The Pediatric Artificial Pancreas (PEDAP) trial: A Randomized Controlled Comparison of the Control-IQ technology Versus Standard of Care in Young Children in Type 1 Diabetes

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KEY ROLES

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PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	R. Paul Wadwa John Lum Roy Beck	R. Paul Wadwa	23 Nov 2020	Original protocol
2.0	John Lum	R. Paul Wadwa	21 Dec 2020	Pre-clinical revisions to accommodate requests for changes by IRB and FDA reviewers
3.0	John Lum	R. Paul Wadwa	13 Jan 2021	Pre-clinical revisions to accommodate request by IRB reviewers for changes to framing of extension phase participation
4.0	John Lum	R. Paul Wadwa	29 Jan 2021	Pre-clinical revisions to visit window details in Chapters 5 and 6 to ensure that window definitions are consistent between RCT and Extension period and that associated body text agrees with visit window table text. **Initial version used for study.**
5.0	Shannon Hiser, John Lum	R. Paul Wadwa	7 May 2021	Addition of inclusion criterion requiring U.S. residency; typo correction in 9.2.4
6.0	John Lum	R. Paul Wadwa	16 Jun 2021	Addition of SUS Questionnaire, addition of the use of the new version of Control-IQ for the extension phase of the study, updated statistical analyses for the extension phase of the study.
7.0	John Lum	R. Paul Wadwa	15 Jul 2021	Per FDA request, inclusion of all study participants in the 13 week + 3 day call, 14-week call, and 15-week visit
8.0	John Lum	R. Paul Wadwa	10 Sep 2021	Addition of ancillary study during Extension Phase to obtain system performance data during meal/exercise challenges; associated revisions to Stats chapter, plus minor unrelated Stats edits.
9.0	John Lum	R. Paul Wadwa	04 Oct 2021	Revisions to exercise and meal bolus challenges to address FDA requests during IDE review
10.0	John Lum	R. Paul Wadwa	26 Oct 2021	Revisions to exercise and meal bolus challenges to address IRB requests during IRB review
11.0	John Lum	R. Paul Wadwa	03 Dec 2021	Introduction of Extended Use period

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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
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

Signature Page

Translation of the UVA Advanced Automated Insulin Delivery Systems to Clinical Care in Young Children: Glycemic Control, Regulatory Acceptance, and Optimization of Day to Day Use

Protocol Identifying Number: PEDAP

IND/IDE Sponsor: University of Virginia

Version Number: 11.0

03 DEC 2021

Protocol Chair	
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Signature/Date	
Medical Monitor	
Name, Institution	Roy Beck, MD, Ph.D. / Jaeb Center for Health Research
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CLINICAL CENTER PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: **The Pediatric Artificial Pancreas (PEDAP) trial: A Randomized Controlled Comparison of the Control-IQ technology Versus Standard of Care in Young Children in Type 1 Diabetes**

Protocol Version/Date: 11.0 / 03 DEC 2021

I have read the protocol specified above. In my formal capacity as a Clinical Center Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, 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 clinical center.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: 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: _____

Clinical Center Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	The Pediatric Artificial Pancreas (PEDAP) trial: A Randomized Controlled Comparison of the Control-IQ technology Versus Standard Care in Young Children in Type 1 Diabetes
Précis	A randomized controlled trial of at-home closed loop system vs. standard care (defined as either multiple daily injections of insulin [MDI] or use of an insulin pump without hybrid closed-loop control capabilities [low-glucose suspend or predictive low-glucose suspend functionality is permitted]) in youth age 2 to <6 years old.
Investigational Device	t:slim X2 with Control-IQ and Dexcom G6 system
Objectives	The objective of the study is to assess efficacy, quality of life, and safety of a closed loop control (CLC) system (t:slim X2 with Control-IQ Technology) in a randomized controlled trial with partial crossover.
Study Design	First phase: a 13-week parallel group randomized clinical trial with 2:1 randomization to intervention with the closed loop system vs. standard care (SC); Second Phase: following the RCT, a 13-week period where the Standard Care (SC) group will transition to use CLC and the experimental arm will extend the use of CLC for the same period. After 26 weeks, participants may continue using CLC for an additional Extended Use period. A subset of participants will be invited to join an optional exercise/meal challenge ancillary study.
Number of Clinical Centers	~3 US clinical centers
Endpoints	<u>Efficacy</u> The primary outcome for the RCT is time in target range 70-180 mg/dL (TIR) measured by CGM in CLC group vs. SC group over 13 weeks The primary outcome for the extension phase assessed separately for each treatment group is change in TIR comparing extension phase with RCT phase. <u>Quality of Life</u> Patient-reported outcome questionnaires will be completed. <u>Safety</u> The key safety outcomes are severe hypoglycemia and ketoacidosis.
Population	**Inclusion Criteria** 1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 6 months and using insulin for at least 6 months 2. Familiarity and use of a carbohydrate ratio for meal boluses. 3. Age ≥2 and <6 years old 4. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 5. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol 6. 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. 7. Total daily insulin dose (TDD) at least 5 U/day 8. Body weight at least 20 lbs

PARTICIPANT AREA	DESCRIPTION
	9. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 10. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff. 11. Parent/guardian proficient in reading and writing English 12. Live in the United States, with no plans to move outside the United States during the study period **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 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. Currently using any closed-loop system, or using an insulin pump that is incompatible with use of the study CGM 13. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 14. Employed by, or having immediate family members employed by Tandem Diabetes Care, 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 150 screened participants with the goal of randomizing 102 participants.
Treatment Groups	• Intervention Group: t:slim X2 with Control-IQ Technology and Study CGM. • Control Group: Standard care (SC) - defined as either multiple daily injections of insulin (MDI) or use of an insulin pump without hybrid closed-loop control capabilities (low-glucose suspend or predictive low-glucose suspend functionality is permitted) in conjunction with study CGM All participants will be offered to extend the study for an additional 13 weeks, with the SC group switching to the t:slim X2 with Control-IQ System after the 13-week RCT period. After 26 weeks, participants may continue using CLC for an additional Extended Use period.
Participant Duration	~26-32 weeks for RCT and Extension Phase, depending on duration of run-in phase; up to an additional ~7 months in Extended Use period
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants not currently using an insulin pump and Dexcom G5 or Dexcom G6 CGM with minimum data requirements will initiate a run-in phase of 2 to 6 weeks that will be customized based on whether the participant is already

PARTICIPANT AREA	DESCRIPTION
	a CGM user. Participants who skip or successfully complete the run-in will be randomly assigned 2:1 to an intervention using Tandem t:slim X2 with Control-IQ Technology or the standard care control group using existing insulin therapy in conjunction with study CGM. All participants will continue their participation by using the t:slim X2 with Control-IQ system in an Extension Phase. [Figure 1] After 26 weeks, participants may continue using CLC for an additional Extended Use period through no later than July 31, 2022. A subset of participants will complete an optional exercise/meal challenge ancillary study.

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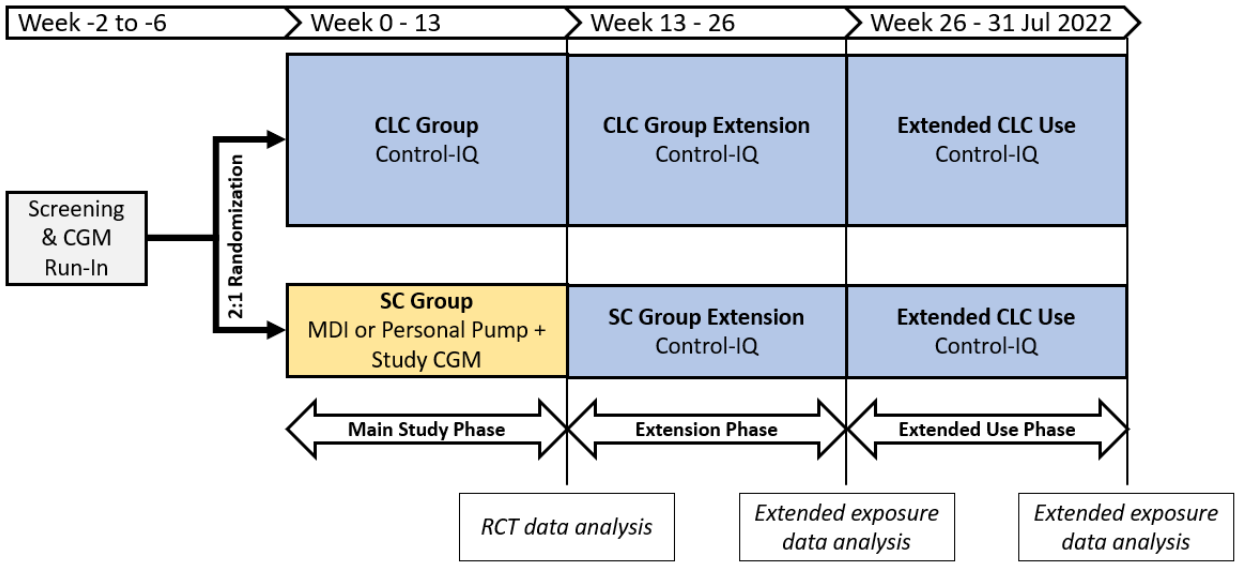
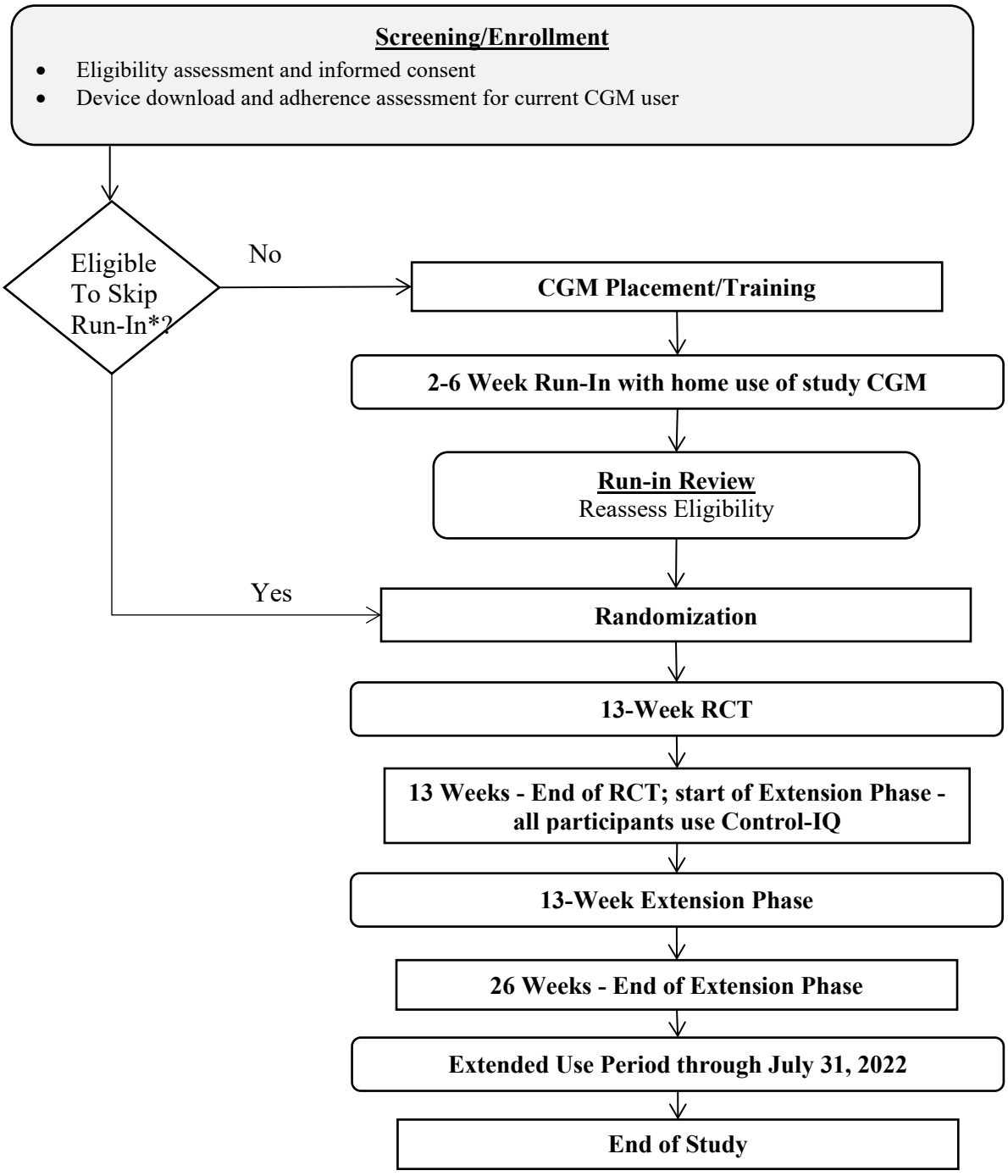


Figure 1: Study Design: Participants Randomized 2:1 Control-IQ Control (CLC) vs. Standard Care (SC) Groups. Extension phase with partial crossover of SC Group switching to use Control-IQ. Subsequent Extended Use period through no later than July 31, 2022.

SCHEMATIC OF STUDY DESIGN



*Current use of Dexcom G5 or G6 CGM with readings captured on at least 11 out of the previous 14 days

Figure 2: Overview of Study Design

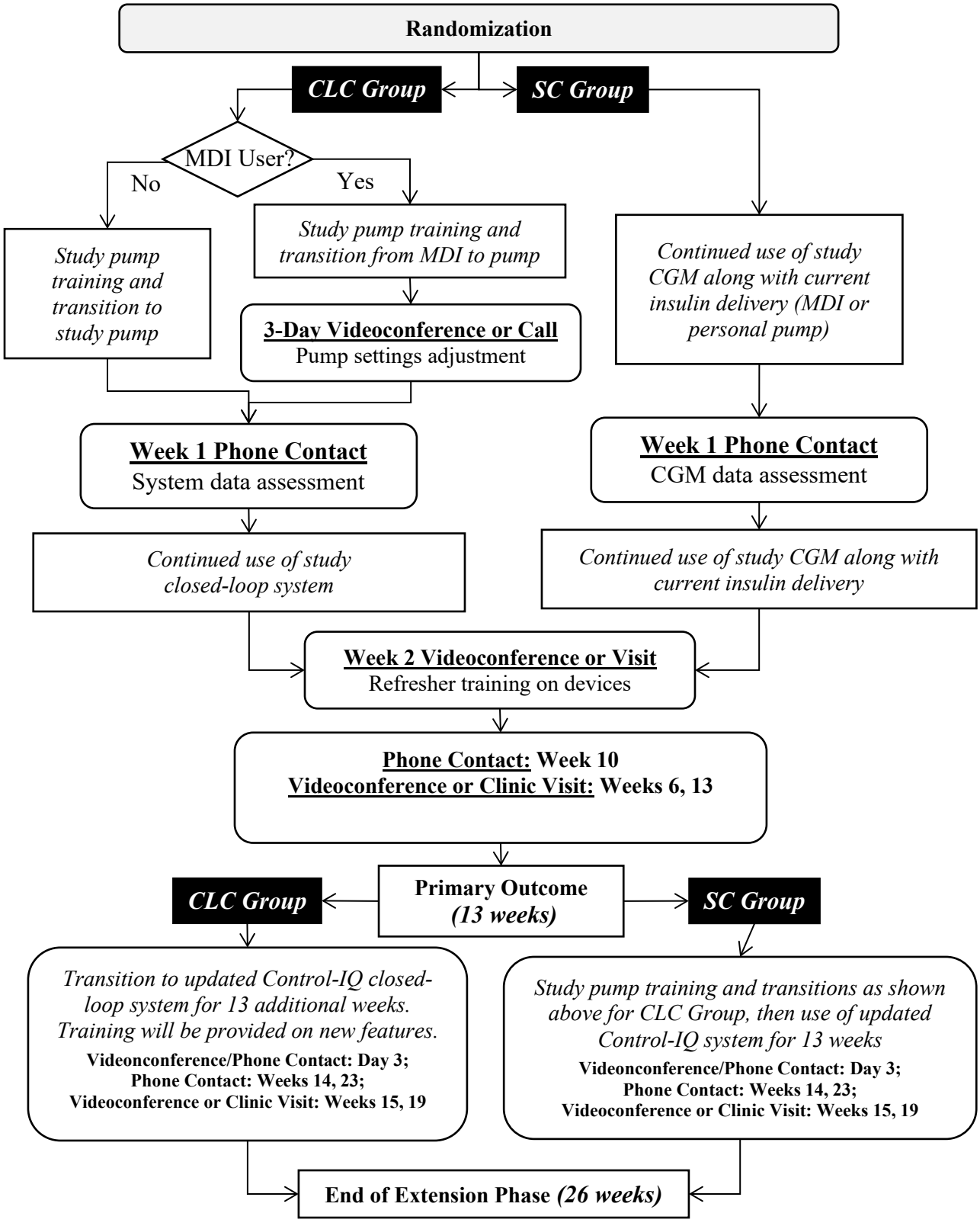
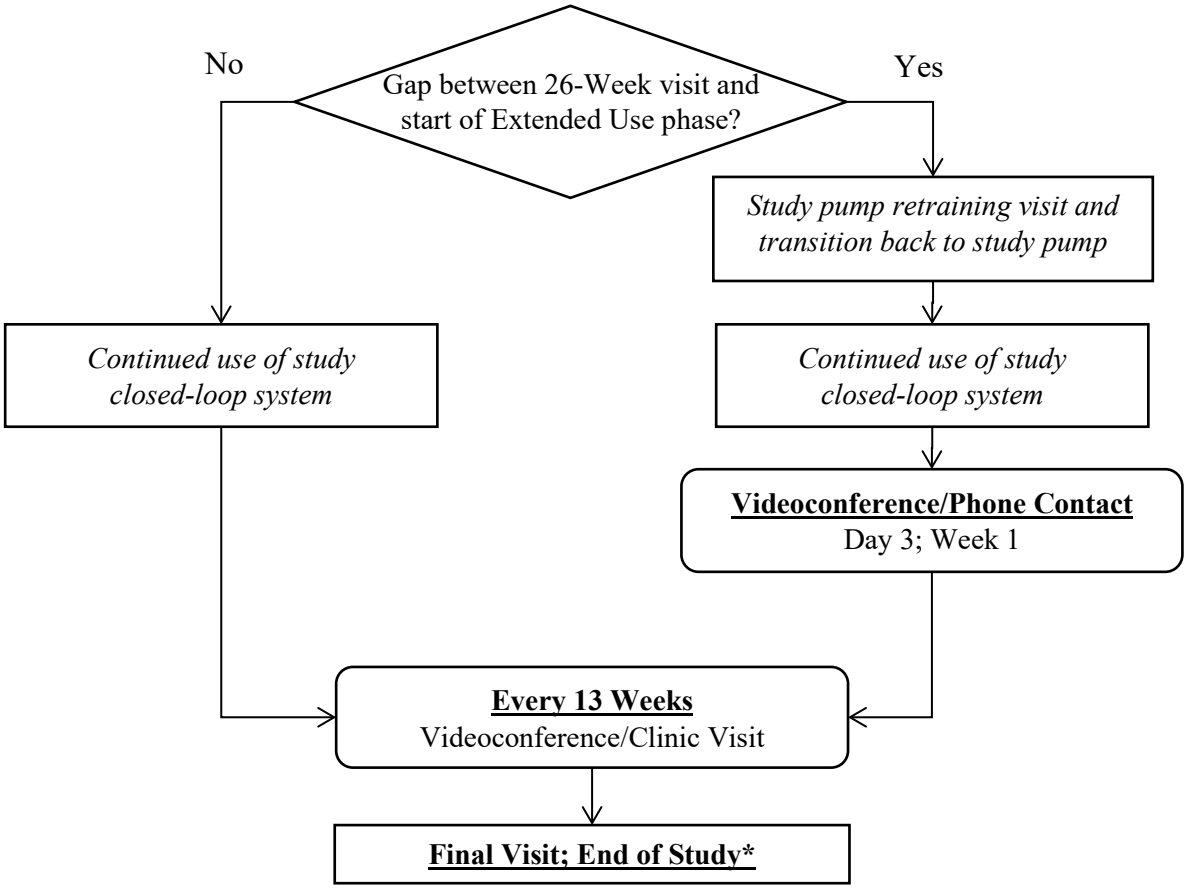


Figure 3: Schematic of Study Design (Post-Randomization through 26 Weeks)



* Final Visit to occur no later than July 31, 2022

Figure 4: Schematic of Study Design (Extended Use Period)

	Pre	Pre	0	3d[1]	1w	2w	6w	10w	13w	13w + 3d	14w	15w	19w	23w	26w
Visit (V), Videoconference (VC), or Phone (P)	**VC/V**	**VC/V**	**VC/V**	**VC/ P**	**P**	**VC/V**	**VC/ V**	**P**	**VC/ V**	**VC/ P**	**P**	**VC/ V**	**VC/ V**	**P**	**VC/ V**
Comment	**Screen/ Enroll**	**Run-in**	**Rand**												
Eligibility Assessment	**X**	**X**	**X**												
HbA1c (Central lab)			**X**						**X**						**X**
Device Data download(s)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review diabetes management and AEs		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Questionnaires as defined in section 9.2	**X**								**X**						**X**

[1] *Only for participants on MDI at enrollment assigned to the CLC group*

Table 1. Schedule of Study Visits and Procedures (through 26-Week Visit)

Days/Weeks after 26-Week Visit =>	0[2]	3d[2]	1w[2]	13w	26w, 39w, etc.	Final Visit
Visit (V), Videoconference (VC), or Phone (P)	VC/V	VC/ P	VC/ P	VC/V	VC/V	VC/V
Eligibility Assessment[1,2]	X					
Study Pump Retraining[2]	X					
HbA1c (Central lab)				X	X	
Device Data download(s)		X	X	X	X	X
Review diabetes management and AEs		X	X	X	X	X

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287 [1] *Participants are eligible to initiate Extended Use period if they completed the 26-Week Visit within the prior 4 months*

288 [2] *Only for participants who had a gap between the 26-Week Visit and the initiation of the Extended Use period during*
289 *which they stopped use of the study pump and reverted to MDI or personal pump insulin therapy*

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291 **Table 2. Schedule of Study Visits and Procedures (Extended Use Period)**

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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 pair of pivotal trials that demonstrated the system's safety and efficacy, first in participants ≥14 years old (1) and then subsequently in participants ≥6 years old (2).

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 levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6.

Figure 5. t:slim X2 with Control-IQ and Dexcom G6 system

1.2 Rationale

The objective of this randomized clinical trial is to assess the efficacy and safety of the Control-IQ closed loop system over a 13-week period compared with standard care. In addition, the data from this trial may be used for subsequent regulatory submissions for this system in the age group studied.

The extension phase will allow for additional exposure time to the Tandem t:slim X2 with Control-IQ Technology and evaluation of the SC arm after crossing over to use Control-IQ for a 13-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 blood glucose 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 Questionnaires and Focus Groups

As part of the study, parents of participants will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. Parents may also participate in a focus group session to explore their feelings about using the closed-loop system. It is possible that some people may find these questionnaires or focus groups to be mildly upsetting. Similar questionnaires and focus groups have been used in previous research and these types of reactions have been uncommon.

1.3.1.8 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

One purpose of this research is to reduce the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop system to control the glucose level and is intended to develop data to support future device approval in the age group studied. 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).

There is no restriction on the number of participants to be enrolled by each clinical center toward the overall recruitment goal.

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. 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 102 participants randomized. A maximum of 150 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:

- Approximately two-thirds of the participants with most recent available HbA1c ≥ 7.5%
- Approximately 30 participants in the age range ≥24 months to <48 months
- At least 20% of participants who are on multiple daily injections (MDI) rather than pump

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, electronic 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 and child are interested in the study, the investigator will schedule a virtual or in-person visit to discuss study, and if the parent and child agree to participate, 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.

As part of the informed consent process, the parent will be asked to sign an authorization for release of personal information. This may be done electronically with the consent, or on paper if the site requires their own process. 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 informed consent form has been electronically signed and HIPAA authorization has been provided.

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 6 months and using insulin for at least 6 months
2. Familiarity and use of a carbohydrate ratio for meal boluses.
3. Age ≥2 and <6 years old
4. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff.
5. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol
6. 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.
    - *Study will not be providing insulin; therefore, participants will need to have access to either lispro or aspart*
7. Total daily insulin dose (TDD) at least 5 U/day
8. Body weight at least 20 lbs
9. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3)
10. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff.
11. Parent/guardian proficient in reading and writing English
12. 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

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 (specified in the study procedure manual); the investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications
12. Currently using any closed-loop system, or using an insulin pump that is incompatible with use of the study CGM
13. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
14. Employed by, or having immediate family members employed by Tandem Diabetes Care, 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 Eligibility Assessment and Baseline Data Collection

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. The screening visit must be completed within 28 days of participant enrollment.

2.5 Historical Information

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.

2.6 Screening Testing and Procedures

At the Screening Visit the following procedures will be performed:

- 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 provided for participants who do not already have a scale at home.
- Determination of most recent HbA1c level from medical records or verbal report
- Participants' parents will complete a set of baseline questionnaires, described in section 9.2.

2.7 Screen Failures

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

Chapter 3: CGM Run-In Phase

3.1 CGM Run-in Phase Overview

This phase must begin (supplies shipped) within 3 days of completion of the Screening visit. The purpose of this CGM run-in phase is to 1) assess compliance with study procedures and 2) to introduce the study CGM to study participants without current use of a Dexcom CGM.

Participants who currently use a Dexcom G5 or G6 with CGM data captured on at least 11 out of the previous 14 days prior to the time of enrollment can skip the run-in phase. Participants who do not currently use a Dexcom G5 or G6 CGM, or who do use that CGM but have readings captured on fewer than 11 out of the previous 14 days prior to time of enrollment, will be required to participate in the CGM run-in phase.

Participants and their parent(s) will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.

3.2 Initiation of CGM

Study CGM supplies will be provided to the participant either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

Once the supplies have been received, the participant and parent will be instructed to use the study CGM on a daily basis. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

3.2.1 CGM Training

CGM training (in-person or via videoconference) will be provided by a qualified trainer to participants not currently using a personal CGM identical to the study CGM as to how to use it in real-time to make management decisions and how to review the data after an upload for retrospective review. The participating child will participate in training sessions to the degree judged appropriate by the parent and trainer. CGM training will include:

- Instruction on how to insert the sensor and transmitter, including observation/supervision of placement of a sensor
- Instruction on how to calibrate the CGM unit, if needed
- Guidance on accessing the CGM trace, either through a manufacturer-provided software app or via a study-provided CGM receiver unit, or via a personal insulin pump if participants use a pump that integrates with the study CGM
- Parents will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

A copy of the study CGM user's guide will be provided to the participant's parents.

3.3 Blood Glucose and Ketone Testing

Participants will receive supplies for blood glucose and ketone testing.

- Blood glucose testing
  - Participants will be provided with a study blood glucose meter, test strips, and standard control solution to perform quality control (QC) testing at home per manufacturer guidelines.
  - All study blood glucose meters will be QC tested with control solution if available prior to dispensation and during all office visits. 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.
  - Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.
  - Participants will be given guidelines for treatment of low or high blood glucose.
- Blood ketone testing
  - Participants will be provided with a study blood ketone meter, test strips, standard control solution to perform QC testing at home per manufacturer guidelines, and software/hardware needed to download meter datafiles.
  - All study blood ketone meters will be QC tested with control solution if available prior to dispensation and during all office visits. 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.
  - Participants will be instructed to perform blood ketone testing as described in section 7.1.6.
  - Participants will be given guidelines for treatment of elevated blood ketones
- 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).

3.4 Assessment of Successful Completion of the Run-in Phase

Enrolled participants will have a follow-up visit or videoconference approximately 14 days after initiation of the run-in phase to assess progress or successful completion of the phase. If needed, one or more interim visits or videoconference/phone contacts may occur to assist the participant with any CGM use issues. Procedures will include downloading of the study CGM data and the following:

Assessment of compliance with the use of CGM for at least 11 out of the prior 14 days

Assessment of skin reaction in areas where a CGM sensor was worn or other safety issues associated with CGM use

Assessment of eligibility to continue to the randomized control trial (RCT) phase of the study

Participants Using a Personal CGM at Enrollment

Participants who had currently been using a personal CGM at the time of enrollment (but did not meet requirements to skip run-in) and satisfy the CGM use criteria above without any major safety issues and otherwise meet study eligibility requirements can be randomized.

Participants who fail to meet the minimum CGM use requirement, or who the investigator believes may benefit from an extension of the CGM run-in period, may at the investigator's discretion be allowed to continue CGM run-in for a maximum of two additional 2-week periods. These participants will have a follow-up visit or videoconference approximately 14 days after each prior assessment for a reassessment using the same procedures as described above.

Participants who do not meet CGM use requirements after three 2-week periods of CGM run-in or otherwise fail to meet study eligibility requirements will be withdrawn from the study.

Participants Not Using a Personal CGM at Enrollment

Participants who had not currently been using a personal CGM at the time of enrollment will be assessed as described above. If there are no major safety issues and the investigator believes that the participant will remain adherent to use of the study CGM, the participant will be asked to continue the run-in phase for an additional 2-week period to establish baseline glycemic control while using the study CGM. These participants will have a follow-up visit or videoconference approximately 14 days for a second follow-up visit with the same visit procedures as described above.

Participants who fail to meet the minimum CGM use requirement at the second follow-up, or who the investigator believes may benefit from a further extension of the CGM run-in period, may at the investigator's discretion be allowed to continue CGM run-in for one additional 2-week period. These participants will have a follow-up visit or videoconference approximately 14 days after the second follow-up visit for a reassessment using the same procedures as described above.

Participants who do not meet CGM use requirements after three 2-week periods of CGM run-in or otherwise fail to meet study eligibility requirements will be withdrawn from the study.

3.5 Optimization of Insulin Therapy

Data will be obtained from CGM and/or pump downloads prior to CGM run-in review contacts. Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) or injection strategies will be made in response to major trends observed in the CGM data, with flexibility for clinicians to adhere to guidelines and practices established at each individual practice rather than a fixed set of heuristics for all clinical centers.

Chapter 4: Randomization Visit

4.1 Visit Timing

The visit, which may be in-clinic or virtual, may occur on the same day as the Screening or Run-in Review Visit, or on a subsequent day. If deferred, the randomization visit should occur no more than 14 days after successful completion of the run-in phase or within 14 days of screening if run-in is skipped.

4.1.1 Randomization

Eligible participants will be randomly assigned to one of two treatment groups in a 2:1 ratio:

1. Control-IQ Closed-Loop Control (CLC) Group
2. Standard Care (SC) Group

The participant's randomization group assignment is determined by completing a Randomization Visit case report form on the study website. The randomization list will use a permuted block design, stratified by clinical center.

The participant will be included in the data analysis regardless of whether or not the protocol for the assigned randomization group is followed. Thus, the investigator must not randomize a participant until he/she is convinced that the participant/parent will accept assignment to either of the two groups.

It was decided that it was more important to stratify randomization by clinical center than by factors such as baseline time in range, HbA1c, or device use since these factors will be easier to adjust for in analysis than will clinical center.

4.1.2 Baseline HbA1c Determination

A capillary blood sample will be obtained for baseline HbA1c determination. Capillary collection supplies will be provided to the participant within 3 days of randomization. This may occur either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

Chapter 5: Main Study Procedures

5.1 Visit and Contact Schedule

During the RCT period, visits and contacts will be scheduled as outlined in Table 3 below:

Table 3: RCT Visit and Phone Contact Schedule

Target Day/Week	Contact Type[1]	Target/Allowable Window (around Target Day/Week)
3 days[2]	VC/P	± 2 days
1 week	P	± 2 days
2 weeks	VC/V	± 4 days
6 weeks	VC/V	± 7 days
10 weeks	P	± 7 days
13 weeks	VC/V	± 7 days

[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

[2] Only for participants on MDI at enrollment assigned to the CLC group; timing will be with respect to the start of home use of the study system, rather than with respect to the start of the RCT

Additional contacts or visits may occur as needed.

5.2 CGM Initiation and Training

Participants who skipped CGM run-in will be provided with study CGM supplies and training as described in section 3.2 and instructed to use the study CGM on a daily basis. Participants currently using a personal CGM identical to the study CGM may skip the training.

Provision of CGM supplies and training should be completed within 3 days of randomization.

5.3 Procedures for the CLC Group

The study pump, associated supplies, and training will be provided to participants assigned to the CLC group within 3 days of randomization. Dispensation of supplies may occur either in-person at the clinic, or via delivery by other means (personal delivery, overnight shipment, etc.).

5.3.1 Study Pump Training

Parents of participants will receive study pump training by a qualified trainer. The participating child will participate in training sessions to the degree judged appropriate by the parent and trainer. Pump training (in-person or via videoconference) will be provided by a qualified trainer to all CLC Group participants.

Parents will be fully instructed on the study insulin pump. The trainer will discuss differences from the participant's personal pump, if applicable, in important aspects such as calculation of insulin on board and correction boluses and optional additional 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.

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 if they are not already using the t:slim X2 bolus calculator. Parent/guardians with prior education/experience with using this bolus calculator will be offered refresher training.

- The study team will assist the parent in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters, if applicable. The participant's personal pump, if any, will be removed.
- 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.

5.3.2 Initiation of Pump by MDI Participants

For MDI participants being started on the study pump, an initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures' manual. Further adjustments to total daily dose (TDD) and intraday basal rate profile may be made during the initial 2-week use period.

Participants and parent(s) will complete training on the study pump as described above, with additional emphasis on topics relevant to new pump users, 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 study team will assist the participant/parent in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's insulin requirements.

5.3.3 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.

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

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 or study pump training components, as applicable, 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 8.2) 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.

5.3.4 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.

5.3.5 Study Device Download

Parents will be instructed to download the study CGM and pump and ketone meter prior to each phone or videoconference contact or on at least an every 4-week basis throughout the remainder of the study.

5.3.6 3-Day Phone Contact

For participants who were on MDI at the time of enrollment, study staff will perform a phone call or videoconference with the parent within 3 (±2) 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 and follow the procedure for insulin pump optimization described above using the study CGM available data from the previous two weeks.

5.3.7 1-Week Phone Contact

Study staff will perform a phone call/videoconference with the parent within 7 (±2) days following randomization.

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 and follow the procedure for insulin pump optimization described above using the study CGM available data from the previous two weeks.

5.3.8 2-Week Visit

Participants will have a follow-up visit 14 (±4) days from the date of randomization.

The parent will be offered review training to address any questions on the use of the study device including meal bolus strategies and strategies related to pump use and exercise.

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 and follow the procedure for insulin pump optimization described above using the study CGM available data from the previous two weeks.

- At in-clinic visits, the blood glucose meter and study ketone meter will be downloaded and QC tested with control solution.

5.4 Procedures for the SC Group

Participants in the SC group will continue to use their existing insulin therapy (personal pump or MDI) for the treatment of their diabetes, in conjunction with use of the study CGM, study blood glucose meter, and study ketone meter.

If a participant is using a pump with an LGS/PLGS feature, he/she will be allowed to continue using this feature during the trial.

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.

5.4.1 Study Device Data Download

Parents will be instructed to upload/email data from the study CGM and study ketone meter using commercially available software prior to each phone or videoconference contact below for clinician review. Parents will be provided with any software and hardware needed to perform these data uploads.

5.4.2 1-Week Phone Contact

Study staff will perform a phone call/videoconference with the participant 7(±2) days following randomization.

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

5.4.3 2-Week Visit

Participants will have a follow-up visit 14 (±4) days from the date of randomization.

The parent will be offered review training on the use of SC during the remainder of the study, including meal bolus strategies and strategies related to exercise.

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 review uploaded CGM data, answer any questions related to device use, and provide any recommendations for insulin therapy adjustment.

- If visit is in-clinic, the study blood glucose meter and study ketone meter will be downloaded and QC tested.

The parent will be instructed to upload data from the study CGM and ketone meter at least once every 4 weeks for the remainder of the study.

5.5 Follow-up Visits and Phone Contacts for Both Groups

After the first 2 weeks, the schedule for remaining follow-up contacts is the same for both treatment groups. Study staff will discuss with the parent that periodic 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.

5.5.1 Visits

A follow-up in-clinic visit will occur at 6 weeks (±7 days). The following procedures are performed in both groups, unless otherwise specified below:

Assessment of compliance with study device use by review of any available device data

Assessment of adverse events, adverse device effects, and device issues

Download of device data (study system or personal pump and study CGM, study BG meter, study ketone meter); in the case of videoconferences, participants will upload or email available data prior to the visit, including CGM, pump, and ketone meter, so that clinic staff can review and download the data

5.5.2 Phone Contacts

A follow-up phone call or videoconference will occur at 10 weeks (±7 days). At the discretion of the investigator, this scheduled phone contact may be replaced by an in-clinic visit.

The following procedures are performed in both treatment groups:

- Review of available CGM, ketone meter, and/or system data to identify any safety issues associated with current insulin therapy and diabetes management approach
- Assessment of adverse events, adverse device effects, and device issues

Additional phone contacts may be performed as needed.

5.5.3 Optimization of Insulin Therapy

If needed for safety reasons at the criteria of the physician at each clinical center, optimization may be done via phone contacts, videoconferences, or in-clinic visits.

Data will be obtained from CGM and/or pump downloads during the contact. Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) or injection strategies will be made in response to major trends observed in the CGM data, with flexibility for clinicians to adhere to guidelines and practices established at each individual practice rather than a fixed set of heuristics for all clinical centers.

5.5.4 13-Week Visit

All participants will have a 13-Week (±7 days) visit during which the following will occur:

- Collection of a blood sample to send to the central laboratory for HbA1c determination.
- Completion of questionnaires
- Weight and height measurements will be repeated
- Assessment of adverse events, adverse device effects, and device issues
- Download of device data (study system or personal pump and study CGM, study BG meter, study ketone meter) as available

5.6 Early Termination Visit (If Applicable)

Participants will be asked to come for an end of study visit in the event of withdrawal or early termination.

5.7 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.

Chapter 6: Extension Phase Procedures

At the conclusion of the 13-week RCT, all participants will use the Control-IQ closed-loop system during a 13-week Extension Phase.

An updated version of the Control-IQ system with enhanced usability will be used during the Extension Phase. Participants assigned to the SC group during the RCT period will receive training based on the updated pump as described below. Participants assigned to the CLC group will receive a brief training session to review any new or changed features of the pump.

Initiation of the updated Control-IQ pump may be deferred by up to 2 weeks if needed, with the participant continuing on the treatment used during the RCT period during this time and the overall duration of the Extension Phase increasing by up to 2 weeks.

6.1 Visit and Contact Schedule

During the Extension period, visits and contacts will be scheduled as outlined in Table 4 below:

Table 4: Extension Phase Visit and Phone Contact Schedule

Target Day/Week[1]	Contact Type[2]	Target/Allowable Window (around Target Day/Week)
13 weeks + 3 days	VC/P	± 2 days
14 weeks	P	± 2 days
15 weeks	VC/V	± 4 days
19 weeks	VC/V	± 7 days
23 weeks	P	± 7 days
26 weeks	VC/V	± 7 days

[1] The "13 weeks" and subsequent visit targets reflect a participant who had no delay between the 13-week visit of the RCT and initiation of use of the updated Control-IQ pump. Targets and associated windows may be shifted by up to 2 weeks for participants whose initiation is delayed.

[2] 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

6.2 Study Pump Initiation

Participants assigned to the SC group during the initial 13-Week RCT period will initiate use of the updated study pump either the same day as the 13-Week visit or within 2 weeks of this visit. The procedures described in section 5.3 above will be followed to initiate these participants on the study pump.

Participants assigned to the CLC group during the RCT period will switch to the updated version of the Control-IQ system and will receive training on its new features. This will occur either the same day as the 13-Week visit or within 2 weeks of this visit.

6.3 Visits, Videoconferences, and Phone Calls for All Participants

6.3.1 13-Week + 3-Day Phone Contact

Study staff will perform a phone call or videoconference with the parent within 3 (±2) days following initiation of Extension Phase study pump use. Procedures will mirror those described in section 5.3.6 above.

6.3.2 14-Week Phone Contact

Participants will have a phone call or videoconference at 14 Weeks (±2 days). Procedures will mirror those described in section 5.3.7 above.

6.3.3 15-Week Visit

Participants will have a follow-up visit at 15 Weeks (±4 days). Procedures will mirror those described in section 5.3.8 above.

6.3.4 19-Week Visit

A follow-up in-clinic visit will occur at 19 weeks (±7 days). Procedures will mirror those described in section 5.5.1 above.

6.3.5 23-Week Phone Call

A follow-up phone call will occur at 23 weeks (±7 days). Procedures will mirror those described in section 5.5.2 above.

6.3.6 26-Week Visit

A follow-up in-clinic visit will occur at 26 weeks (±7 days). Procedures will mirror those described in section 5.5.4 above.

Participants will have the opportunity to participate in Focus Group sessions as described in section 9.3 below.

Participants will be given the option to continue use of the Control-IQ closed-loop system during an additional Extended Use period as described in the next chapter. Participants who do not wish to continue to the Extended Use period will be switched back to the insulin pump or MDI therapy that was in use prior to the study.

6.3.7 Optimization of Insulin Therapy

If needed for safety reasons at the criteria of the physician at each clinical center, optimization may be done via phone contacts, videoconferences, or in-clinic visits as described in section 5.5.3 above.

6.4 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.

6.5 Participant Access to Study Device at Study Closure

Participants not continuing to the Extended Use period will return all investigational study devices and supplies (insulin pump, CGM and related supplies). Participants may keep the study ketone meter and study glucometer if these devices are not marked for investigational use only.

Chapter 7: Extended Use Period Procedures

At the 26-Week Visit of the Extension Phase, participants will be given the option to continue use of the Control-IQ closed-loop system during an additional Extended Use period. Participants who completed the 26-Week Visit before the addition of this Extended Use period to the study protocol will be eligible to rejoin the study and participate as long as they completed their 26-Week Visit within the prior 4 months.

The same version of the Control-IQ system in use during the 13-Week Extension Phase will be used during the Extended Use period.

Informed Consent will be obtained from eligible participants who are interested in participating in the Extended Use period. The informed consent process will mirror the process described above in section 2.1.1.

7.1 Visit and Contact Schedule

During the Extended Use period, visits and contacts will be scheduled as outlined in Table 5 below:

Table 5: Extended Use Period Visit and Phone Contact Schedule

Target Day/Week with respect to initiation of Extended Use period	Contact Type[1]	Target/Allowable Window (around Target Day/Week)
0 days (Retraining) [2]	VC/V	N/A
3 days[2]	VC/P	± 2 days
1 week[2]	VC/P	± 2 days
13 weeks	VC/V	± 7 days
26 weeks	VC/V	± 7 days
Final Visit	VC/V	N/A

[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

[2] Only for participants who had a gap between the 26-Week Visit and the initiation of the Extended Use period during which they stopped use of the study pump and reverted to MDI or personal pump insulin therapy

7.2 Visits, Videoconferences, and Phone Calls for Participants Re-Initiating Study Pump Use After a Gap in Use

7.2.1 Study Pump Retraining Visit

Participants who had a gap between the 26-Week Visit and the initiation of the Extended Use period during which they reverted to MDI or personal pump insulin therapy will have a visit to receive retraining on the study pump prior to re-initiation of study pump use.

The procedures described in section 5.3 above will be followed to re-initiate these participants on the study pump.

7.2.2 3-Day Phone Contact

Study staff will perform a phone call or videoconference with the parent within 3 (±2) days following re-initiation of study pump use. Procedures will mirror those described in section 5.3.6 above.

7.2.3 1-Week Phone Contact

Participants will have a phone call or videoconference within 7 days (±2 days) following re-initiation of study pump use. Procedures will mirror those described in section 5.3.7 above.

7.3 Visits, Videoconferences, and Phone Calls for All Participants

7.3.1 13-Week Visit and Subsequent Visits Every 13 Weeks

A follow-up in-clinic visit will occur 13 weeks (±7 days) after the start of the Extended Use period. The following procedures will be performed in both groups:

- Collection of a blood sample to send to the central laboratory for HbA1c determination
- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Download of device data (study system or personal pump and study CGM, study BG meter, study ketone meter); in the case of videoconferences, participants will upload or email available data prior to the visit, including CGM, pump, and ketone meter, so that clinic staff can review and download the data

Every 13 weeks (±7 days) thereafter, another follow-up clinic visit will occur involving the same procedures described above.

7.3.2 Final Visit

A final follow-up in-clinic or videoconference visit will occur no later than July 31, 2022. Procedures will mirror those described in section 7.3.1 above, except that no blood sample will be collected.

Participants will be switched back to the insulin pump or MDI therapy that was in use prior to the study.

7.3.3 Optimization of Insulin Therapy

If needed for safety reasons at the criteria of the physician at each clinical center, optimization may be done via phone contacts, videoconferences, or in-clinic visits as described in section 5.5.3 above.

7.4 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.

7.5 Participant Access to Study Device at Study Closure

Participant will return all investigational study devices and supplies (insulin pump, CGM and related supplies) at study closure. Participant may keep the study ketone meter and study glucometer if these devices are not marked for investigational use only.

Chapter 8: Study Devices

8.1 Description of the Investigational Device

8.1.1 Insulin Pump

The study system will include the Tandem t:slim X2 with Control-IQ technology.

8.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors. The CGM sensor will be replaced at least once every 10 days.

8.1.3 Blood Glucose Meter and Strips

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

8.1.4 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.

8.1.5 Study Device Accountability Procedures

Device accountability procedures will be detailed in the clinical center procedures manual.

8.1.6 Blood Ketone Testing

Participants to perform QC testing at home per manufacturer guidelines.

All study blood ketone meters will be QC tested with control solution if available during all office visits. 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, test strips, and control solution if a meter fails QC testing at home.

Participants will be instructed on how to perform blood ketone testing.

Participants will be given guidelines for treatment of elevated blood ketones.

8.2 Safety Measures

8.2.1 CGM Calibration

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

8.2.2 System 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.

8.2.3 Hypoglycemia Threshold Alert 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.

8.2.4 Hyperglycemia Threshold Alert and Safety Protocol

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

The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ High Alert) when the system has increased insulin delivery, but detects a CGM value above 200 mg/dL and does not predict the value will decrease in the next 30 minutes.

If the participant receives a Control-IQ High Alert, a message appears on the 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 check the site for occlusion and test blood glucose.

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, take correction insulin, change insulin (pump) infusion site and contact study staff.

If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours.

Chapter 9: Testing Procedures, Questionnaires, and Focus Groups

9.1 Laboratory Testing

9.1.1 HbA1c:

Performed at the Randomization visit, 13-Week visit, and 26-Week visit

Blood samples will be sent to the central laboratory for sample analysis using an NGSP approved method.

9.2 Questionnaires

The questionnaires listed below are completed by participants' parents at Screening, 13 weeks, and 26 weeks for all participants except as noted. The questionnaires will be family and age appropriate and are described briefly below. The procedures for administration are described in the clinical center procedures manual.

Pediatric Quality of Life – Parent

Pediatric Inventory for Parents

INSPIRE Survey – Parent

Pittsburgh Sleep Quality Index (PSQI) – Parent

Fear of Hypoglycemia Survey-Parents (HFS-P)

Hypoglycemia Confidence Scale (HCS)

System Usability Scale (SUS) (Closed-Loop participants only at 13 and 26 weeks)

Administration time is approximately 35 minutes.

9.2.1 PedsQL Diabetes Module – Parent

This is a 32-item scale developed and validated for the measurement of diabetes-specific quality of life. Participants record the extent to which their child experienced each of 32 problems related to diabetes in the prior month.

Administration time is approximately 5 minutes.

9.2.2 Pediatric Inventory for Parents

This is a widely-used, 42-item measure of parenting stress designed for parents of youth with type 1 diabetes.

Administration time is approximately 6 minutes.

9.2.3 INSPIRE Survey – Parent

The INSPIRE (Insulin Delivery Systems: Perceptions, Ideas, Reflections and Expectations) survey was developed to assess various aspects of a user's experience regarding automated insulin

delivery for both patients and family members. The surveys include various topics important to patients with type 1 diabetes and their family members based upon >200 hours of qualitative interviews and focus groups. The parent pre-assessment survey and parent post-assessment survey both contain 19 items. Response options for all surveys include a 5-point Likert scale from strongly agree to strongly disagree, along with an N/A option.

Administration time is approximately 5 minutes.

9.2.4 Pittsburgh Sleep Quality Index (PSQI) – Parent

An abbreviated 9-question version of the Pittsburgh Sleep Quality Index (PSQI), a validated tool for assessing self-reported sleep quantity and quality, will be completed by parents. Seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality.

Administration time is approximately 3 minutes.

9.2.5 Hypoglycemia Fear Survey-Parent (HFS-P)

The Hypoglycemia Fear Survey-Parent is a validated tool of 25 items to assess parents' anxiety and behavior concerning possible hypoglycemia. Items are rated on a 5-point Likert scale (0=never, 4=always), with higher scores indicating higher fear of hypoglycemia.

Administration time is approximately 4 minutes.

9.2.6 Hypoglycemia Confidence Scale

The scale comprises 8 items and measures confidence hypoglycemia can be treated or prevented in various situations.

Administration time is approximately 3 minutes.

9.2.7 System Usability Scale (SUS)

The System Usability Scale (SUS) is a 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. The questionnaire presents statements with five response options (anchoring the options from strongly disagree to strongly agree) and asks users to rate their agreement to the statements. User scores are transformed into a composite score, from 0 to 100, and this score is taken as an overall measure of the system's usability; higher scores indicate better perceived usability.

Administration time is approximately 5 minutes.

9.3 Focus Groups

Focus groups will be completed following the 26-Week Visit. The focus groups will be conducted virtually using HIPAA-approved software.

Focus groups will include 3-5 individuals and a script of open-ended questions to gather feedback and reactions to the closed loop system, the clinical trial, and QoL changes. There will also be time for discussion of content raised by parents. If parents are able to have the child participant attend briefly to answer a few questions, this will be attempted.

Sessions will be audio- and video-taped and transcribed by a professional transcription service. Otherwise, these recordings will not be shared for any non-study purposes. Transcriptions will use a code for participants, such as "Participant 1", and will not contain names or other identifiers of participants.

Chapter 10: Unanticipated Problem, Adverse Event, and Device Issues Reporting

10.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Problems meeting IRB reporting requirements will be reported to the IRB within 7 calendar days of the site becoming aware of the problem. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

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

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven calendar days of recognition. The Director of the Human Research Protection Program 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.

10.2 Adverse Events

10.2.1 Definitions

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

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

Results in death.

Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).

Requires inpatient hospitalization or prolongation of existing hospitalization.

Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).

Is a congenital anomaly or birth defect.

Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in section 10.3). *An event that occurs solely due to participant (i.e., user) error in which the device functions properly generally will not be considered an ADE unless it is determined that the instructions on the screen of the device or user manual (or similar training materials) may have contributed to the event (note: the event may still meet criteria for reporting as an adverse event)*.

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

10.2.2 Reportable Adverse Events

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

1. An SAE or an AE associated with a visit to a hospital emergency department
2. An ADE as defined in section 10.2.1, unless excluded from reporting in section 10.3
3. An AE as defined in section 10.2.1 occurring in association with a study procedure
4. An AE as defined in section 10.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. An AE as defined in section 10.2.1 that affects the participant's ability to complete any study procedures

6. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
7. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

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

10.2.3 Hypoglycemic Events

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

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

10.2.4 Hyperglycemic/Ketotic Events

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

the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below

evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis

blood ketone level ≥1.0 mmol/L, even if there was no communication with a health care provider at the time of the event

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

Symptoms such as polyuria, polydipsia, nausea, or vomiting;

Serum ketones ≥1.5 mmol/L or large/moderate urine ketones;

Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO_2) <15; and

Treatment provided in a health care facility

When a hyperglycemia/ketotic qualifies as an SAE as defined in section 10.2.1, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in section 10.2.1 is met.

10.2.5 Relationship of Adverse Event to Study Device

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

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

Yes

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

No

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

10.2.6 Severity (Intensity) of Adverse Events

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

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.

- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

10.2.7 Expectedness

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

10.2.8 Coding of Adverse Events

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

10.2.9 Outcome of Adverse Events

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

RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.

RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.

FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.

NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.

- An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

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

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as UADEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant

completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

10.3 Reportable Device Issues

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

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

CGM sensor lasting fewer days than expected per manufacturer

CGM tape adherence issues

Battery lifespan deficiency due to inadequate charging or extensive wireless communication

Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.

Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

10.4 Timing of Event Reporting

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

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee. 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 is confirmed, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per

21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

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

10.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within 24 hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB).

The Protocol Chair 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.

10.6 Stopping Criteria

10.6.1 Participant Discontinuation of Study Device

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA event (or a malfunction that could have led to severe hypoglycemia or DKA), use of the study pump 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 closed-loop functionality 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 pump by a participant will be discontinued if any of the following occur:

The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety

The participant's parent requests that the treatment be stopped

Two distinct episodes of DKA as defined in section 10.2.4

Two distinct severe hypoglycemia events as defined in section 10.2.3

One episode of DKA as defined in section 10.2.4 and one severe hypoglycemia event as defined in section 10.2.3

Each DKA or severe hypoglycemia event will be reviewed by the Medical Monitor and by the DSMB with respect to determination of cause and whether the occurrence of the event can be attributed to use of the Control-IQ closed-loop feature.

An additional requirement for continued study pump use following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor and DSMB concur. If either the Medical Monitor or DSMB determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the study pump, 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

10.6.2 Criteria for Suspending or Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 10.2.4), use of the study pump will be suspended while the problem is diagnosed.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The study Medical Monitor and DSMB will review all adverse events and adverse device events that are reported during the study. SH and DKA event review will occur for each such event on an expedited basis, and compiled safety data, including SH and DKA event rates, will be reviewed at approximately 6-month intervals. The DSMB will be provided with age-specific DKA and SH rates from the T1D Exchange registry for means of comparison. The Medical Monitor or DSMB may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

Chapter 11: Miscellaneous Considerations

11.1 Drugs Used as Part of the Protocol

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

11.2 Collection of Medical Conditions and Medications

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

Medical Conditions during the study: 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), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

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.

11.3 Prohibited Medications, Devices, Treatments, and Procedures

Participants using glulisine 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 in the case they are randomized to experimental arm.

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 investigational 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.

11.4 Precautionary Medications, Treatments, and Procedures

Not applicable.

11.5 Prophylactic Medications, Treatments, and Procedures

Not applicable.

11.6 Rescue Medications, Treatments, and Procedures

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

11.7 Participant Compensation

Participant compensation will be specified in the informed consent form.

11.8 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.

11.9 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 12: Statistical Consideration

12.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

12.2 Statistical Hypotheses

The primary outcome for this study is CGM-measured % in range 70-180 mg/dL over a 13-week period. The intervention will be considered effective if the Closed-Loop Control [CLC] is superior to Standard Care [SC] using a statistical significance of α=0.05 and the model specified below in Section 6 (i.e., $p < 0.05$).

The null/alternative hypotheses are:

a. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180 mg/dL over 13 weeks between SC and CLC
b. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 13 weeks is different for SC and CLC.

12.3 Sample Size

Based on data from the DCLP5 study mentioned above, we conservatively estimate the standard deviation (SD) for the primary outcome, time in range (TIR), to be 10%. A sample size of N=90 subjects (60 in the CLC arm and 30 in the SC arm) therefore will give 90% power to detect a 7.5% improvement in TIR with a two-sided test and type 1 error of 5%. Accounting for potential attrition rate of up to 10%, the total sample size for the PEDAP Study is estimated at N=102.

The following table shows the minimum detectable difference with a total sample size N=90 for key secondary outcomes. The observed standard deviations are taken from the DCLP5 study.

Outcome	Standard Deviation			Correlation with Baseline	Effective SD [a]	Detectable Difference with N=90 [b]
	CLC (n=78)	SC (N=22)	Pooled (N=100)			
% >250 mg/dL [c]	5.5%	9.9%	6.5%	0.69	4.7%	3.4%
Mean Glucose [d]	18	26	20	0.68	14	10
HbA1c	0.8%	0.9%	0.8%	0.70	0.6%	0.4%
% <70 mg/dL [c]	1.07%	1.13%	1.08%	0.61	0.86%	0.63%
% <54 mg/dL [c]	0.23%	0.23%	0.23%	0.54	0.19%	0.14%

a – After accounting for the baseline value as a covariate in the regression model.
b – With 90% power and two-sided type 1 error rate = 5%.
c – Outcomes with a skewed distribution winsorized at the 10th and 90th percentiles.
d – Units for mean glucose are mg/dL.

12.4 Efficacy Outcome Measures

12.4.1 Primary Efficacy Endpoint

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

12.4.2 Secondary Efficacy Endpoints

12.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis

The following secondary endpoints will be tested in a hierarchical fashion as described in section 12.7.1.

- CGM-measured % above 250 mg/dL
- CGM-measured mean glucose
- HbA1c at 13 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL

12.4.2.2 Other Secondary Efficacy Endpoints

The following endpoints are considered exploratory. Type 1 error for these endpoints will be controlled using the false discovery rate (FDR) instead of the familywise error rate (FWER).

CGM-Measured:

- % above 180 mg/dL
- % in range 70-140 mg/dL
- glucose variability measured with the coefficient of variation (CV)
- glucose variability measured with the standard deviation (SD)
- % <60 mg/dL
- low blood glucose index (LBGI)*
- hypoglycemic events (defined as at least 15 consecutive minutes <54 mg/dL)
- hyperglycemic events (defined as at least 90 consecutive minutes >300 mg/dL)
- % >300 mg/dL
- high blood glucose index (HBGI)*
- % in range 70-180 mg/dL improvement from baseline to 13 weeks ≥5%
- % in range 70-180 mg/dL improvement from baseline to 13 weeks ≥10%
- % time in range 70-180 mg/dL >70% and % time <70 mg/dL <4%

HbA1c:

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

- HbA1c absolute improvement from baseline to 13 weeks >1.0% or HbA1c <7.0% at 13 weeks

Questionnaires

- PedsQL Diabetes Module – total score and 5 subscales:
  - Diabetes
  - Treatment I
  - Treatment II
  - Worry
  - Communication
- Pediatric Inventory for Parents (PIP) 2 domains each with a total score and 4 subscales for (5x2=10 difference scores)
  - Frequency
    - Total Score
    - Communication
    - Medical Care
    - Role Function
    - Emotional Functioning
  - Difficulty
    - Same total + 4 subscales as above for Frequency
- INSPIRE (CLC arm only)
- Pittsburgh Sleep Quality Index (PSQI) global score
- Fear of Hypoglycemia Survey for Parents (HFS-P) – total score, 2 subscales and 4 factor scores:
  - Behavior
    - Avoidance
    - Maintain high BG
  - Worry
    - Helplessness
    - Social consequences

*Note that LBGI and HBGI will be calculated using all available CGM readings as described below. Therefore, they may not be comparable to the same metrics calculated with SMBG data.

Other:

- Insulin
  - Total daily insulin (units/kg)
  - Percentage of total insulin delivered via basal
- Weight and Body Mass Index (BMI)

12.4.3 CGM Metrics Calculations

Randomization is preceded by 2-6 weeks of CGM run-in, which will be used in the calculation of baseline CGM metrics. For participants who are eligible to skip the run-in, comparable

amount of CGM data from their own sensors will be taken before randomization visit to calculate baseline CGM metrics.

CGM data starting from randomization visit through the 13-week visit will be included in the calculation of each CGM metric. Percentages in range 70-180 mg/dL (and all other CGM-based metrics) will be calculated giving equal weight to each CGM point for each participant.

12.5 Analysis Datasets and Sensitivity Analyses

All analyses comparing the CLC arm with SC arm will follow intention-to-treatment approach, which means participants will be analyzed in the treatment arm assigned by randomization regardless of actual system use. All randomized participants will be included in the primary analysis and secondary hierarchical analyses of CGM metrics. For other secondary outcomes, only participants with non-missing outcome data will be included.

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

12.5.1 Per Protocol Analyses

Per-protocol analyses will be performed for primary outcome and secondary hierarchical outcomes only if >5% of participants will be excluded:

- CLC arm: Closed loop mode active for at least 80% of the time
- SC arm: CGM use for at least 80% of the time

12.5.2 Other Sensitivity Analyses

Confounding

A sensitivity analysis will also be conducted if potential confounding factors collected at baseline are detected.

The imbalance will be assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value. The person making this judgement will be unaware of whether there is an association between baseline variables and study outcome. All variables obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored.

Exclude First 2 Weeks of CGM Data

The primary analysis will be repeated by excluding the first 2 weeks of post-randomization CGM data.

Missing Data

Missing data will be handled using direct likelihood method for the primary analysis. It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and

there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

To that end, sensitivity analyses will be performed to explore whether results are similar for primary analysis when using different methods. The following methods will be applied:

- Rubin's multiple imputation with treatment group in the imputation model
- Available cases only
- Multiple imputation with pattern mixture model assuming the dropout trajectory of the CLC group was that of the SC group (Mallinckrodt and Clark, 2003) (3)

12.6 Analysis of the Primary Efficacy Endpoint

Summary statistics (mean ± SD or median (quartiles)) will be reported by treatment group for the CGM-measured % in range 70-180 mg/dL at baseline, 13 weeks intervention and change from baseline to 13 weeks.

CGM-measured % in range 70-180 mg/dL between two treatment arms will be compared using a linear mixed effects regression model while adjusting for baseline CGM-measured % in range 70-180 mg/dL, age, prior CGM and pump use, and clinical center (random effect). A point estimate, 95% confidence interval and two-sided p-value will be reported for the treatment effect based on the linear regression model and a 5% level will be used to declare statistical significance. Residual values will be examined for an approximate normal distribution. If values are highly skewed then robust regression using M-estimation will be used instead. However, previous experience suggests that the residual values for % time glucose in target range will follow an approximately normal distribution. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the sensitivity analyses by including factors potentially associated with the outcome for which there is an imbalance between groups (12.5.2).

In the primary analysis, any missing data at baseline or follow-up will be handled using direct likelihood. A longitudinal linear regression model will be fit with the percent of time in range at baseline and follow-up as the dependent variable. This model will adjust for age, prior CGM use and pump use as fixed effects and clinical center as a random effect. This model adjusts for baseline time in range by forcing the treatment groups to have the same mean value at baseline.

12.7 Analysis of the Secondary Endpoints

Point estimates and confidence intervals for the treatment arm differences will be presented for all secondary metrics. The models will adjust for the corresponding baseline metric, age, prior CGM and pump use, and clinical center (random effect).

12.7.1 Hierarchical Analyses

To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing procedure will be used. If the primary analysis for time in range described above results in a statistically significant result ($p < 0.05$), then testing (similar to the model described above for the primary outcome) will proceed to the next outcome metric in the following order:

- CGM-measured % in range 70-180 mg/dL (primary outcome)
- CGM-measured % above 250 mg/dL
- CGM-measured mean glucose
- HbA1c at 13 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL

This process continues iteratively moving to the next variable down on the list until a non-significant result ($p \geq 0.05$) is observed, or all six variables have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any variables below on the list are not formally tested.

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment arm for each hierarchical outcome. A 95% confidence interval for the treatment arm difference will also be calculated for all five secondary hierarchical outcomes listed above. However, a confidence interval that excludes zero will not be considered a statistically significant result if an outcome variable higher on the hierarchical list failed to reach statistical significance.

Analysis for each of the CGM metrics listed above for the hierarchical analysis will parallel the analysis described for the primary outcome in Section 12.6.

HbA1c at 13 weeks will be compared between the two treatment arms using a linear model while adjusting for baseline HbA1c, age, prior CGM and pump use, and clinical center (random factor). Missing data will be handled using direct likelihood in a regression model including all available central laboratory HbA1c measurements at baseline and 13-week visits.

For all above analyses, regression diagnostics will be employed analogous to as described in Section 12.6 for the primary outcome.

12.7.2 Other Endpoint Analyses

For all other secondary endpoints, only participants with non-missing data will be included in analyses (available cases method). Summary statistics (mean ± SD, median (IQR) or n (%)) appropriate to the distribution will be tabulated for them at baseline, 13 weeks and for the changes from baseline to 13 weeks. For continuous outcomes, linear regression models will be used to compare the treatment effects while adjusting for corresponding baseline values (e.g., baseline % in range 70-140 mg/dL for comparing change in % in range 70-140 mg/dL from pre-randomization CGM wear to 13 weeks post-randomization period), age, prior CGM and pump use, and clinical center as a random effect. Comparisons of body weight and BMI will also be adjusted for gender.

For CGM-measured hypoglycemia/hyperglycemia events, event rates per week will be compared using similar linear mixed effects regression models as described above for the primary outcome.

Binary HbA1c and CGM Outcomes

For the binary HbA1c outcomes, risk-adjusted percentages by treatment group will be computed at 13 weeks from a logistic regression model. The logistic regression will adjust for baseline HbA1c (as a continuous factor), age, prior CGM and pump use as fixed effects, and clinical site as a random effect. Similar analyses will be done for the binary CGM outcomes.

Questionnaires

For each questionnaire, mean ± SD or percentiles appropriate to the distribution will be given by treatment group at baseline and 13 weeks. Group comparisons will be conducted for the total score (mean score) and subscales from participant version and parent version separately using similar linear models as described above. The INSPIRE and SUS post-treatment surveys will only be administered to the CLC group at the 13-week visit, and thus the scores will only be tabulated.

Focus Groups

Qualitative data from focus groups will be analyzed using NVIVO (release 11.2; QSR International) to organize and manage the entire corpus of focus group data. Analysis begins with an initial coding procedure to capture and describe the range of responses to the intervention. A second, more focused and detailed level of coding will be applied to major categories of findings in the initial review to determine themes in response to the clinical trial, use of the closed loop system, and quality of life changes. The video data from the co-regulation interaction will be submitted to the validated coding system and frequencies of positive and negative interactions, treatment discussions, and CLC comments will be calculated with simple descriptive statistics. Change from pre to post treatment will be analyzed in the similar GLM framework to evaluate whether there is improvement in co-regulation across the study.

Boxplots

Boxplots stratified by treatment group will be given for the primary outcome and each of the key secondary endpoints in specified time periods over the 13-week course of follow-up.

12.8 Safety Analyses

All randomized participants will be included in these analyses and all their post-randomization safety events will be reported. Any pre-randomization adverse events will be tabulated separately and will include any participants who were never randomized.

Safety analyses of the main study (randomized trial phase) will include events occurring on or after randomization until and including the 13-week visit or Day 105 from randomization, whichever occurs first. Safety analyses of the extension phase will include subsequent events until the last visit date or the last event date (whichever is later).

For the following outcomes, the number of events will be tabulated by treatment group. Formal statistical comparisons (main study phase only) will be performed if there are enough events (at least 5 events combined between the two treatment groups):

- Number of SH events and SH event rate per 100 person-years

- Number of DKA events and DKA event rate per 100 person-years
- Other serious adverse events
- Any adverse event rate
- Number of calendar days with any ketone level ≥1.0 mmol/L (if ≥5 total calendar days combined)
- Worsening of HbA1c from baseline to 13 weeks by >0.5%
- Investigational device related (intervention group only):
  - Adverse device effects (ADE)
  - Serious adverse device events (SADE)
  - Unanticipated adverse device effects (UADE)

For DKA and SH events, if enough events, the rates will be compared between the two treatment arms during the main study phase using a robust Poisson regression. The regression will adjust for the participant-reported number of SH events 12 months prior to the start of the study and clinical center as random effect. The amount of follow up will be included as an offset covariate to compare the rates. A similar analysis will be done for DKA, if at least 5 total DKA events among both treatment groups.

12.9 Intervention Adherence

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

- Sensor use –percent time of use, overall for 13-week visit

For CLC arm only, the following will be tabulated to assess adherence:

- Closed loop system use–percent time of use, overall for 13-week visit
- % time in different operational modes - overall and by specified time periods

12.10 Protocol Adherence and Retention

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

- Number of protocol and procedural deviations
- Flow chart accounting for all enrolled participants up to randomization
- Flow chart of all randomized participants at all scheduled visits and phone contacts post treatment initiation
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment and reasons

12.11 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed by treatment group for the following:

- Age
- Sex
- Race/Ethnicity
- Parent's income, education, and/or insurance status
- Diabetes duration
- Insulin method before enrollment (pump vs. MDI)
- CGM use before enrollment
- HbA1c
- BMI %
- Participant-reported number of SH and DKA 12 months prior to the start of the study
- Baseline CGM metrics including:
  - % in range 70-180 mg/dL
  - % time > 180 mg/dL
  - Mean glucose
  - % time < 70 mg/dL
  - % time < 54 mg/dL

12.12 Device Issues

The following tabulations and analyses will be performed by treatment group 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 – overall and by month

12.13 Planned Interim Analyses

No formal interim efficacy analyses are planned. The analysis of the RCT will be performed on completion of the RCT prior to the completion of the extension phase.

In addition, the DSMB will review safety data at intervals, with no formal stopping rules.

12.14 Subgroup Analyses

In exploratory analyses, the primary outcome (time 70-180 mg/dL), % time <70 mg/dL and HbA1c at 13 weeks will be assessed separately in various subgroups. Subgroups will be defined according to the baseline value of the factors, which will be noted in the SAP. Tests for interaction with treatment group will be performed.

Interpretation of subgroup analyses will be viewed with caution, particularly in the absence of an overall significant difference. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous. If there is insufficient sample size in a given subgroup, the cutpoints for continuous measures may be adjusted per the observed distribution of values. Cutpoint selection for display purposes will be made masked to the outcome data.

12.15 Multiple Comparison/Multiplicity

Primary Analysis

Since there will be a single comparison for the primary outcome (CGM-measured % 70-180 mg/dL), no adjustment is needed.

Secondary Hierarchical Analyses

The hierarchical testing procedure described above in section 12.7.1 will be used to control the overall type 1 error for the primary outcome plus five key secondary outcomes identified above.

All Other Secondary Analyses

For comparison of all other efficacy endpoints, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure (4).

P-values from safety analyses, sensitivity analyses, and per-protocol analyses will not be adjusted for multiple comparisons.

12.16 Exploratory Analyses

CGM Metrics

In addition to the analysis for the CGM-measured endpoints described earlier, separate analyses will be conducted for daytime and nighttime of the following metrics:

- % time in range 70-180 mg/dL
- Mean glucose
- % above 180 mg/dL
- % below 70 mg/dL
- coefficient of variation

Above selected CGM metrics also will be reported by restricting the CGM data in the CLC arm based on following criteria. No p-values will be calculated for following analyses.

- using only the CGM data when the closed-loop is active

Additional Insulin Metrics

The following insulin metrics will be tabulated by treatment groups at baseline, 13 weeks and for the changes from baseline to 13 weeks. No p-values will be calculated for these metrics.

- Total daily basal insulin (units/kg)
- Total daily bolus insulin (units/kg)
- Total daily manual bolus (units/kg)
- Total daily automated bolus (units/kg)
- Total daily short-acting injections for injection users

The following will be calculated for the CLC group in the 1-week prior to randomization and by 1-week follow-up periods from pump data only:

- Total daily insulin (units/kg)
- 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

12.17 Extension Phase

Analyses for the extension phase will be primarily exploratory.

For both treatment arms, summary statistics will be given for all outcomes listed above in Section 12.4 at RCT baseline (pre-randomization), 13 weeks, and 26 weeks. In addition, boxplots will be constructed for each of the outcome metrics listed above showing both treatment arms over the course of the combined RCT and extension (where both arms using CLC) phases.

Formal statistical comparisons between the two study phases (i.e., primary RCT and extension phases) will be performed for key outcome measures including:

- CGM-measured % in range 70-180 mg/dL
- CGM-measured % above 250 mg/dL
- CGM-measured mean glucose
- HbA1c at 13 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL
- PedsQL Diabetes Module – total score
- Pediatric Inventory for Parents (PIP)
    - Frequency domain total score
    - Difficulty domain total score
- INSPIRE Survey
- Pittsburgh Sleep Quality Index (PSQI) global score
- Fear of Hypoglycemia Survey for Parents (HFS-P) – total score
- Hypoglycemia Confidence Scale (HCS)
- System Usability Scale (SUS)

For each of these outcomes a longitudinal regression model will be fit combining data from the RCT and extension phases accounting for the correlated data from repeated measures. Treatment group will be a time dependent factor in this model. A point estimate and 95% confidence interval will be given for the estimated effects of each CLC version used during the study, both with respect to SC and with respect to one another. Safety analyses of the Extension Phase will include events occurring on or after the Extension training visit until the end of the 26-Week visit

or the end of Day 105 from the Extension training visit — whichever occurs first. Safety outcomes will include those specified in section 12.8 with the exception of worsening of HbA1c.

Summary statistics appropriate to the distribution will be tabulated without any formal comparisons by treatment group for the safety outcomes noted in section 12.8.

12.17.1 Exclusion of Ancillary Study Data

According to Chapter 14, during the extension phase, 30 – 40 participants will be sought to enroll in an ancillary study to test the Control-IQ system with meal bolus and exercise challenges. The analyses for this ancillary study are specified in Section 14.5. Data collected from the start of each of these challenges until 5:59 AM the following morning will be excluded from the analysis of the extension phase.

12.18 Extended Use Period

Analyses for the extended use phase will be exploratory.

Summary statistics will be given for all outcomes listed above in Section 12.4 for each of the 13-week periods following initiation of the Extended Use period. In addition, boxplots will be constructed for each of the outcome metrics listed above for these periods.

Safety analyses of the Extended Use period will include events until the last visit date or the last event date (whichever is later). Safety outcomes will include those specified in section 12.8 with the exception of worsening of HbA1c.

Chapter 13: Data Collection and Monitoring

13.1 Case Report Forms and Device Data

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

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

13.2 Study Records Retention

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

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

13.3 Quality Assurance and Monitoring

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

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

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

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

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

13.4 Protocol Deviations

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

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

Chapter 14: Ethics/Protection of Human Participants

14.1 Ethical Standard

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

14.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB 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.

14.3 Informed Consent Process

14.3.1 Consent Procedures and Documentation

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

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

14.3.2 Participant and Data Confidentiality

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

Chapter 15: Ancillary Study to Test Control-IQ System with Meal Bolus and Exercise Challenges

15.1 Objective

This Ancillary Study will assess the safety of using the study system during exercise and meal bolus-related challenges. Outcome data are expected to be used to support regulatory filings for the device system.

15.2 Sample Size

Participation in the Ancillary Study will be offered to participants who are currently in the Extension Phase of the main study. The goal for sample size is to have 30-40 individuals participate in the Ancillary Study.

15.3 Eligibility Criteria

Participants must be currently in the Extension Phase of the main study, with at least 2 weeks and no more than 11 weeks completed to ensure sufficient comfort with the study pump and sufficient time to complete the protocol below.

Inclusion in the Ancillary Study requires investigator judgment that it is safe for the individual to participate.

15.4 Study Procedures

On the day of enrollment into the Ancillary Study, informed consent will be obtained from interested participants, and eligibility will be verified.

A paper logbook will be provided to participants that includes a page to record details about each challenge and procedural instructions about how participants will conduct these challenges. This material will be reviewed with each participant.

During home use, each participant will perform 3 exercise and meal bolus-related challenges (details below) appropriate for the age of the participant. Each challenge will be separated from the other challenges by at least 48 hours. Before starting each challenge, caregivers of the child must assure the child has a working CGM and Control-IQ is active. If activity is paused during an exercise-related challenge, the challenge may be continued to allow for continuation of the activity if the participant is able and willing to continue.

Participants will receive a guidance document for performing the challenges that includes the following safety mitigations:

- The participant's parent or guardian must remain with the child at all times and monitor CGM readings frequently during and for at least two hours after completion of each challenge.

- The hyperglycemia safety protocol described in section 8.2.4 will be followed during each challenge.
- The parent/guardian must have an on-call phone number for the study team prior to initiation of each challenge.
- CGM glucose must be ≥120 mg/dL prior to initiation of each exercise-related challenge.
- Exercise may not be initiated during an exercise-related challenge if the CGM trend arrows on the study insulin pump indicate Falling glucose (down arrow) or Rapidly Falling glucose (double down arrow).
- Snacks and glucagon must be available for use during and after each exercise-related challenge.
- Control-IQ exercise activity mode must be activated at least 30 minutes prior to the start of exercise during each exercise-related challenge and kept active for at least 30 minutes after completion of the exercise period.
- Additional carbohydrate may be given as needed at the start of, during, or after each exercise-related challenge.
- The temporary basal rate feature of the study pump may be used if desired to reduce insulin delivery during the exercise period of each exercise-related challenge.
- Fingersticks will be performed for any low CGM value <70 mg/dL, and any exercise should be stopped if BG is confirmed <70 mg/dL. Exercise may be stopped for concerns for CGM decreasing at any time, even if CGM is >70 mg/dL.
- A parent/guardian will sleep in the same home as the child overnight and closely monitor CGM readings following days when one of the challenges was performed.

Contact with the study investigator may be initiated at any time.

Challenge Details:

Missed Meal Bolus Challenge: Participants will skip their meal bolus for an afternoon meal of at least 20 grams carbohydrate. The meal timing and carb amount and any additional snacks given will be recorded on a study exercise log. Additional insulin boluses may be given for hyperglycemia as needed. The hyperglycemia safety protocol described in section 8.2.4 will be followed.

Full Meal Bolus Plus Exercise Challenge: Participants will receive a full meal bolus for an afternoon meal of at least 20 grams carbohydrate. The pump's Exercise Activity setting will be turned on upon completion of the meal. Beginning 30 minutes after completion of the meal, a parent/guardian will try to keep the child physically active (walking, running, playing) for at least 30 minutes if possible, or longer if desired. This can be mixed with mild activity. The meal timing and carb amount, the actual stop and start time of exercise, any associated hypoglycemia treatments, and any additional snacks given will be recorded on a study exercise log.

Exercise Challenge: At least 2 hours after the child finishes an afternoon meal, a parent/guardian will try to keep the child physically active (walking, running, playing) for at least 30 minutes if possible, or longer if desired. This can be mixed with mild activity. The pump's Exercise Activity setting will be turned on 90 minutes after completion of the meal. The meal timing and carb amount of the last meal prior to exercise, the actual start and stop time of exercise, any associated hypoglycemia treatments, and any additional snacks given will be recorded on a study exercise log.

A challenge may be stopped for any reason, including participant non-cooperation, or concern for hypoglycemia, or repeated hypoglycemia.

15.5 Outcomes and Analysis Plan

A separate statistical analysis plan will be written for the Ancillary Study.

Outcomes will include the following:

Key Safety Outcomes:

- Severe hypoglycemia
- Other adverse events

All adverse events will be listed. Listings will include Participant ID, the event, whether the event was serious, whether the event was related to the study device, the event outcome, and a description of the event.

Other Outcomes

- CGM-measured % <54 mg/dL overnight (all challenge types)
- CGM-measured % <70 mg/dL overnight (all challenge types)
- CGM-measured % >180 mg/dL overnight (all challenge types)
- CGM-measured % <54 mg/dL during the two hours immediately following the start of exercise for each exercise-related challenge
- CGM-measured % <70 mg/dL during the two hours immediately following the start of exercise for each exercise-related challenge
- CGM-measured % >180 mg/dL during the four hours following the announced meal, or until the next meal bolus is given, for the missed meal bolus challenge
- CGM-measured % >300 mg/dL during the four hours following the announced meal, or until the next meal bolus is given, for the missed meal bolus challenge

The percentage of time spent below 54 mg/dL from 10 PM – 5:59 AM the night of an exercise challenge will be compared with percentage of time spent below 54 mg/dL the previous night using a linear mixed effects regression model. A point estimate, 95% confidence interval and two-sided p-value will be reported for the challenge effect based on the linear regression model and a 5% level will be used to declare statistical significance. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. Analysis of the percentage of time spent below 70 mg/dL 10

PM – 5:59 AM the night of an exercise challenge will be performed in the same manner.

The percentage of time spent above 180 mg/dL from 10 PM – 5:59 AM the night of a missed meal bolus challenge will be compared with percentage of time spent above 180 mg/dL the previous night using a linear mixed effects regression model. A point estimate, 95% confidence interval and two-sided p-value will be reported for the challenge effect based on the linear regression model and a 5% level will be used to declare statistical significance. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then robust regression using M-estimation will be used instead. Analysis of the percentage of time spent above 300 mg/dL 10 PM – 5:59 AM the night of a missed meal bolus challenge will be performed in the same manner.

CGM-measured % <54 mg/dL during the two hours immediately following the start of exercise for each exercise challenge will be compared between the two exercise challenge groups using a paired *t*-test. CGM-measured % <70 mg/dL during this same period will be analyzed in the same manner.

For each challenge type, the mean, standard deviation, and range will be given for the outcomes listed above relevant to the challenge type. Summary statistics for the overnight periods preceding the challenges will be presented with summary statistics for each challenge type.

Safety Monitoring

Safety oversight will be the same as for the main study, as described in Chapter 10:.

Chapter 16: References

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2. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, Emory E, Hsu LJ, Oliveri M, Kollman CK, Dokken BB, Weinzimer SA, DeBoer MD, Buckingham BA, Cherñavvsky D, and Wadwa RP, for the iDCL Trial Research Group: A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med. 2020 Aug 27;383(9):836-845. doi: 10.1056/NEJMoa2004736.
3. Mallinckrodt CH, Clark WS, et al: Assessing responses profiles from incomplete longitudinal clinical trial data under regulatory considerations, J. Biopharm. Stat., 2003; 13(2): 179-190.
4. Benjamini, Y. and Hochberg, Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Statist. Soc. B, 57, 289–300.