- The parent will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon.

Pump training specific to the Control-IQ Technology functions will include:

- How to turn on and off Control-IQ technology
- How to understand when Control-IQ is increasing or decreasing basal rates
- How to administer a meal or correction boluses
- What to do when exercising while using the system
- How to enable the sleep function and set the sleep schedule
- The parent will be assessed for understanding of the system interface and how to react to safety/alert messages.

The parent will be given a User Guide as a reference.

3.2.1 Determination of Initial of Pump Settings

For participants currently using an insulin pump, the study investigator may choose to enter the existing daily pump settings profiles directly into the web-based UVA Clinician Portal.

For participants not currently using an insulin pump or without an established daily pump settings profile, initial pump settings will be determined by the study AI algorithm. This will be achieved by study staff providing the following information to a web-based UVA Clinician Portal:

- The participant's personal CGM data from approximately two weeks prior to initiating pump use
- Entering the participant's average total daily insulin dose
- Body weight

The recommended pump settings will include daily profile values for basal rate, correction factor, carbohydrate ratio, and sleep activity.

After the recommended settings are provided, they will be reviewed by a study physician. The study physician may make necessary adjustments for safety prior to confirming that the values are successfully entered into the study pump. Both the AI-recommended and approved settings will be recorded on the Clinician Portal.

Parents will be instructed that any subsequent changes to the pump profile settings related to insulin delivery must be discussed with the study team prior to implementation.

3.2.2 t:connect Mobile App for Data Upload to Study Server

The participant/parent will be expected to upload pump and CGM data at least once per day during the course of the main phase of the study. This data upload will be achieved using the t:connect Mobile App, which will be installed on the participant/parent's personal phone. Participants/parents will be trained on configuring the app to connect to a study-provided t:connect account and ensuring that pump data upload to t:connect at least once per day.

Study data uploaded to the t:connect server will be periodically copied to the database of the study-specific Clinician Portal to support AI-driven settings adjustments during the course of the study.

3.2.3 System Use Guidelines

The participant/parent will be instructed to use the system in closed-loop mode except 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, the parent will be instructed to turn off Control-IQ for approximately four hours and notify study staff. In case of recurring instances of exogenous insulin delivery, the study team will determine if there are any safety or study integrity concerns to warrant withdrawal of the study participant.

The parent will also be instructed to contact study staff if the participating child has illness with an elevated temperature >100.4 degrees Fahrenheit (>38.0 degrees Celsius), other periods of significant illness, significant changes in physical activity level or food intake related to 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.

Parents will be provided with sufficient supplies to last until the subsequent visit.

Parents 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 the system. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties. Parents will also receive study staff contact information to ask any questions they may have during the study.

Study staff will discuss with the parent that routine contact is required and will make arrangements with the parent for the contacts. If the parent cannot be reached, the participant's other contact methods will be utilized, including the emergency contact. Parents who are not compliant with the arranged contacts on two separate occasions may be discontinued at the discretion of the investigator.

Upon completion of the CGM and study pump training components, study staff will document, using a checklist, that the parent is familiar with the functions/features/tasks addressed during the training.

Parents will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines (section 4.3) for when their glucose levels are >300 mg/dL for more than 90 minutes or >400 mg/dL at any time or <70 mg/dL or ketones ≥1.0 mmol/L.

Parents will be instructed that any changes to the pump profile settings related to insulin delivery must be discussed with the study team prior to implementation.

3.2.4 Home Use of the Study System

After training on the study system has been completed, participants will proceed with home use (meaning free-living use at school, home, etc.) of the study pump.

Parents may use available manufacturer-provided 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.

3.2.5 Study Device Download

Parents will be instructed to upload the study CGM and pump prior to each phone or videoconference contact throughout the study.

3.2.6 Baseline HbA1c Determination

A capillary blood sample will be obtained for baseline HbA1c determination. Capillary collection supplies will be provided to the participant in conjunction with the study pump training visit. This may occur either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

3.3 Study Visits

3.3.1 3-Day Visit

Study staff will perform an in-clinic visit or videoconference with the parent within 3 (±1) days following initiation of study pump use. The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use
- Study staff will use the Clinician Portal to obtain updated pump settings to apply to the study pump. As described above, the settings will be reviewed by a study physician prior to being entered on the study pump.

3.3.2 Subsequent Scheduled Study Visits

The remaining scheduled study visits at 1, 2, 4, 6, and 8 weeks will occur either in-clinic or via videoconference in accordance with the schedule and windows shown in Table 4-1 above.

Procedures for the scheduled visits will be identical to those described for the 3-Day Visit in section 3.3.1 above—including AI-driven pump settings adjustment—with the following visit-specific variations:

- 8 Week visit:
    - There will be no AI-driven study pump settings adjustment, and participants will be switched to the post-study insulin pump or MDI therapy that is desired by the participant's parent/legal guardian.
        - For participants who were on MDI at study enrollment, the possibility of switching to a commercially-available insulin pump after study completion should be discussed within the first 1-2 weeks of study pump use, to allow time for planning any required insurance- or prescription-related activities. The primary diabetes care team (outside of the study period) should be involved in this process.
    - Study participants will return study devices as specified in section 4.4 below.

3.3.3 3-Day Post-Study Safety Contact

Study staff will perform a phone call or videoconference with the parent within 3 (±1) days following the 8-week final visit. This visit may also be conducted in person at the clinical site. The following will occur:

- Assessment of adverse events, adverse device effects, and device issues
- Confirmation that participant has successfully transitioned to the desired post-study insulin therapy

3.3.4 Unscheduled Visits

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

During an unscheduled visit, the study investigator may elect to request an off-cycle optimization of pump settings from the UVA Clinician Portal and update the participant's pump settings accordingly.

Chapter 4: Study Devices

4.1 Description of the Investigational Device

The investigational components of the device system are the UVA Clinical Portal and insulin pump described below. The hardware components described in section 4.2 are all individually FDA-approved or -cleared commercial devices.

4.1.1 UVA Clinician Portal

The UVA Clinician Portal is an investigational software system that includes a front-end web site for monitoring participant data and determining AI-recommended pump settings and back-end logic responsible for suggesting pump settings based on data previously collected for the participant. Data from t:connect are automatically transferred to the Portal on a recurring basis every few hours.

4.1.2 Insulin Pump

The study system will include an unmodified Tandem t:slim X2 with Control-IQ technology. This is an FDA-approved device for ages 6 and older but is not approved for younger children at the time of this protocol version. There are no changes to its hardware or firmware components. These study pumps will be labeled as investigational devices.

4.2 Components of the Investigational Device System

4.2.1 Continuous Glucose Monitoring

The study CGM will include an unmodified Dexcom G6 or G7 transmitter and sensors. This is an FDA-approved device system for children as young as 2 years of age, with no changes to its hardware or firmware components. The CGM sensor will be replaced at least once every ten days. Participants will be permitted to switch between G6 and G7 components during the study if needed.

4.2.2 Phone Running t:connect Mobile App

Study data upload from pump and CGM will be achieved using the t:connect Mobile App, which will be installed on the parent/participant's personal phone during the study. This is a commercially-available, FDA-cleared software app with no modifications.

4.2.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the CONTOUR Next One meter and strips in accordance with the manufacturer's labeling.

4.2.3.1 Blood Glucose Meter Testing

- All study blood glucose meters will be QC tested with control solution prior to dispensation. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter and test strips if there is a suspicion that the meter is not reading accurately at home.
- Participants will be instructed on when and how to perform blood glucose testing.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements.

- Participants will be given guidelines for treatment of low or high blood glucose

4.2.4 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meter and strips in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra device will not be used.

4.2.4.1 Blood Ketone Testing

- All study blood ketone meters will be QC tested with control solution prior to dispensation. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. The participant will be instructed to contact study staff for a replacement of the meter and test strips if there is a suspicion that the meter is not reading accurately at home.
- Participants will be instructed on when and how to perform blood ketone testing.
- Participants will be reminded to use the study blood ketone meter for all fingerstick blood ketone measurements.
- Participants will be given guidelines for treatment of elevated blood ketones.

4.2.5 Study Device Accountability Procedures

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

4.3 Safety Measures

4.3.1 CGM Calibration

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

4.3.2 Pump Failure

If the CGM signal becomes unavailable for more than 20 minutes consecutively, Control-IQ or closed loop will not operate to automatically adjust insulin. If the CGM is not connected, the system will revert to usual function of the pump and deliver insulin with the insulin dosing parameters programmed in the system for that individual. Resumption of closed-loop will occur automatically once CGM signal is available again.

If the study system is unable to activate Control-IQ for any reason, the pump will automatically revert to preprogrammed basal insulin delivery without any need for instruction from the user.

If the pump detects a system error that does not allow it to operate, the Malfunction Alarm will display and the participant will be instructed to contact Tandem Technical Support via the study team.

4.3.3 Hypoglycemia Threshold Alarm and 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, but will be instructed to choose a value no less than 70 mg/dL.

The t:slim X2 with Control-IQ system will issue a predictive hypoglycemia alert (Control-IQ Low Alert) when the system predicts BG <70 mg/dL within the next 15 minutes (<80 mg/dL when exercise mode is activated).

If the participant receives a Control-IQ Low Alert, a message appears on the user interface (UI) that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is prompted to test blood sugar and treat with carbs.

4.3.4 Hyperglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change this setting, 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 labelling.

If a participant's CGM reading is >300 mg/dL for over 90 minutes or ≥400 mg/dL at any point, or if CGM reading is >250 mg/dL more than 3 hours after a meal, the participant took correction insulin, and CGM didn't decrease by at least 50 mg/dL, the participant will be instructed to take the following steps:

- Inspect infusion site for problems.
- 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 ≥1.0 mmol /L, contact study staff for further instructions, which may include replacing the insulin infusion set.
- If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours and notify the study team.

4.4 Participant Access to Study Device at Study Closure

Participants will return all insulin pump, CGM, and related supplies at their final visit. Participant may keep the study ketone meter and study glucometer and test strips if all study data have been downloaded and these devices are not marked for investigational use only.

Chapter 5: Testing Procedures

5.1 Laboratory Testing

1. HbA1c:
   - Sample collected within 3 days of closed-loop initiation.
   - Blood samples will be sent to the central laboratory for sample analysis using an NGSP approved method.

Chapter 6: Unanticipated Problem, Adverse Event, and Device Issue Reporting

6.1 Unanticipated Problems

Site investigators will promptly report all potential unanticipated problems meeting the criteria below on an eCRF. Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven (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 Sponsor also will report to the IRB all potential unanticipated problems not directly involving a specific site such as unanticipated problems that occur study-wide or at another participating entity such as a vendor. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the JCHR Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting to fulfill the reporting obligations of the HRPP.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

To further clarify, an adverse event is any unintended disease or injury, or untoward clinically significant clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. For this purpose, a participant is considered enrolled once the participant has signed the consent form. Reportable AEs for this protocol are defined in section 6.2.2.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. See 21 CFR 312 for more information.

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 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): An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device. (Note that an Adverse Event CRF is to be completed in addition to a Device Deficiency or Issue CRF, unless excluded from reporting as defined in section 6.3).

Comparator: Medical device, therapy (e.g., active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

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. For cleared devices, 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.

Use Error: User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

6.2.2 Reportable Adverse Events

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

1. An SAE as defined in section 6.2.1
2. An ADE, unless excluded from reporting in section 6.3
3. An AE as defined in section 6.2.1 occurring in association with a study procedure
4. An AE as defined in which leads to temporary or permanent discontinuation of a study device

5. An AE as defined in section 6.2.1 that affects the participant's ability to complete any study procedures
6. An AE as defined in section 6.2.1 for which a visit is made to a hospital emergency department
7. Hypoglycemia meeting the reporting criteria in section 6.2.3
8. Hyperglycemia meeting the reporting criteria in section 6.2.4
9. An AE as defined in section 6.2.1 considered to be related to either ineffective insulin (e.g., insulin exposed to high temperature that loses potency), signs or symptoms related to insulin infusion, or changing of type of insulin related to an AE.

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events. 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 CRF online. Each AE CRF is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

6.2.3 Hypoglycemic Events

Hypoglycemia is only reportable as an adverse event when one of the following criteria is met:

- A hypoglycemic event occurred meeting the following definition of severe hypoglycemia: 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 glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia
- Hypoglycemia occurred that was associated with an ADE as defined in section 6.2.1
- Study device discontinued due to hypoglycemia

When a severe hypoglycemia event occurs (as defined above), a Hypoglycemia CRF should be completed in addition to the Adverse Event CRF. Severe hypoglycemia events should be considered serious adverse events with respect to reporting requirements. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered unrelated to the device (per section 6.2.1) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.4 Hyperglycemic/Ketotic Events

Hyperglycemia or ketosis is only reportable as an adverse event when one of the following criteria is met:

- 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

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
    - 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
- Hyperglycemia occurred that was associated with an ADE as defined in section 6.2.1
- Study device discontinued due to hyperglycemia

When a hyperglycemia/ketotic event qualifies as an SAE as defined in section 6.2.1, a Hyperglycemia/DKA CRF should be completed in addition to the Adverse Event CRF. Events meeting DKA criteria should be considered serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered serious adverse events unless one of the SAE criteria in section 6.2.1 is met.

When a hyperglycemia/DKA event occurs during use of a study device, it generally will be considered unrelated to the device (per section 6.2.1) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.5 Relationship of Adverse Event to Study Device or Study Procedure

The site 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 or a study procedure. The Medical Monitor also will make this assessment, which may or may not agree with that of the site investigator. Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative.

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

- **Unrelated:** The AE is clearly not related to a study device/procedure and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.
- **Unlikely Related:** The AE does not follow a reasonable temporal sequence during or after use of study device/procedure and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.
- **Possibly Related:** The AE occurred in a reasonable time during or after use of study device or a study procedure; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study device.
- **Probably Related:** The AE occurred in a reasonable time during or after use of study device or a study procedure; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study device.
- **Definitely Related:** The AE occurred in a reasonable time during or after use of study device or a study procedure; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study device.

Events determined to be *Possibly Related, Probably Related,* or *Definitely Related* will be considered to meet the *reasonable possibility* causality standard for relatedness and necessitate reporting as required (see 21 CFR 312.32 for more information).

6.2.6 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.

6.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device/procedure, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the approved labelling of the Control-IQ study pump.

6.2.8 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.

6.2.9 Outcome of Adverse Events

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

- RECOVERED/RESOLVED (COMPLETE RECOVERY) – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.. 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.
- ONGOING (NOT RECOVERED/NOT RESOLVED) – An ongoing AE/SAE is defined as an ongoing event 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.

- ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as UADEs or related SAEs 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.

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

6.3 Reportable Device Issues

All UADEs and ADEs as defined in section 6.2.1 will be reported on both a Device Issue CRF and AE CRF, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

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 CRF assuming criteria for a UADE or ADE have not been met:

- CGM sensor lasting fewer days than expected per manufacturer
- CGM tape adherence issues
- Pump infusion set insertion lasting fewer days than expected per manufacturer
- 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

Use error (as defined above) will only be reported on a device issue form if an Adverse Event results from the error. In these cases, both a Device Issue and an Adverse Event form will be completed.

6.4 Timing of Event Reporting

SAEs possibly related to a study device or procedure and UADEs must be reported by the investigator to the Sponsor within twenty-four (24) hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the AE CRF and Device Issue CRF if applicable. If the AE CRF is not initially completed, it should be completed 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 respective CRF within seven (7) days of the site becoming aware of the event.

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

Each site 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. Where the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events within seven calendar days.

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within ten (10) working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Sponsor in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than five (5) working days after the Sponsor makes this determination and no later than fifteen (15) working days after first receipt notice of the UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification, and must submit to their overseeing IRB as required.

The investigators are also required to report, without unjustified delay, all reportable device deficiencies that could have led to a UADE, including device deficiencies, irrespective of whether an adverse event occurred.

6.5 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 twenty-four (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 Protocol Chair/Coordinating Investigator 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 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 DSMB review will be documented in a separate DSMB document.

6.6 Stopping Criteria

6.6.1 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 device 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 study device 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 device by a participant will be discontinued if any of the following occur and the participant will be withdrawn from the study:

- 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
- Two distinct episodes of DKA as defined in section 6.2.4
- Two distinct severe hypoglycemia events as defined in section 6.2.3
- One episode of DKA as defined in section 6.2.4 and one severe hypoglycemia event as defined in section 6.2.3

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 device.

An additional requirement for continued study device use following a single DKA or severe hypoglycemia event will be that the site investigator believes that the event is unlikely to recur and that it is safe for the participant to continue to use the system. Additionally, 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 study device, use will be discontinued.

Even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.

6.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in section 6.2.1, study activities could be similarly suspended if the Medical Monitor deems suspension of study activities or stoppage of the study necessary based on the totality of safety data available or if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

Chapter 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

Participants will use standard care lispro or aspart rapid-acting insulin prescribed by their personal physician.

7.2 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: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), (2) worsening of an existing condition, and (3) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions (including medical conditions that do not require recording), and/or adverse events 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. 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.

7.3 Prohibited Medications, Devices, Treatments, and Procedures

Participants using an insulin not approved for the study pump at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

Treatment with any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals) will not be permitted.

The body-worn study devices (t:slim X2 insulin pump, study CGM systems) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

7.4 Precautionary Medications, Treatments, and Procedures

Not applicable.

7.5 Prophylactic Medications, Treatments, and Procedures

Not applicable.

7.6 Rescue Medications, Treatments, and Procedures

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

7.7 Participant Compensation

Participant compensation will be specified in the informed consent form.

7.8 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.

7.9 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 8: Statistical Considerations

8.1 Statistical and Analytical Plans

The approach to statistical analysis is summarized below. A detailed statistical analysis plan (SAP) will be written and finalized prior to the start of the study.

8.2 Statistical Hypotheses

The primary outcomes for this study are safety outcomes: hypoglycemia and hyperglycemia measured by adverse events and CGM. Statistical hypotheses are stated for the CGM-measured outcomes only.

CGM-measured percentage below 54 mg/dL and CGM-measured percentage above 250 mg/dL will be tested for non-inferiority over an 8-week period.

The null/alternative hypotheses are:

Percentage below 54 mg/dL:

a. *Null Hypothesis*: The difference in mean CGM-measured % below 54 mg/dL between the 8 weeks follow-up and baseline is greater than or equal to +0.5% (non-inferiority).
b. *Alternative Hypothesis*: The difference in mean CGM-measured % below 54 mg/dL between the 8 weeks follow-up and baseline is less than +0.5%.

Percentage above 250 mg/dL:

a. *Null Hypothesis*: The difference in mean CGM-measured % above 250 mg/dL between the 8 weeks follow-up and baseline is greater than or equal to +3% (non-inferiority).
b. *Alternative Hypothesis*: The difference in mean CGM-measured % above 250 mg/dL between the 8 weeks follow-up and baseline is less than +3%.

8.3 Sample Size

The study has not been formally powered to test any a priori hypothesis. The goal is to have at least 30 participants complete the 8-week trial period. Some outcomes will be compared between these participants and a sample of participants from the prior PEDAP study.

8.4 Endpoints

8.4.1 Safety Endpoints

- Severe Hypoglycemia (SH) events and SH event rate per 100 person-years
- Diabetic ketoacidosis (DKA) events and DKA event rate per 100 person-years
- Reportable hyperglycemia adverse events with or without ketosis
    - Events related to the study device
    - Events not related to the study device
- Reportable hypoglycemia adverse events that are not severe
- Number of calendar days with any ketone level ≥1.0 mmol/L

Hierarchical Safety Endpoints

- CGM-Measured
    - % Time >250 mg/dL (non-inferiority)

- % Time <54 mg/dL (non-inferiority)

Additional Safety Endpoints

- Other serious adverse events
- Any adverse event rate per 100 person-years
- Adverse device effects (ADE)
- Serious adverse device events (SADE)
- Unanticipated adverse device effects (UADE)

8.4.2 Efficacy Endpoints

Hierarchical Efficacy Endpoints (tested for superiority compared with baseline)

- CGM-Measured
  - % Time in range 70–180 mg/dL
  - Mean glucose
  - % Time >250 mg/dL
  - % Time <70 mg/dL
  - % Time <54 mg/dL

Secondary Endpoints

- CGM-Measured
  - % Time in range 70–140 mg/dL
  - % Time >180 mg/dL
  - % Time >300 mg/dL
  - % Time <60 mg/dL
  - Glucose standard deviation
  - Glucose coefficient of variation
  - High blood glucose index (HBGI)
  - Low blood glucose index (LBGI)
  - Weekly hyperglycemic event rate
  - Weekly hypoglycemic event rate
  - Binary
    - % Time in range 70–180 mg/dL improvement from baseline to 8 weeks ≥5%
    - % Time in range 70–180 mg/dL improvement from baseline to 8 weeks ≥10%
    - % Time in range 70–180 mg/dL >70% and % time <70 mg/dL <4%
- Insulin
  - Total daily insulin (units/kg)
  - Percentage of total insulin delivered via basal

Exploratory Endpoints

- Insulin
    - Total daily basal insulin (units/kg)
    - Total daily bolus insulin (units/kg)
    - Total daily manual bolus (units/kg)
    - Total daily automated bolus (units/kg)
    - Number of manual insulin doses per day
    - Number of manual insulin doses with carb announcement per day
    - Average daily profile basal rate divided by total daily insulin in percentage points
    - Average carbohydrate ratio daily profile (C:I) multiplied by total daily insulin
    - Average insulin sensitivity factor daily profile (G:I) multiplied by total daily insulin

8.5 Analysis Datasets and Sensitivity Analyses

To be included in included in analyses of CGM and insulin outcomes, participants must provide at least 168 hours of CGM data for each of the baseline and trial phase and spend at least 50% of the study period in closed-loop mode.

All participants who enroll in the PEDAP-AI study will be included in the safety analyses of endpoints that are not measured by CGM. Analyses will include all events that occur between enrollment and the 3-Day Post-Study Safety contact or the end of the 71st day after the date of the Closed Loop Initiation visit—whichever is earlier. For participants who do not complete the study, the date of the final contact will be used in place of the 3-Day Post-Study Safety contact date.

8.6 CGM Metrics Calculations

Baseline values for each CGM metric will be computed from the most recent 28 days of CGM data before the Screening visit.

During the 8-week treatment period, CGM metrics will be calculated from the beginning of study pump use until the end of the day before the final visit.

8.7 Insulin Metrics Calculations

Insulin metrics for comparisons between baseline and follow-up describe the seven days prior to the visits.

Baseline insulin metrics will use data reported from the Diabetes Screening CRF. Insulin metrics at 8 weeks will be calculated using Tandem pump data. Insulin pump data on at least 5 of 7 days will be required to calculate insulin metrics. Weight will only be recorded at the screening visit. All calculations of units/kg will use this weight.

8.8 Analysis of the Hierarchical Endpoints

Summary statistics will be reported for the hierarchical endpoints at baseline and during follow-up as well as for differences from baseline. 24-hr profile plots will be drawn for follow-up. Boxplots will be drawn for baseline and follow-up. Scatter plots will be drawn for follow-up versus baseline. 95% confidence intervals will be constructed for the change from baseline to 8 weeks. For % <54 mg/dL and % >250 mg/dL, tests of non-inferiority will be conducted using paired *t*-tests. The limits will be 0.5% for % <54

mg/dL and 3% for % >250 mg/dL. If these outcomes are determined to be non-inferior, they will be tested for superiority in a hierarchy with % 70–180 mg/dL, mean glucose, and % <70 mg/dL. Tests of superiority will be two-sided paired *t*-tests. If the distribution of changes is skewed, then robust methods will be used instead.

To preserve the overall type 1 error among the formal comparisons, a hierarchy will be used in the following order:

- CGM % >250 mg/dL (non-inferiority; limit = 3%)
- CGM % <54 mg/dL (non-inferiority; limit = 0.5%)
- CGM % 70–180 mg/dL (superiority)
- Mean glucose (superiority)
- CGM % >250 mg/dL (superiority)
- CGM % <70 mg/dL (superiority)
- CGM % <54 mg/dL (superiority)

If any of these comparisons result in a p-value >0.05, then formal testing will stop and p-values will not be generated for any subsequent tests on the list. Note that the point estimates and confidence intervals will be generated for metrics regardless of statistical significance.

8.9 Analysis of Secondary Endpoints

Summary statistics will be reported for baseline, follow-up, and difference from baseline. For all continuous outcomes, boxplots will be drawn for baseline and follow-up and scatter plots will be drawn for follow-up versus baseline. 24-hr profile plots will be drawn for continuous CGM-measured endpoints during follow-up.

Change over time will be compared with a paired *t*-test when the change appears approximately normal, and using robust methods when the change is skewed. Ninety-five percent confidence intervals of the changes from baseline will be derived from these tests.

For the binary outcome % time in range 70–180 mg/dL >70% and % time <70 mg/dL <4%, the proportion will be compared between baseline and follow-up with Barnard's exact test. A ninety-five percent confidence interval of the change from baseline will be derived from this test.

8.10 Comparison with PEDAP Historical Control

Results from this PEDAP-AI study will be compared with those from a sample of participants from the prior PEDAP study. For this analysis, participants from the prior PEDAP study will be limited to those who were using MDI before initiating use of the study pump, and whose baseline HbA1c values are no more than 0.2 percentage points outside of the range observed among the PEDAP-AI participants. These comparisons will be restricted to a follow-up period of approximately two weeks. For PEDAP-AI participants, this will be the period from the adjustment of pump settings at the 6-Week visit until the beginning of the day of the 8-Week visit. For the PEDAP historical control group, the follow-up metrics will be calculated from RCT study phase data for those who were assigned to the CLC group, and Extension phase data for those who were assigned to the SC group. In either case, follow-up data will come from the 14 days prior to the 56th day after the date of closed loop initiation.

Comparisons between the PEDAP-AI group and the PEDAP historical control group will be made for all of the hierarchical and secondary efficacy endpoints listed in section 8.4.2. Continuous endpoints will be compared between the PEDAP-AI and PEDAP cohorts using a linear model adjusting for the baseline

value, age at initiation of closed loop use, and clinical center as fixed effects. Binary endpoints will be compared using a logistic model that adjusts for the same effects. Summary statistics for baseline, follow-up, and change from baseline will be reported by study, along with the adjusted differences between the studies and their 95% confidence intervals. Boxplots displaying baseline and follow-up for both groups will be drawn for continuous outcomes.

8.11 Analysis of Exploratory Endpoints

No p-values will be calculated for exploratory analyses. Summary statistics for total daily basal insulin and total daily bolus insulin will be tabulated for baseline, 8 weeks, and change from baseline to 8 weeks. For all other outcomes, summary statistics will be tabulated for 8 weeks. Boxplots for the follow-up period will be drawn for all outcomes. Boxplots for baseline will be given for total daily basal insulin and total daily bolus insulin. Summary statistics for the final 2-week period will be displayed side-by-side with those of the PEDAP historical control group.

8.12 Additional Tabulations and Plots

Summary statistics will be tabulated by daytime (6:00 am – 9:59 pm) and nighttime (10:00 pm – 5:59 am) during baseline and the 8 weeks of follow-up for each of the continuous CGM-measured outcomes listed in section 8.4.2.

During the trial period, the closed-loop system will include a periodic parameter adjustment driven by an AI-based Advisor system. Tabulations, 24-hour profile plots, and boxplots of the continuous CGM-measured outcomes listed in section 8.4.2 will be generated for each of the six adaptation periods and the two 4-week periods of the study.

8.13 Safety Analyses

Hierarchical safety endpoints will be analyzed according to the directions in section 8.8. All safety endpoints listed in section 8.4.1 will be summarized in tables. Details of each reportable adverse event will be provided in a listing.

8.14 Intervention Adherence

The following will be tabulated for the 8-week study period to assess intervention adherence:

- Percent time of CGM sensor use
- Percent time of closed-loop system use
- Percent time in different operational modes
- Percent of AI recommendations that are accepted

8.15 Protocol Adherence and Retention

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

- Number of protocol and procedural deviations
- Flowchart accounting for all enrolled participants
- Flowchart of all participants at all scheduled visits and phone contacts after treatment initiation
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment and reasons

8.16 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of all participants included in the primary analysis will be summarized in a table with statistics appropriate to the distribution of each variable.

8.17 Device Issues

The following will be tabulated for the 8-week study period to assess device issues:

- Device malfunctions requiring study team contact and other reported device issues
- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system

Details of device issues will be provided in a listing.

8.18 Planned Interim Analyses

No formal interim efficacy analyses are planned.

The DSMB will review safety data at intervals, with no formal stopping rules.

8.19 Subgroup Analyses

With only 30 participants, the ability to evaluate subgroups is limited. However, percentage of time spent >250 mg/dL and % of time spent <54 mg/dL over 8 weeks will be explored separately in baseline HbA1c, race/ethnicity, and sex. No p-values will be calculated for these analyses.

8.20 Missing Data

All comparisons will be restricted to available cases.

8.21 Multiple Comparison/Multiplicity

For the baseline versus follow-up comparisons of the metrics mentioned in section 8.8, the overall type 1 error will be preserved using the hierarchical procedure described above. For all other analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure (4).

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

The main study data are collected from the study pump downloads or on the electronic case report forms (CRFs). When data are directly collected in electronic CRFs in real time, 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.

9.2 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. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.3 Quality Assurance and Monitoring

Designated JCHR personnel 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 plan will be developed and revised as needed during the study, consistent with FDA's risk-based monitoring guidance, "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. The monitoring plan details 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 monitoring 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 critical data and processes. Elements of the monitoring plan 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
- Investigational Product accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time 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. Clinical sites will provide direct access to all trial-related facilities/equipment, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.4 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. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall 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 10: Ethics/Protection of Human Participants

10.1 Ethical Standards

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.

10.2 Institutional Review Boards

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

10.3 Informed Consent Process

10.3.1 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. Written IRB-approved consent materials and consent discussions must be in a language understandable to the participants and their parent(s). The commercial materials to support device usage is currently only available in English, as such only English proficient participants and LARs may enroll.

Extensive discussion of risks and possible benefits of participation will be provided to the participants' parent(s). Consent forms will be IRB-approved and the parent(s) of the participants will be asked to read and review the document. The investigator will explain the research study to the parent(s) and answer any questions that may arise. All parent(s) will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of the rights of research participants. Parent(s) will have the opportunity to carefully review the written consent form and ask questions prior to signing.

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

10.3.2 Participant and Data Confidentiality

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research (JCHR). This will not include the participant's or their parent'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 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 and the University of Virginia Center for Diabetes Technology.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). 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 11: References

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