The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas in Pediatrics

A Study of t:slim X2 with Control-IQ Technology

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Version Number: v2.5

May 24, 2019

KEY ROLES

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PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	R. Paul Wadwa Daniel Cherñavvsky Katrina Ruedy Roy Beck	R. Paul Wadwa	15NOV2018	Original protocol.
1.1	Jessica Rusnak	Daniel Cherñavvsky	21NOV2018	
1.2	Sarah Borgman	Katrina Ruedy	28NOV2018	
2.0	Mary Oliveri	Daniel Cherñavvsky	10DEC2018	Modified study design to include extension phase to the experimental group
2.1	Katrina Ruedy	Daniel Cherñavvsky	20Dec2018	Clarifications added for consistency throughout protocol
2.2	Jessica Rusnak	Daniel Cherñavvsky	15Jan2019	Adding inclusion criteria and clarification regarding use of Basal IQ feature; updated incorrect section references
2.3	Jessica Rusnak	Katrina Ruedy	4Feb2019	Removing and adding questionnaires to be completed by participants and parents/guardians
2.4	Katrina Ruedy	Daniel Cherñavvsky	01Apr2019	Correcting discrepancies in revised questionnaire descriptions and other minor clarifications.
2.5	Katrina Ruedy	Marc Breton	01Jun2019	Corrections to statistical analysis chapter; update of Sponsor name from Daniel Cherñavvsky to Marc Breton

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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

The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas in Pediatrics A Study of t:slim X2 with Control-IQ Technology

Protocol Identifying Number: DCLP5 Pediatrics

IND/IDE Sponsor: University of Virginia

Version Number: v.2.5

24MAY2019

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CLINICAL CENTER PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: **The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas in Pediatrics- A Study of t:slim X2 with Control-IQ Technology**

Protocol Version/Date: v2.5 / 24MAY2019

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 International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas in Pediatrics- A study of t:slim X2 with Control-IQ Technology
Précis	A randomized controlled trial of at-home closed loop system vs. standard of care (defined as either sensor-augmented pump or any kind of low predictive low blood glucose suspend [PLGS; LGS] if participant is currently using) in youth age 6 to 13 years old.
Investigational Device	t:slim X2 with Control-IQ and Dexcom G6 system
Objectives	The objective of the study is to assess efficacy 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 16-week parallel group randomized clinical trial with 3:1 randomization to intervention with the closed loop system vs. standard of care (SC); followed by a 12-week period where the Standard of Care (SC) group will transition to use CLC and the experimental arm will extend the use of CLC for the same period
Number of Clinical Centers	Up to 4 US clinical centers
Endpoint	The primary outcome for the first phase is time in target range 70-180 mg/dL measured by CGM in CLC group vs. SC group over 16 weeks The primary outcome for the extension phase is improving time in range 70-180 mg/dL by CGM when SC (control group) transitions to t:slim X2 with Control-IQ compared with the same group during the Main Phase.
Population	**Key Inclusion Criteria** • Type 1 Diabetes • Ages ≥ 6 and ≤ 13 years old **Key Exclusion Criteria** • Use of any non-insulin glucose-lowering agents except metformin • Actively using any other closed-loop system
Sample Size	First phase: Up to 150 screened participants with the goal of randomizing 100 participants in this 16-week randomized trial. Extension phase will consist of a partial crossover: All randomized participants will participate in an extension phase for another 12 weeks (total 28 weeks). The SC group (control group) will crossover to use Tandem t:slim X2 with Control-IQ for 12 weeks. The experimental arm will continue on the Control-IQ for 12 weeks.
Treatment Groups	• Intervention Group: t:slim X2 with Control-IQ Technology and Study CGM. • Control Group: Standard of care (SC) (defined as either sensor-augmented pump or any kind of low or predictive low blood glucose suspend [PLGS; LGS] if participant is currently using), and study CGM • All participants will be offered to extend the study for 12 weeks and the SC group will use the t:slim X2 with Control-IQ System after the first 16-week phase
Participant Duration	16-20 weeks (depending on duration of run-in phase) plus ~12-week extension phase

PARTICIPANT AREA	DESCRIPTION
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants not currently using an insulin pump and Dexcom G4, G5 or Dexcom G6 CGM with minimum data requirements will initiate a run-in phase of 2 to 4 weeks that will be customized based on whether the participant is already a pump or CGM user. Participants who skip or successfully complete the run-in will be randomly assigned 3:1 to the use of closed-loop control (CLC group) system using Tandem t:slim X2 with Control-IQ Technology vs SC for 16 weeks. All participants will be provided the option of using t:slim X2 with Control-IQ system in a 12 week Extension Phase. [Figure 1]

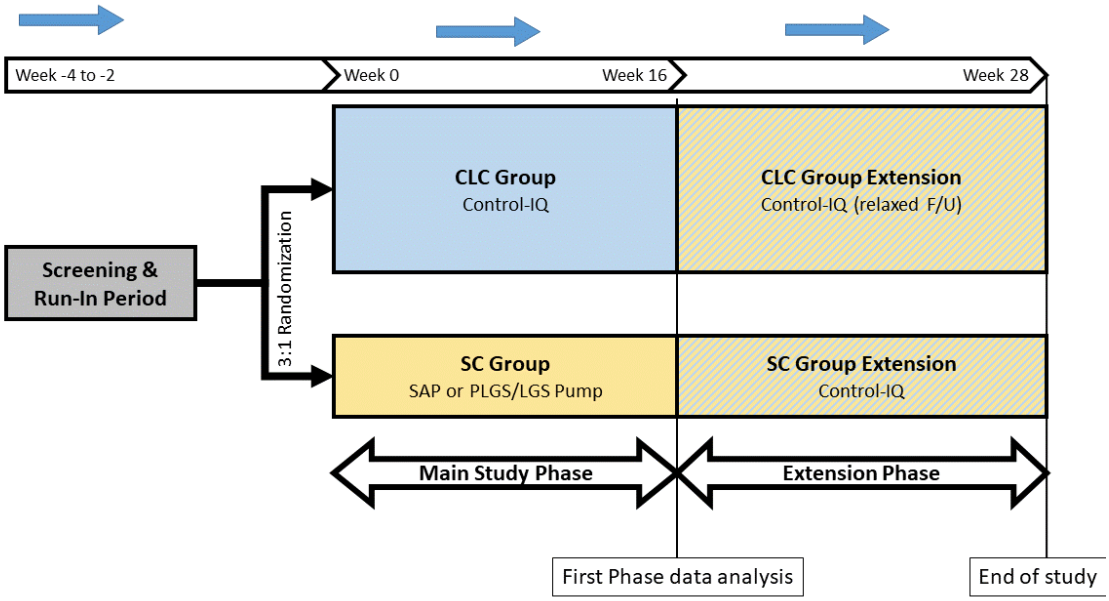
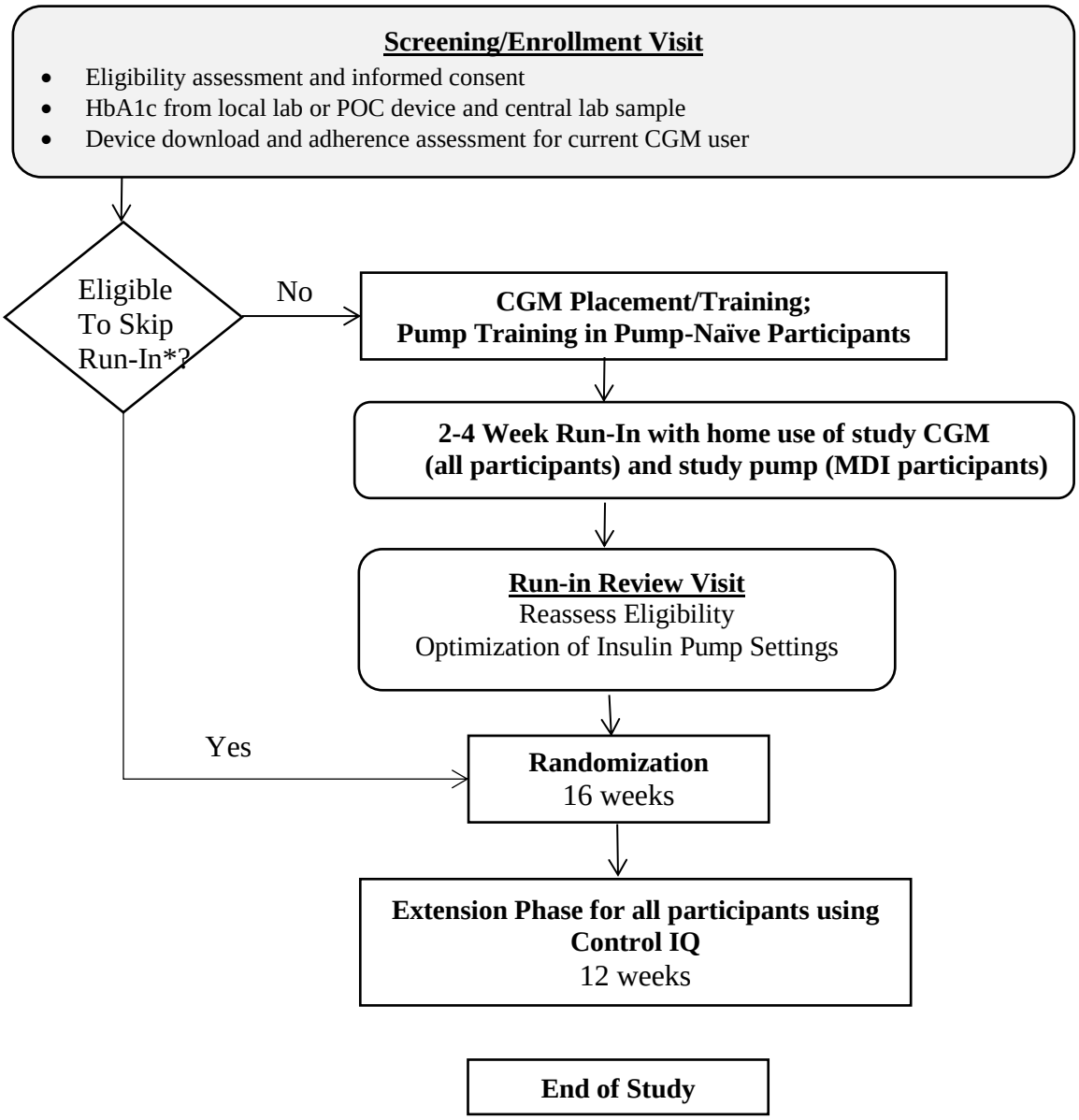


Figure 1: Study Design: Participants Randomized 3:1 Control-IQ Control (CLC) vs. Standard of Care (SC) Groups. Extension phase with partial crossover of SC group switching to use Control IQ.

SCHEMATIC OF STUDY DESIGN



*Current use of insulin pump and Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days

Figure 2: Schematic of Complete Study Design

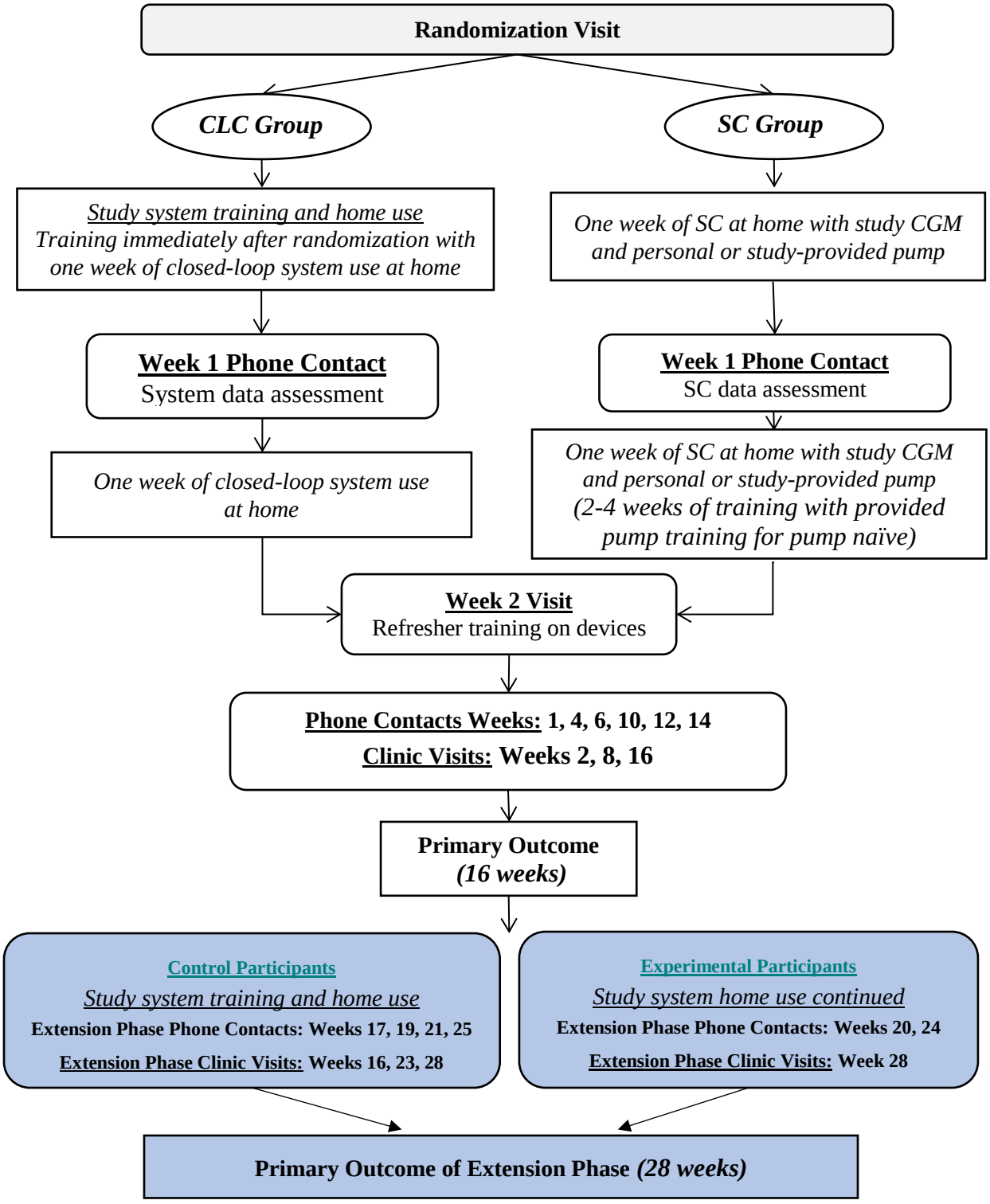


Figure 3: Schematic of Study Design (Post-Randomization)

	Pre	Pre	0	1w	2w	4w	6w	8w	10w	12w	14w	16w
Visit (V) or Phone (P)	**V**	**V**	**V**	**P**	**V**	**P**	**P**	**V**	**P**	**P**	**P**	**V**
Comment	**Screen/ Enroll**	**Run-in**	**Rand**									
Eligibility Assessment	**X**	**X**	**X**									
HbA1c (DCA Vantage or similar point of care device, or local lab)	**X**		**X**									**X**
HbA1c (Central lab)			**X**									**X**
C-peptide (Central lab) and blood glucose assessment			**X**									
Pregnancy test (females of child-bearing potential)	**X**		**X**					**X**				**X**
Device Data download(s)	**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**
Questionnaires as defined in section 8.2			**X**									**X**

Table 1. Schedule of Study Visits and Procedures (Primary Study Phase)

Experimental Group	20w	24w	28w
Visit (V) or Phone (P)	P	P	V
Comment			
Eligibility Assessment			
HbA1c (DCA Vantage or similar point of care device, or local lab)			X
HbA1c (Central lab)			X
C-peptide (Central lab) and blood glucose assessment			
Pregnancy test (females of child-bearing potential)			X
Device Data download(s)	X	X	X
Review diabetes management and AEs	X	X	X
Questionnaires as defined in section 8.2			X

248 **Table 2: Schedule of Visits and Procedures (Extension Phase for Experimental Group)**

Control Group	17w	19w	21w	23w	25w	28w
Visit (V) or Phone (P)	P	P	P	V	P	V
Comment						
Eligibility Assessment						
HbA1c (DCA Vantage or similar point of care device, or local lab)						X
HbA1c (Central lab)						X
C-peptide (Central lab) and blood glucose assessment						
Pregnancy test (females of child-bearing potential)				X		X
Device Data download(s)	X	X	X	X	X	X
Review diabetes management and AEs	X	X	X	X	X	X
Questionnaires as defined in section 8.2						X

Table 3: Schedule of Visits and Procedures (Extension Phase for SC Group)

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.). DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described on the rest of IDEs mentioned below (i.e.in IDEs G160097, G160181, G150240, G140169/S010). For complete algorithmic and clinical background, we refer to these IDEs and to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of these systems (see list of 25 peer-reviewed papers and scientific presentations under Bibliography). Overall, this control algorithm has been implemented in two mobile platforms (DiAs and inControl) and has been tested in 30 clinical trials by 450 adults and children with type 1 diabetes for over 350,000 hours of use to date in the U.S. and overseas.

As described in the Background, this project is a result from a sequence of clinical trials that have tested extensively the control system and in several centers in the U.S. and overseas. The following 21 IDEs reflect this progress:

1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011;
2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013;
6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;
7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013;
8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014;
11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015;

13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015;
14. IDE #G160047: Closed-loop in young children 5-8 years old using DiAs platform; 03/29/2016;
15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: the International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
16. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16
17. IDE#G170255: Protocol 3 for "Pilot Trial of t:slim X2 with Control-IQ Technology";11/16/17 and IDE#G170255/S001 Protocol 3 for "Training Study of t:slim X2 with Control-IQ Technology"; 11/16/17
18. IDE#G170267: "Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued"; 11/21/17
19. IDE#G150240/S008: A long-term home use study, enrolling 18-70 years old TID participants since January 2018; it is anticipated that this study will be completed April 2019.
20. IDE#G170255: A pilot study of 5 adult subjects completed in December 2017.
21. IDE#G170267: Three 48-hour winter ski camps trial T1D participants; one site enrolled 13-18 years old participants in January 2018. The other two sites enrolled participants aged 6-12 years old. At the conclusion of these ski camps, subjects continued with the study device for 72 hours use at home (March & April 2018).

In the G170255 pilot study (mean age 52.8 yrs; 3F/2M, mean A1c 6.5%), the system was challenged with a variety of scenarios including: Pump disconnection, CGM sensor removal without stopping session, CGM sensor change, Basal Rate change, Cartridge Change, Extended Bolus, Calibration at non-ideal conditions, Stopping Control-IQ, Reset Sleep Time, Restaurant Meals and Exercise (treadmill/walk). The study demonstrated excellent connectivity with 98% time in closed-loop control and 94%-time CGM is available during 196 hours of use. [28]

The results of the home portion of the IDE#G170267/ski camp trial (Table 5) were as follow: The Control-IQ significantly improved time in target range 70-180 mg/dL (71.0±6.6 vs. 52.8±13.5%; p=0.001) and mean sensor glucose (153.6±13.5 vs. 180.2±23.1 mg/dL; p=0.003) without increasing hypoglycemia time <70 mg/dL (1.7 [1.3-2.1] vs. 0.9 [0.3-2.7]%; ns). The HCL system was active for 94.4% of the study period. Subjects reported that use of the system was associated with less time thinking about diabetes, decreased worry about blood sugars, and decreased burden in managing diabetes. [33]

No AE or SAE happened during these trials related to the equipment used.

METRIC (COMPUTED DURING CLOSED-LOOP USE)	OVERALL	DAYTIME	NIGHTTIME
Mean glucose (mg/dL)	**129**	**135**	**121**
Coefficient of variation (median)	27%	27%	21%
% below 54 mg/dL (median)	0.7%	0.0%	0.0%
% below 60 mg/dL (median)	1.1%	2.0%	0.0%
% below 70 mg/dL (median)	2.9%	4.1%	1.0%
Percent in range 70-180 mg/dL (mean)	**87%**	**82%**	**94%**
% above 180 mg/dL (median)	5%	8%	6%
% above 250 mg/dL (median)	0%	0%	0%
% above 300 mg/dL (median)	0%	0%	0%

335 **Table 4. Pilot Study results based on time in closed-loop**

336

	OVERALL			DAYTIME [7AM - 11 PM]			NIGHTIME [11PM - 7AM]		
	Control-IQ	**SAP**	**p-value**	**Control-IQ**	**SAP**	**p-value**	**Control-IQ**	**SAP**	**p-value**
70 - 180 mg/dL (%)	**71.0 ± 6.6**	**52.8 ± 13.5**	**0.001**	**69.1 ± 10.1**	**54.4 ± 14.2**	**0.010**	**74.9 ± 10.1**	**49.6 ± 18.8**	**0.001**
< 50 mg/dL (%)	0 [0-0.1]	0 [0-0.4]	ns	0 [0-0]	0 [0-0.6]	ns	0 [0-0]	0 [0-0]	ns
< 54 mg/dL (%)	0.2 [0-0.5]	0.2 [0-0.6]	ns	0 [0-0.4]	0.3 [0-0.9]	ns	0 [0-0]	0 [0-0]	ns
< 60 mg/dL (%)	0.7 [0.2-1]	0.5 [0-0.9]	ns	0.3 [0-1.1]	0.7 [0-1.3]	ns	0 [0-0.2]	0 [0-0]	ns
< 70 mg/dL (%)	1.7 [1.3-2.1]	0.9 [0.3-2.7]	ns	1.6 [0.7-2.6]	1.4 [0.5-3.4]	ns	0.7 [0-2.6]	0 [0-0]	0.190
> 180 mg/dL (%)	**26.7 ± 7.2**	**44.7 ± 13.8**	**0.001**	**28.1 ± 11.1**	**42 ± 14.4**	**0.017**	**23.8 ± 9.9**	**49.9 ± 19.3**	**0.001**
> 250 mg/dL (%)	**7.2 ± 4.5**	**16.1 ± 10.3**	**0.015**	**8.3 ± 6.4**	**14.8 ± 11**	**0.097**	**5.2 ± 8**	**18.7 ± 12.9**	**0.007**
> 300 mg/dL (%)	**2.9 ± 2.7**	**5.3 ± 3.9**	**0.102**	**3.5 ± 3.9**	**4.4 ± 4.5**	**ns**	**1.8 ± 4**	**7.1 ± 6.5**	**0.030**
Mean glucose (mg/dL)	**153.6 ± 13.5**	**180.2 ± 23.1**	**0.003**	**157 ± 20.2**	**175.7 ± 24.7**	**0.064**	**147.1 ± 16.4**	**188.8 ± 30.2**	**0.001**
Coefficient of Variation (%)	36.6 ± 4.9	36.5 ± 5.4	ns	35.7 ± 5.3	36.8 ± 6.1	0.185	33.4 ± 7.1	32.9 ± 6.4	ns
Insulin use (U/day)	33.2 ± 15.5	27.8 ± 12.3	ns	26.4 ± 12.8	22.3 ± 9.6	ns	6.8 ± 2.8	5.5 ± 3	ns
CHO treatment (g)	15.5 ± 16.9	35.5 ± 55.5	ns	14.7 ± 16.7	34.5 ± 55.7	ns	0.9 ± 2	1.2 ± 2.6	ns

337 **Table 5. Glycemic Outcomes Measured by CGM: Ski camp and home use trial**

338 **Closed-Loop Control System**

339 The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology is described
340 in Master File MAF-2032/A008. Control-IQ Technology is derived from inControl previously
341 described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is an "artificial
342 pancreas" (AP) application that uses advanced closed loop control algorithms to automatically
343 manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to
344 keep blood glucose in a targeted range. The system components include the t:slim X2 with
345 Control-IQ Technology and the Dexcom CGM G6.

Figure 4. 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 16-week period compared with standard of care. In addition, the data from this trial may be used for subsequent PMA application for this system.

The 12-week extension phase will allow for additional exposure time to the Tandem t:slim X2 with Control-IQ Technology and evaluation of the SC arm when crossover to use Control IQ for 12-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 Venipuncture Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

1.3.1.2 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. 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.

1.3.1.3 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.

1.3.1.4 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.

1.3.1.5 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.

1.3.1.6 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 Questionnaire

As part of the study, participants (parent and child) will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

1.3.1.8 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 a future PMA-application. The individual participant may not benefit from study participation.

1.3.3 Risk Assessment

Based on the facts that (1) children and adolescents 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 46.405 which is a minor increase over minimal

risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and 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).

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

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. 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 100 participants randomized for the first 16-week phase of this trial. A maximum of 150 individuals may be enrolled into screening for the study in order to achieve this goal considering an approximately 30% withdrawal and screen failure rate.

For the extension phase, all 100 participants that were randomized and completed the main study will complete the 12-week extension phase. The participants randomized to SC in the main study will crossover to use t:slim x2 with Control IQ. The interventional arm in the main study will continue using the Control IQ system for 12 additional weeks.

Study participants will be recruited from up to 4 clinical centers in the United States without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each clinical center toward the overall recruitment goal.

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

- At least one-third of participants with HbA1c ≥8.0% and one-third of participants with HbA1c <7.9%
- At least one-third of participants in the age range 6-10 and one-third of participants 11-13 years old
- At least 20% of participants who are on multiple daily injections (MDI) rather than pump
- At least 20% of participants who are CGM-naïve (defined as not using a CGM in the prior 3 months)

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent and child assent 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. Potential participants meeting the IRB's minimum age of assent will be given a Child Assent Form to read and discuss with his/her parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form (if applicable) will be signed. A copy of the consent form will be provided to the participant and his/her parent and another copy will be added to the participant's study record.

As part of the informed consent process, each participant and/or parent/legal guardian will be asked to sign an authorization for release of personal information. 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 participant, questions will be answered about the details regarding authorization.

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

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 one year and using insulin for at least 6 months
2. Familiarity and use of a carbohydrate ratio for meal boluses.
3. Age $\geq$ 6 and $\leq$ 13 years old
4. Weight $\geq$25 kg and $\leq$140 kg
5. For females, not currently known to be pregnant

   If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
6. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff.
7. Willingness to suspend use of any personal closed loop system that they use at home for the duration of the clinical trial once the study CGM is in use
8. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol
9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study for participants using the t:slim X2. This includes:
   - Participants randomized to Control IQ
   - Participants on the SC group on MDI treatment that will be provided a Tandem pump to switch to CSII
   - Participates that are already in CSII randomized to SC during the extension phase when transition to Control IQ
10. Total daily insulin dose (TDD) at least 10 U/day
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3)

12. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff.

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 other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
2. Hemophilia or any other bleeding disorder
3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk (specified on the study procedure manual)
4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study
5. 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 Screening Procedures

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

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

2.4.1 Data Collection and Testing

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

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

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information (retained at the clinical center and not entered into study database)
- Medical history
- Concomitant medications

- Physical examination to include:
- Weight, height
- Vital signs including measurement of blood pressure and pulse
- Comprehensive Metabolic Panel to assess kidney and liver functioning

Blood draw for:

- HbA1c level measured using the DCA Vantage or comparable point of care device or local lab
    - Measurement performed as part of usual clinical care prior to obtaining informed consent for participation in the trial may be used
    - Measurement must be made within two weeks prior to enrollment
    - Sample to be sent to a central lab
- Urine or serum pregnancy test for all women of child-bearing potential and sexually active.

Screening procedures will last approximately 1-2 hours.

Chapter 3: Run-In Phase

3.1 Run-in Phase Overview

This phase may begin immediately after enrollment is complete or may be deferred for a maximum of 28 days. The purpose of this run-in phase is to 1) assess compliance with study procedures, 2) to introduce the study CGM to study participants without current use of a CGM and 3) to introduce an insulin pump to participants who have not previously used an insulin pump.

Participants who currently use an insulin pump and a Dexcom G4, 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. If a participant is using a pump with a Low Glucose Suspend (LGS) feature, they will be allowed to continue using this feature. Participants who do not currently use a Dexcom G4, G5, or G6 CGM will be required to participate in the CGM run-in phase. Participants currently using a Dexcom G4, G5, or G6 CGM with CGM 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. During the CGM run-in phase, participants will use the study CGM for a minimum of 11 days with a goal of at least 14 days.

All 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.

Additionally, MDI and study pump naïve participants will participate in a pump run-in phase that will run 2 to 6 weeks before randomization is assigned. If both pump run-in phase and CGM run-in phase are indicated, they will run concurrently. Training is detailed below.

3.2 Initiation of CGM

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

The participant will be observed placing the sensor. The study CGM user's guide will be provided for the participant to take home.

3.3 Initiation of Pump

Pump-naïve participants will use the study insulin pump and CGM for up to 4 weeks before randomization is assigned.

Participants who are pump-naïve will be provided with a study pump similar to the pump used with the closed-loop system, but with the closed-loop control feature either absent or deactivated and will be instructed to use the pump on a daily basis. 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 course of the run-in period that can be concomitant with the CGM run-in phase.

Participants and parent(s) will complete training on the study pump as detailed below.

- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board (IOB) and correction boluses.
- The study pump will have the Basal-IQ feature, and participants will be able to use this feature at investigator discretion.

Additional topics are not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.

- For pump-naïve participants, the study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's insulin requirements.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

Note: For the extension phase, participants in the control group will be trained on the use of the Control IQ system. Follow up phone contacts and in-clinic visits are described in Table 3.

3.4 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 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 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, and standard control solution 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 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 a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

3.5 Assessment of Successful Completion of the Run-in Phase

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

- Assessment of compliance with the use of either or both CGM and/or study pump (if applicable)
- Assessment of compliance with the use of:
  - CGM,
  - study pump,
  - CGM and study pump
- Assessment of skin reaction in areas where a CGM sensor was worn
- Assessment of eligibility to continue to the randomized control trial (RCT) phase of the study

The appropriate study equipment will be downloaded and reviewed after the first 2 weeks of the run-in phase have been completed; participants will be evaluated for compliance and progress. If that run-in phase occurred without any major safety issues, participants who are completing only the CGM run-in can be randomized. Those completing study pump and CGM may continue the run-in phase for another 2-4 weeks at PI discretion. In addition, MDI or study-pump naïve participants will be contacted by study staff within approximately 24hrs, 72hrs, and 1 week after pump initiation to answer any questions related to device use prior to the 2-week visit. All participants may have unlimited contact with the study team as needed.

To enter the randomized trial from the run-in phase, participants must have obtained CGM readings on at least 11 out of the previous 14 days of the run-in phase (if applicable) and pump-naïve patients must have successfully used the study pump each day (if applicable). If a participant fails to meet either or both of these criteria, or if it is determined that the participant will benefit from additional time with equipment training, then the run-in period may be extended at the discretion of the investigator. One or two additional periods may occur, each a minimum of 11 days with a goal of at least 14 days, with another clinic visit to assess results after each period using the same criteria as above. The run-in duration will therefore vary from approximately 2 to 6 weeks, depending on the participant. Additional visits and phone contacts for further training are at investigator discretion.

An assessment of CGM and pump knowledge will be made and the participant must demonstrate sufficient competency to proceed to the RCT. The trainer and participant will review the individual items listed on the pump training checklist to ensure competency.

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

If the participant is eligible to continue in the study, study staff will follow the procedure for insulin pump optimization described below in section 3.6.

3.6 Optimization of Insulin Pump Settings

- Data-driven optimization of pump settings will occur at the following times:
- For the first phase: Prior to Randomization:
    - At the Run-in Review Visit
- Following Randomization visit and initiation of Extension Phase:
    - If needed at the criteria of the physician at each clinical center, optimization may be done by phone contacts or in clinic visits.
    - If the study participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Data will be obtained from CGM and/or pump downloads at the visit. Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) 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 Randomization Visit

The visit 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 screening (if Run-in skipped) or successful completion of the run-in phase.

A urine pregnancy test will be repeated for all females of child-bearing potential if this visit is not on the same day as the Screening Visit.

4.1.1 HbA1c

HbA1c will be measured using DCA Vantage or similar point-of-care (POC) device or local lab if this visit is not on the same day as the Screening Visit. A blood sample also will be drawn to send to the central laboratory for baseline HbA1c determination to be used in outcome analyses.

4.1.2 Baseline C-Peptide Assessment

A blood sample will be drawn to send to the central laboratory for a random, non-fasting C-peptide determination to characterize baseline residual insulin production. In conjunction, blood glucose may be measured using a blood glucose meter or a blood sample may be drawn to send to the central laboratory for a blood glucose assessment.

4.1.3 Randomization

Eligible participants will be randomly assigned to one of two treatment groups in a 3:1 ratio:

1. Control-IQ Closed-Loop Control (CLC) Group
2. Standard of 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 in view of the relatively small number at each clinical center.

4.1.4 Questionnaires

Participants will complete a set of baseline questionnaires, described in section 8.2 adapted for age, prior to randomization.

Chapter 5: Main Study Procedures

5.1 Procedures for the CLC Group

Participants assigned to the CLC group will receive study system training. These training sessions can occur on the same day or extend to up to one additional day if needed within 1-7 days from randomization; participants will not take the study system home until training has been completed.

The parent/guardian will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon. The parent/guardian will be asked to attend any/all of the other training procedures.

5.2 Study System Training

Participants will receive study system training by a qualified trainer. The study system includes the Tandem t:slim X2 with Control-IQ technology and associated Dexcom G6 CGM.

CGM training will include:

- The participant will be instructed and supervised on how to insert the sensor and transmitter.
- The participant will learn how to calibrate the CGM unit
- The participant will learn how to access the CGM trace via the t:slim X2 with Control-IQ user interface
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

Pump training will include:

- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

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 bolus on the t:slim X2 with Control-IQ system
- What to do when exercising while using the system
- How to enable the sleep function and set the sleep schedule
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The participant will be given a User Guide as a reference.

5.2.1 System Initiation

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

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

The participant's parent/legal guardian will be required to attend the training procedures and will be trained in all aspects aforementioned. All training will be conducted considering age of participant and parent involvement on diabetes treatment.

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

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with t:slim X2 with Control-IQ. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties. Participants will also receive study staff contact information to ask any questions they may have during the study.

Study staff will discuss with the participant that routine contact is required and will make arrangements with the participant for the contacts. If the participant cannot be reached, the participant's other contact methods will be utilized, including the emergency contact. Participants 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 t:slim X2 with Control-IQ training, study staff will document, using a checklist, that the participant is familiar with the function/feature and/or capable of performing each of the tasks specified.

Participants will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines (section 7.2) for when their glucose levels are >300 mg/dL for more than two hours or >400 mg/dL at any time or <70 mg/dL or ketones ≥1.5 mmol/L.

5.2.2 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 t:slim X2 with Control-IQ technology system.

Participants 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.

5.2.3 Study Device Download

Participants will be instructed to download the study device prior to each phone visit or on at least every 3-week basis throughout the remainder of the study.

5.2.4 1-Week Phone Contact

Study staff will perform a phone call with the participant within 7 (±1) 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

Participants will then complete an additional week of home use with the study system. Participants will return to clinic 14 (±3) days from the date of randomization.

5.2.5 2-Week Visit (Training Review and Insulin Pump Optimization)

The participant 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 in section 3.6 using the study CGM available data from the previous two weeks.
- The blood glucose meter and study ketone meter will be downloaded and QC tested with control solution.

5.3 Procedures for the SC Group

Participants in the SC group will use an insulin pump that they usually use for the treatment of their diabetes or a study pump provided by the study team if they are transitioning from MDI to pump for the study, in conjunction with the study CGM, study blood glucose meter, and study ketone meter. Study pump training and/or study CGM training will be provided if the participant is initiating use of these devices at this point.

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

Participants 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.

5.3.1 Study Device Data Download

Participants will be instructed to upload data from the study CGM using commercially available software prior to the 1-week phone contact and prior to the 2-week clinic visit for clinician review. Participants will be provided with any software and hardware needed to perform these data uploads.

5.3.2 1-Week Phone Contact

Study staff will perform a phone call with the participant 7(±1) 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

The participant will continue on SC for a second week, then return to the clinic 14 (±3) days from the date of randomization.

5.3.3 2-Week Visit (Training Review and Insulin Pump Optimization)

The participant will be offered review training on the use of SC during the remainder of the study, 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 review uploaded CGM data, answer any questions related to device use, and follow the procedure for insulin pump optimization described in section 3.6.
- The study blood glucose meter and study ketone meter will be downloaded and QC tested with

at least two different concentrations of control solution if available.

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

5.4 Follow-up Visits and Phone Contacts for Both Groups

The schedule for remaining follow-up visits and phone contacts is the same for both treatment groups. Study staff will discuss with the participant that periodic contact is required and will make arrangements with the participant for the contacts. If the participant or parent/guardian, cannot be reached, the participant's other contact methods will be utilized, including the emergency contact.

5.4.1 Follow-up Visits

Follow-up visits in clinic will occur at:

- 2 week (±3 days)
- 8 weeks (±1 week)
- 16 weeks (+1 week) – end of Main Study Phase

5.4.1.1 Procedures at Follow-up Visits

Procedures performed in both groups at each visit, 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)

5.4.2 Phone Contacts

In addition to the 1-week phone contact described above for the respective treatment groups, the following phone contacts will be made:

- 4 weeks (±3 days)
- 6 weeks (±3 days)
- 10 weeks (±3 days)
- 12 weeks (±3 days)
- 14 weeks (±3 days)

At each phone contact, the following procedures are performed in both treatment groups:

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

Additional phone contacts may be performed as needed.

5.4.3 Data from Study Devices

All participants will be asked to upload data from the CGM at least once every 4 weeks during the extension phase. The study staff will confirm that the data were received.

5.4.4 16-Week Final First Phase Visit

All participants will return to the clinic for a 16-Week (+7 days) final clinic visit during which the following will occur:

- HbA1c determination using the DCA Vantage or similar point of care device
- Collection of a blood sample to send to the central laboratory for HbA1c determination
- Completion of questionnaires
- Weight and height measurement 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)

5.5 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.

5.6 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.

5.7 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 6: Extension Phase Procedures

At the conclusion of the 16-week visit, all participants will have the option to use of the Control-IQ closed-loop system.

6.1 Closed Loop Control Participants

Participants who have completed the 16-week Main Study Phase will be provided the option to continue the use the t:slim with Control-IQ System for an additional 12 weeks.

The following phone contacts will be made for CLC Group participants in the Extension Phase:

- 20 week (±3 days)
- 24 week (±3 days)

At each phone contact, the following procedures are performed:

Review of available CGM and/or system data to identify any safety issues associated with insulin pump settings and current diabetes management approach

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

6.2 SC Group Participants

Training on pump (section 5.2) use will be provided and therapy optimization will occur as follows:

- If needed at the criteria of the physician at each clinical center, optimization may be done at either phone contacts or in clinic visits.
- If the study participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Data will be obtained from CGM and/or pump downloads at the visit. Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) 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 characteristics for all clinical centers.

The following phone contacts will be made for SC Group participants in the Extension Phase:

- 17 weeks (±3 days)
- 19 weeks (±3 days)
- 21 weeks (±3 days)

- 25 weeks (±3 days)

At each phone contact, the following procedures are performed:

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

Follow-up visits for SC group during the Extension Phase in clinic will occur at:

- 23 Weeks (±1 week)
- 28 Weeks (+1 week) – End of Study

Procedures Specific to the 28 Week Visit

- HbA1c determination using the DCA Vantage or similar point of care device
- Collection of a blood sample to send to the central laboratory for HbA1c determination
- Completion of questionnaires
- Weight measurement will be repeated, in addition to height
- Insulin Pump Optimization as described above

6.3 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.

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

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 7: Study Devices

7.1 Description of the Investigational Device

7.1.1 Insulin Pump

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

7.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors when using the Tandem t:slim X2 with Control-IQ technology. This may not be an FDA-approved device system at the start of the study, but may become approved during the course of the study. The CGM sensor will be replaced at least once every 10 days.

7.1.3 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.

7.1.4 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.

7.1.5 Study Device Accountability Procedures

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

7.1.6 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.

7.2 Safety Measures

7.2.1 CGM Calibration

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

7.2.2 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 t:slim X2 detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the participant will be instructed to contact Tandem Technical Support via the study team.

7.2.3 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.

7.2.4 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 2 hours or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.

- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is ≥1.5 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 8: Testing Procedures and Questionnaires

8.1 Laboratory Testing

8.1.1 Comprehensive Metabolic Panel (CMP)

A blood sample will be obtained at screening to assess kidney and liver functioning.

8.1.2 HbA1c:

- Performed locally at the Screening visit, Randomization visit and the 16-week visit.
- A blood sample will be obtained and sent to central lab at the Randomization visit, at the 16-week visit and at the end of the study visit.

8.1.3 Urine Pregnancy:

Performed locally for females of child-bearing potential at the Screening visit and the Randomization visit. This will also be done anytime pregnancy is suspected.

8.1.4 C-peptide and Glucose

Blood samples will be obtained and sent to the central lab at the Randomization visit. Back-up samples will be stored on-site until all samples are resulted.

8.2 Questionnaires

Questionnaires are completed at the Randomization Visit and Week 16 Visit for all participants. Participants who complete the Extension Phase will also complete the questionnaires at Week 28. The questionnaires will be family and age appropriate are described briefly below. The procedures for administration are described in the clinical center procedures manual.

The following questionnaires will be completed at the Randomization Visit:

- Clarke's Hypoglycemia Awareness Scale – Child and Parent (Children age 10+ years at the time of consent will complete as well as all Parents)
- Fear of Hypoglycemia Survey (HFS-II) – Child and Parent
- Problem Areas In Diabetes Survey (PAID) – Child and Parent
- Pediatric Quality of Life – Child and Parent
- INSPIRE Survey – Child and Parent
- Pittsburgh Sleep Quality Index (PSQI) – Parent

The following questionnaires will be completed at the Week 16 and Week 28 Visits:

- Clarke's Hypoglycemia Awareness Scale – Child and Parent (Children age 10+ years at the time of consent will complete as well as all Parents)

- Fear of Hypoglycemia Survey (HFS-II) – Child and Parent
- Problem Areas In Diabetes Survey (PAID) – Child and Parent
- Pediatric Quality of Life – Child and Parent
- INSPIRE Post-Assessment Survey – Child and Parent
- Pittsburgh Sleep Quality Index (PSQI) – Parent
- System Usability Scale (SUS) – Closed-Loop participants only

Administration time is approximately 15 minutes.

8.2.1 Clarke's Hypoglycemia Awareness Scale – Child and Parent

The scale comprises eight questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to hypoglycemia. A score of four or more on a scale of 0 to 7 implies impaired awareness of hypoglycemia.

Administration time is approximately 5 minutes.

8.2.2 Hypoglycemia Fear Survey (HFS-II)/Low Blood Sugar Survey – Child and Parent

The Hypoglycemia Fear Survey-II was developed to measure behaviors and worries related to fear of hypoglycemia in adults with type 1 diabetes. It is composed of 2 subscales, the Behavior (HFS-B) and Worry (HFS-W). HFS-B items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood glucose levels higher, making sure other people are around, and limiting exercise or physical activity). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident). HFS-II was adapted for children and parents. 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 10 minutes (both versions).

8.2.3 Problem Areas In Diabetes Survey (PAID) – Child and Parent

The Problem Areas In Diabetes Survey is a measure of diabetes-related emotional distress and consists of a scale of 16 items for the Parent version and 11 items for the Child version. Patients and parents rate the degree to which each item is currently problematic for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem).

Administration time is approximately 10 minutes.

8.2.4 PedsQL Diabetes Module – Child and Parent

This is a 33-item scale developed and validated for the measurement of diabetes-specific quality of life. Separate forms have been validated for child self-report (5-7 year old; 8-12 year old; and 12-18 year old) and parent report for these same age groups. Participants record the extent to

which they (or their child) experienced each of 33 problems related to diabetes in the prior month.

Administration time is approximately 15 minutes.

8.2.5 INSPIRE Survey – Child and 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 child pre-assessment survey includes 27 items, and the parent pre-assessment survey includes 45 items. The post-assessment child survey includes 17 items, and the parent post-assessment contains 21 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.

8.2.6 Pittsburgh Sleep Quality Index (PSQI) – Parent

Pittsburgh Sleep Quality Index (PSQI) is a 10-item questionnaire that measures the sleep quality and pattern of sleep in adults. 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 5 minutes.

8.2.7 System Usability Scale (SUS) – Closed-Loop participants only

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.

Chapter 9: Adverse Events, Device Issues, and Stopping Rules

9.1 Adverse Events

9.1.1 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 (see section 9.1.2 for reportable adverse events for this protocol).

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).

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, clinical centers will not be asked to distinguish between device complaints and malfunctions.

9.1.2 Reportable Adverse Events

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

1. A serious adverse event
2. An Adverse Device Effect as defined in section 9.1.1, unless excluded from reporting in section 9.2
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. 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.

Pregnancy occurring during the study will be recorded.

9.1.2.1 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 coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

9.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 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
- blood ketone level ≥1.5 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

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 <15; and
- Treatment provided in a health care facility

All reportable Adverse Events—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 adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

9.1.3 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.

9.1.4 Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: 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 or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.

- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

9.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. 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.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

9.1.6 Outcome of Adverse Event

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 clinical center 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).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

9.2 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

9.3 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported on an AE Form.

9.4 Timing of Event Reporting

SAEs and UADEs must be reported to the Coordinating Center within 24 hours via completion of the online serious adverse event form.

Other reportable adverse events, device malfunctions (with or without an adverse event), and device complaints should be reported promptly by completion of an electronic case report form, but there is no formal required reporting period.

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

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to the clinical centers' IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b). 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.

In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible company by the clinical center personnel, to be handled by its complaint management system.

9.5 Stopping Criteria

9.5.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in section 9.1.2.1

If pregnancy occurs, the participant will be discontinued from the study entirely. Otherwise, even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.

9.5.2 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 9.1.2.2), use of the study device system 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 will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

9.6 Independent Safety Oversight

A Data and Safety Monitoring Board (DSMB) will review compiled safety data at periodic intervals (typically every 6 months). In addition, the DSMB will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. 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.

9.7 Risks

The potential risks associated with use of the study device are described in section 1.3.

Additional risks are minor and/or infrequent and include:

- Pain, bruising, redness, or infection from blood draws
- Loss of confidentiality
- Stress from completing quality of life questionnaires

Chapter 10: Miscellaneous Considerations

10.1 Drugs Used as Part of the Protocol

Participants will use either lispro or aspart insulin prescribed by their personal physician.

10.2 Prohibited Medications, 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.

10.3 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.

10.4 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. De-identified participant information may also be provided to Tandem for system evaluation purposes.

Chapter 11: Statistical Consideration

11.1 Statistical and Analytical Plans

The outcome metrics and the statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the first tabulation of data by treatment group (ie, for DSMB review). The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

11.2 Statistical Hypotheses

This study is an extension to children ages 6-13 years old, of the Main Protocol described in IDE G180053, which includes N=168 children ages 14 and up and adults. Thus, the primary outcome for this study is identical to the Main protocol - CGM-measured % in range 70-180 mg/dL.

The hypotheses for the primary outcome are:

a. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180 mg/dL over 16 weeks between SC and CLC

b. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 16 weeks is different for SC and CLC.

11.3 Sample Size

Sample size has been computed for the primary outcome (CGM-measured % in range 70-180 mg/dL). Data from IDE G170267; Device Name: t:slim X2 with Control-IQ Technology; "Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued" were used to calculate sample size specific to this age group. In this study, which was completed in the winter of 2018, 24 school-aged children (6-12 years) with type 1 diabetes participated in a 3-day ski camp (~5 h skiing/day), followed by an additional 72 hour at-home phase under parental supervision. Study participants were randomized 1:1 to SAP and t:slim X2 with Control-IQ Technology. The data from the 72-hour home phase was used for this sample size calculation – *note that the closed-loop control system and the age range of the participants are identical to those proposed in this application:*

Results from home phase of G170267	Control IQ	SAP	F	p value
Percent between 70 and 180mg/dl	71 ± 6.6	52.8 ± 13.5	16.4	0.001

From the DCLP1 study using the same algorithm in an older cohort, the effective standard deviation (after adjusting for the correlation between baseline and follow up) for time in range 70-180 mg/dL over the course of 6 months was 6% (95% CI 5% to 7%) for the CLC group and 7% (95% CI 6% to 8%) for the SAP group.

A total sample size was computed to be N=60 for the following assumptions: (1) 3:1 [CLC:SC] randomization, (2) 90% power, (3) a 10% absolute increase in % time in range 70-180 mg/dL, (4) an effective SD of 10%, and (5) 2-sided type 1 error of 0.05.

The total sample size has been increased to N=100 to account for dropouts and to increase the number of participants who will be exposed to the CLC system for an enhanced safety and feasibility assessment.

11.4 Efficacy Outcome Measures

11.4.1 Primary Efficacy Endpoint

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

11.4.2 Secondary Efficacy Endpoints

11.4.2.1 Secondary Efficacy Endpoints Included in Hierarchical Analysis

The following secondary endpoints will be tested in a hierarchical fashion as described in section 11.7.1.

- CGM-measured % above 180 mg/dL
- CGM-measured mean glucose
- HbA1c at 16 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL
- CGM-measured % above 250 mg/dL
- Glucose variability measured with the coefficient of variation (CV)

11.4.2.2 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:

- % in range 70-140 mg/dL
- glucose variability measured with the standard deviation (SD)
- % <60 mg/dL
- low blood glucose index
- hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- % >300 mg/dL
- high blood glucose index
- % in range 70-180 mg/dL improvement from baseline to 16 weeks ≥5%
- % in range 70-180 mg/dL improvement from baseline to 16 weeks ≥10%

HbA1c:

- HbA1c <7.0% at 16 weeks
- HbA1c <7.5% at 16 weeks
- HbA1c improvement from baseline to 16 weeks >0.5%
- HbA1c improvement from baseline to 16 weeks >1.0%
- HbA1c relative improvement from baseline to 16 weeks >10%
- HbA1c improvement from baseline to 16 weeks >1.0% or HbA1c <7.0% at 16 weeks

Questionnaires

- Fear of Hypoglycemia Survey (HFS-II) – total score, 2 subscales and 4 factor scores:
    - ♦ Behavior (avoidance and maintain high BG)
    - ♦ Worry (helplessness and social consequences)
- Clarke Hypoglycemia Awareness Scores
- Problem Areas In Diabetes Survey (PAID)
- INSPIRE survey scores
- PedsQL Diabetes Module – total score and 5 subscales:
    - ♦ Diabetes
    - ♦ Treatment I
    - ♦ Treatment II
    - ♦ Worry
    - ♦ Communication
- Pittsburgh Sleep Quality Index (Parent only)
- System Usability Scale (SUS)

Other:

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

11.4.3 CGM Metrics Calculations

Randomization is preceded by two 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 16-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.

11.5 Analysis Datasets and Sensitivity Analyses

All analyses comparing the CLC arm with SC arm will follow the intention-to-treat (ITT) principle with each participant analyzed according to the treatment assigned by randomization. All randomized participants will be included in the primary and secondary hierarchical analyses.

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

11.5.1 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

11.5.2 Other Sensitivity Analyses

Confounding

The primary analysis described below will include a pre-specified list of covariates. As an additional sensitivity analysis, any baseline demographic or clinical characteristics observed to be imbalanced between treatment groups will be added as covariates to the analyses of the primary endpoint. The determination of a meaningful baseline imbalance will be based on clinical judgement and not a p-value.

Exclude First 2 Weeks of CGM Data

As noted above in Section 11.4.3, calculation of CGM metrics will include all available post-randomization CGM data. As a sensitivity analysis, CGM metrics will be recalculated by excluding the first two weeks of CGM data following the randomization visit. The primary analysis will be replicated based on the recalculated outcome.

Missing Data

It is worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions will not be sensitive to which statistical method is used. To that end,

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

- Direct likelihood (primary analysis described below)
- Rubin's multiple imputation
- Multiple imputation with pattern mixture model
- Available cases only

11.6 Analysis of the Primary Efficacy Endpoint

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured % in range 70-180 mg/dL and for differences from pre-randomization by treatment group.

Changes from run-in pre-randomization CGM wear to the 16-week post-randomization period in 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). Missing data will be handled using direct likelihood. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. It is expected that the residual values for CGM-measured % in range 70-180 mg/dL will follow an approximate normal distribution.

11.7 Analysis of the Secondary Endpoints

Point estimated 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).

11.7.1 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 with 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 180 mg/dL
- CGM-measured mean glucose
- HbA1c at 16 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL
- CGM-measured % above 250 mg/dL

- Glucose variability measured with the coefficient of variation (CV)

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 eight 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.

For example, in the hypothetical scenario depicted in the table below, the first four outcome variables all have a significant result so testing continues to the fifth variable (CGM % below 70 mg/dL). The result is not significant for that fifth variable ($p = 0.06$) so testing stops. No formal hypothesis test is conducted for the last three variables on the list in this example scenario.

HIERARCHICAL ORDER	OUTCOME VARIABLE	TREATMENT ARM P-VALUE	SIGNIFICANT?	ACTION
1st	CGM % 70-180 mg/dL (primary outcome)	0.001	Yes	Test next variable
2nd	CGM % above 180 mg/dL	0.02	Yes	Test next variable
3rd	CGM mean glucose	0.007	Yes	Test next variable
4th	HbA1c at 16 weeks	0.03	Yes	Test next variable
5th	CGM % below 70 mg/dL	0.06	No	Stop formal testing
6th	CGM % below 54 mg/dL	Not tested	Unknown	N/A
7th	CGM % above 250 mg/dL	Not tested	Unknown	N/A
8th	Glucose CV	Not tested	Unknown	N/A

Table 6. Example Hypothetical Hierarchical Test Results

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 seven 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.

11.7.2 Other Endpoint Analyses

CGM-Measured Outcomes

The analyses for the secondary CGM-measured outcomes will parallel those mentioned above for the primary outcome. For the binary CGM outcomes, risk-adjusted percentages by treatment group will be calculated from a logistic regression model.

HbA1c

Summary statistics (mean ± SD) will be reported for the central lab HbA1c at baseline, 16 weeks and for differences from pre-randomization by treatment group.

Change in HbA1c from baseline to 16 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).

For extension phase, efficacy of the AP will be compared by using the final 12 weeks of the control period vs. the 12-week AP extension phase. Each participant will be their own control.

Missing data will be handled using direct likelihood in a regression model including all available central laboratory HbA1c measurements at baseline and 16-week visits. When available, the local HbA1c measurement will be included in the regression model as an auxiliary variable.

For the binary HbA1c outcomes listed above, risk-adjusted percentages by treatment group will be computed from a logistic regression model. The logistic regression will adjust for the same factors mentioned above for the analysis with HbA1c as a continuous factor (i.e., baseline HbA1c, age, prior CGM and pump use, and clinical center as a random effect).

Questionnaires and Other Outcomes

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

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

11.8 Safety Analyses

All randomized participants will be included in these analyses and all their post-randomization safety events will be reported.

Safety analyses of the main study (randomized trial phase) will include events occurring on or after randomization until and including the 16-week visit or Day 126 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).

Any pre-randomization adverse events will be tabulated separately and will include all participants even if never randomized.

For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group and 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
- Any adverse event' rate per 100 person-years

- Number of calendar days with any ketone level ≥1.0 mmol/L
- CGM-measured hypoglycemic events (≥15 minutes with glucose concentration <54 mg/dL)
- CGM-measured hyperglycemic events (≥15 minutes with glucose concentration >300 mg/dL)

If enough events, the numbers of SH/DKA events 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 events 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. Similar analyses will be done for comparing any adverse event and number of calendar days with ketone events between the two treatment groups, except that clinical center will be the only covariate to be adjusted in the model.

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.

For both the main study and extension phases, the following safety outcomes will be tabulated by treatment group without a formal statistical comparison:

- Other serious adverse events (SAE)
- BG-measured hypoglycemic events (days with at least one BG record <54 mg/dL)
- BG-measured hyperglycemic events (days with at least one BG record >350 mg/dL)
- Worsening of HbA1c from baseline to 16 weeks by >0.5%
- Investigational device related (intervention group only):
    - Adverse device effects (ADE)
    - Serious adverse device events (SADE)
    - Unanticipated adverse device effects (UADE)

11.9 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 and by 4-weekly
- The daily frequency of downloaded BGM use overall and by 4-weekly

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

- % time in different operational modes - overall and by 4-weekly

11.10 Adherence and Retention Analyses

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

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

11.11 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.

Will include:

- Age
- HbA1c
- Gender
- Race/Ethnicity
- Family income, education, and/or insurance status
- Insulin method before enrollment (pump vs. MDI)
- CGM use before enrollment
- Diabetes duration
- BMI (height and weight)
- C-peptide
- Participant-reported number of SH and DKA 12 months prior to the start of the study

11.12 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

- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by month

11.13 Planned Interim Analyses

All above efficacy and safety analyses will be conducted after all subjects completed the primary study phase. No sample size re-estimation will be needed for the extension phase. The data may be used for PMA, with no interruption on the extension phase.

In addition, the DSMB will review safety data at intervals, with no formal stopping rules other than the guidelines provided in the participant-level and study-level stopping criteria (as defined in Section 9.5 of the protocol).

11.14 Subgroup Analyses

In exploratory analyses, the primary outcome (time 70-180 mg/dL), % time <70 mg/dL and HbA1c at 16 weeks will be assessed separately in various subgroups and for continuous variables according to the baseline value as defined below. Tests for interaction with treatment group will be performed and further explored if an interaction will be found in the first place.

Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. In the absence of such an overall difference and if performed, subgroup analyses will be interpreted with caution. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous, except for age which will be analyzed both as a continuous variable and in two age groups. 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.

- Baseline HbA1c
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Baseline CGM time 70-180 mg/dL
- Device use before the enrollment: pump/MDI, CGM/no CGM, and combinations of both
- Age
- Sex
- Race/ Ethnicity
- Clinical center
- BMI (Height and weight)
- Family income, education, and/or insurance status

- C-peptide level

11.15 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 11.7.1 will be used to control the overall type 1 error for the primary outcome plus seven key secondary outcomes identified above.

All Other Secondary Analyses

For all above-mentioned secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

11.16 Exploratory Analyses

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

The CGM-measured analyses will be replicated with only CGM data when the closed-loop was active for the CLC group. The CGM data for the SC group will be the same as mentioned above in the CGM Metrics Calculation section 11.4.3.

Chapter 12: Data Collection and Monitoring

12.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

When data are directly collected in electronic case report forms, this will be considered the source data. Each participating clinical center 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.

12.2 Study Records Retention

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.

12.3 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. 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.

The data of most importance for monitoring at the clinical center 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 clinical center data. Elements of the RBM may include:

- Qualification assessment, training, and certification for clinical centers and clinical center 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 clinical center staff
- Participant retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

12.4 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 clinical center staff. As a result of deviations, corrective actions are to be developed by the clinical center and implemented promptly.

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

Chapter 13: Ethics/Protection of Human Participants

13.1 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.

13.2 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.

13.3 Informed Consent Process

13.3.1 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 and child assent documents 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 and child assent documents 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.

13.3.2 Participant and Data Confidentiality

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical center will permit access to such records.

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

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 and the University of Virginia Center for Diabetes Technology. This will not include the participant's contact or identifying information. 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 centers and by Jaeb research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Jaeb Center for Health Research and the University of Virginia Center for Diabetes Technology. Permission to transmit data will be included in the informed consent.

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