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

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

Protocol Chair
Sue Brown, MD
University of Virginia
Center for Diabetes Technology

Participating Institutions
University of Virginia, Charlottesville, Virginia
Harvard University and the Joslin Diabetes Center, Massachusetts
Sansum Diabetes Research Institute, Santa Barbara, California
Mount Sinai School of Medicine, New York City
Mayo Clinic, Rochester, Minnesota
Barbara Davis Center, University of Colorado, Colorado
Stanford University, California

Coordinating Center
Jaeb Center for Health Research, Tampa, FL

Version Number: v6.1

11 SEP 2019

KEY ROLES

Protocol Chair/Director	
Name, degree	Sue A. Brown, MD
Institution Name	University of Virginia, Center for Diabetes Technology
JCHR Coordinating Center Director	
Name, degree	John Lum, M.S.
Institution Name	Jaeb Center for Health Research
Medical Monitor	
Name, degree	Roy Beck, M.D., Ph.D.
Institution Name	Jaeb Center for Health Research

TABLE OF CONTENTS

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
CLC	Closed-Loop Control
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
JDRF	Juvenile Diabetes Research Foundation
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SAP	Sensor-Augmented Pump
SD	Standard Deviation
TDD	Total Daily Dose
UI	User Interface
UVA	University of Virginia

Signature Page

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

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

Protocol Identifying Number: DCLP3

IND/IDE Sponsor: University of Virginia

Version Number: v.6.1

11 SEP 2019

JCHR Principal Investigator	
Name, degree	John W. Lum, M.S.
Signature / Date	
Protocol Chair/Director	
Name, degree	Sue A. Brown, MD
Signature / Date	

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

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

Protocol Version/Date: v6.1/11 SEP 2019

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

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

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

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

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

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	The International Diabetes Closed Loop (iDCL) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology - Extension Study
Précis	An extension study for participants who completed a prior 6-month randomized controlled trial (RCT) of a closed loop system (Control-IQ) vs. sensor-augmented pump (SAP).
Investigational Device	t:slim X2 with Control-IQ and Dexcom G6 system
Objectives	The objectives of the study are (1) Among individuals who used CLC in the original RCT, to compare continued use of CLC (t:slim X2 with Control-IQ Technology) for 3 months versus switching to a Predictive Low-Glucose Suspend (PLGS) system (t:slim X2 with Basal-IQ Technology) for 3 months. (2) Among individuals who used SAP in the original RCT, to obtain additional safety data by initiating use of the Control-IQ system for 3 months. (3) For all participants, use of the CLC system between the end of 3-month period and the point that the system becomes commercially available in order to gather additional safety data
Study Design	Objective 1: RCT with 1:1 randomization to intervention with CLC vs. PLGS for 3 months. Objective 2: Observational study of initiation and use of CLC for 3 months. Objective 3: Observational study of initiation and use of CLC for 3 months following use of PLGS for 3 months; use of CLC by all participants between end of 3-month period and the point that the system becomes commercially available in order to gather additional safety data.
Number of Sites	Seven US clinical sites
Primary Endpoint	Objective 1: The primary efficacy outcome for the RCT is time in target range 70-180 mg/dL measured by CGM in CLC group vs. PLGS group over 3 months. Safety outcomes also will be assessed Objective 2: The primary outcome is safety outcomes. Efficacy also will be assessed as a pre-post within participant analysis Objective 3: The primary outcome is safety outcomes. Efficacy also will be assessed as a pre-post within participant analysis
Population	**Key Inclusion Criteria** • Successfully completed the original 6-month RCT within the prior 14 days **Key Exclusion Criteria** • Use of any non-insulin glucose-lowering agents except metformin
Sample Size	Sample size is based on the number in the original RCT who successfully complete six months and sign consent to participate in this study (up to approximately 168 total).
Treatment Groups	Objective 1 • Group 1: t:slim X2 with Control-IQ Technology and Study CGM • Group 2: t:slim X2 with Basal-IQ Technology and Study CGM
Participant Duration	3 months

PARTICIPANT AREA	DESCRIPTION
Protocol Overview/Synopsis	Eligible participants in the original RCT who agree to be part of the Extension Study will sign the informed consent form. • Participants assigned to the original RCT SAP group will initiate use of the CLC system for 3 months. • Participants assigned to the original RCT CLC group will be randomly assigned 1:1 to either continue CLC or switch to PLGS for 3 months. • After 3 months, all participants will be given the opportunity to use the CLC system until the point that the system becomes commercially available

186

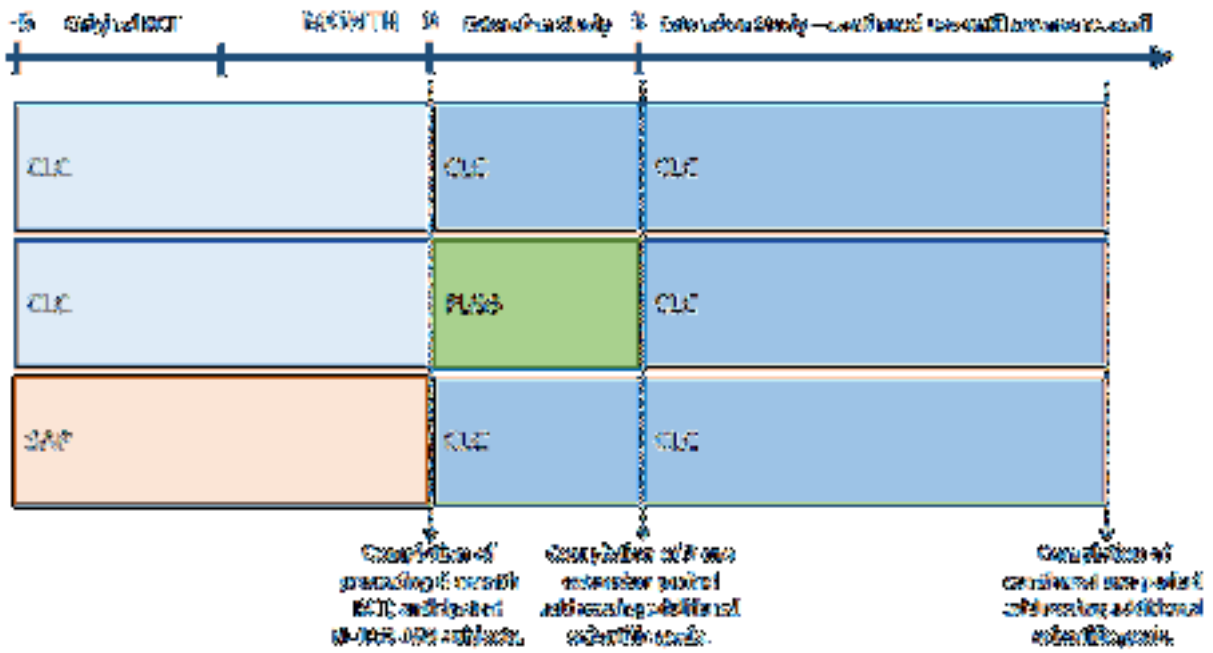
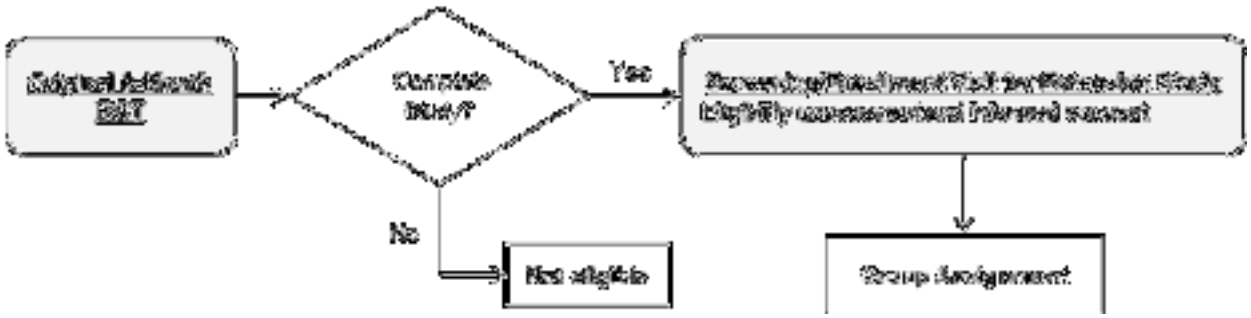


Figure 1: Study Design - Participants entering Extension Study after having completed preceding 6-month RCT. Participants in the original RCT SAP Group will use CLC in the first 3 months of the Extension Study while participants in the original RCT CLC Group will be randomly assigned 1:1 to either continue CLC or switch to PLGS. After 3 months, all participants will be given the opportunity to use CLC until the point that the CLC system becomes commercially available.

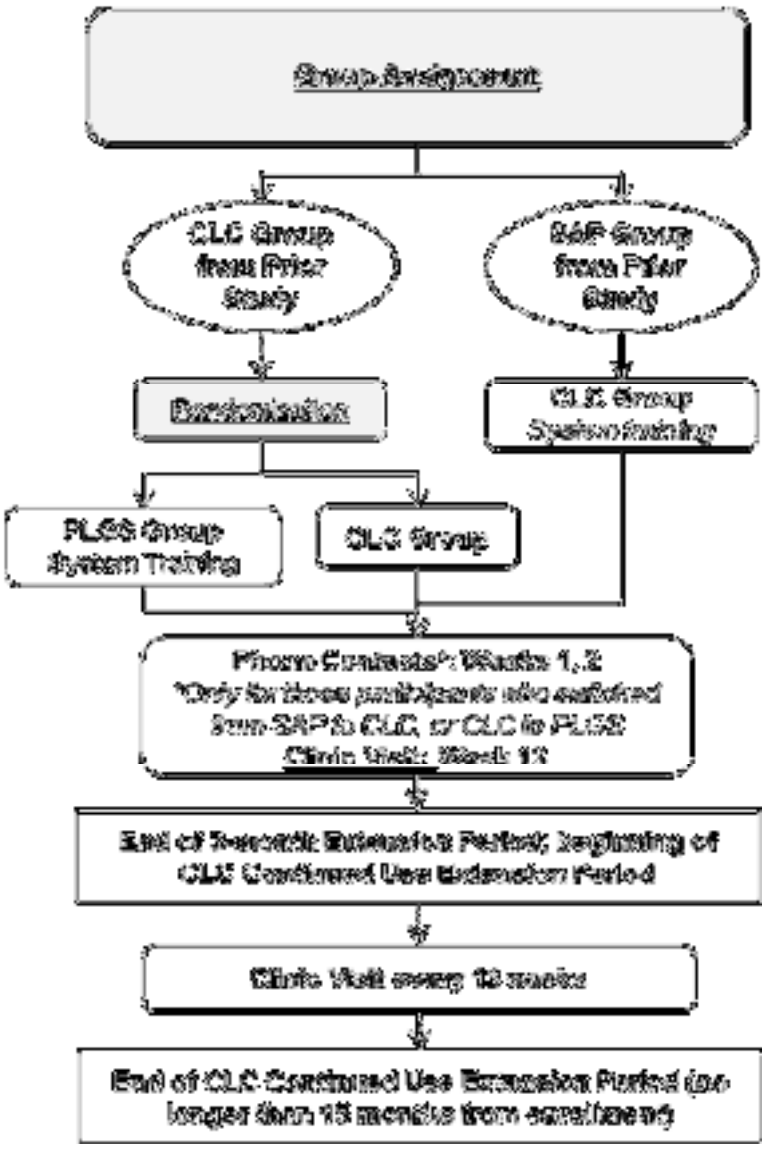
193 # SCHEMATICS OF STUDY DESIGN



194

195 **Figure 2: Schematic of Eligibility Assessment/Enrollment**

196



197

198 **Figure 3. Schematic of Study Design**

Table 1. Schedule of Study Visits and Procedures

	0 Weeks	1w	2w	13w	26w, then every 13 weeks until end	Final Visit
Visit (V) or Phone (P)	**V**	**P[1]**	**P[1]**	**V**	**V**	**V**
Comment	**Screen/Enroll and Rand/Assign**					
Eligibility Assessment	X					
HbA1c (DCA Vantage or similar point of care device, or local lab)	X[2]			X	X	X
HbA1c (Central lab)	X[2]			X		
Pregnancy test (females of child-bearing potential)	X			X	X	
Device Data download(s)		X	X	X	X	X
Review diabetes management and AEs		X	X	X	X	X
Questionnaires as defined in section 5.2	X[2]			X	X[3]	X
Follow-up Phone Call						P

[1] Only performed for those participants who switched from SAP in the original 6-month RCT to CLC in the Extension Study, or from CLC in the original RCT to PLGS in the Extension Study

[2] Will use results obtained at Final Visit of preceding 6-month RCT

[3] 26-Week visit only

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 University of Virginia's (UVA) diabetes assistant (DiAs) system and then implemented in the inControl system. DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described 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 280,000 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 18 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

We further reference pre-submission Q170885 and our discussion with FDA on July 18, 2017 regarding the structure of studies intended to test inControl implemented on t:slim X2. Based on the input provided by the Agency, we initially defined a series of three studies leading to a future pivotal trial of this system (36-48 hr Pilot Study, 2 week at home Training Study, followed by the Pivotal Trial). Since the time of the initial discussion, we have concluded a successful Pilot of 5 Adult (December 2017) and a Ski Camp with 12 Teenagers (January 2018) on the System. We have also received approval for the use of this system in a long-term home study (Project Nightlight/G#150240/S008). The Project Nightlight Study will now replace the previous Training Study as noted in Figure 4.

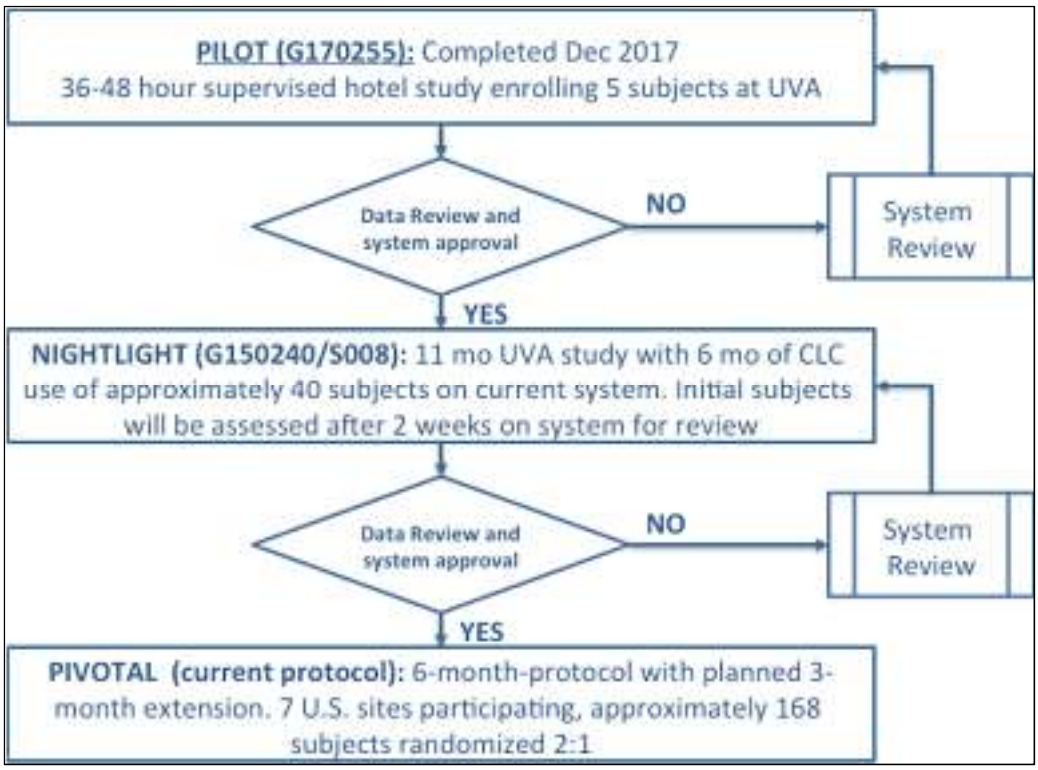


Figure 4: Sequence of planned studies leading to this pivotal trial of the Tandem X2 insulin pump with Control-IQ Technology

A successful pilot of 5 Adults (mean age 52.8 yrs; 3F/2M, mean A1c 6.5%) with Type 1 Diabetes was completed in December 2017. In this pilot study, 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.

Table 2. Pilot Study results based on time in closed-loop

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%

Closed-Loop Control System

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

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

1.2 Rationale

The main objective of the study is to compare continued use of CLC (t:slim X2 with Control-IQ Technology) for 3 months versus switching to a Predictive Low-Glucose Suspend (PLGS) system (t:slim X2 with Basal-IQ Technology) for 3 months following 6 months of Control-IQ use in a preceding study, in a parallel group RCT design.

Another objective is to obtain additional safety data from the Control-IQ system in a large population.

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 this.

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 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 and the receiver is a hand held device. 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 pumps are 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 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 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 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) adults 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 increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) 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 site 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 include only those individuals who successfully completed the original 6-month RCT comparing the CLC system to SAP, with a maximum of 168 participants.

Study participants will participate at the same 7 clinical centers in the United States who participated in the preceding study without regard to gender, race, or ethnicity. Recruitment per site will be based on the number at the site that successfully completed the original RCT.

2.1.1 Informed Consent and Authorization Procedures

Before completing any procedures or collecting any data that are specific for the study, written informed consent will be obtained.

For potential study participants ≥18 years old, the study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

For potential participants under 18 years of age, 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 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 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 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. Successful completion of the original 6-month RCT within the prior 14 days
2. 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 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.

3. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency.
4. Willingness to not use a personal CGM for the duration of the study
5. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol
6. Willingness to use only lispro (Humalog) or aspart (Novolog), and to use no other insulin during the study.
7. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3)

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
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., Dexcom, Inc., or TypeZero Technologies, LLC, 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

2.4.1 . Assessment of Successful Completion of Original RCT

A determination will be made as to whether the participant meets criteria for having successfully completed the original RCT. Successful completion is defined as having participated in the study's 26-week visit and having completed the following associated study visit procedures within the prior 14 days:

- Local HbA1c determination and collection of blood sample for central laboratory HbA1c determination
- Completion of study questionnaires

2.4.2 . Data Collection and Testing

For participants who satisfy the completion criteria above, the remaining inclusion and exclusion criteria will be reviewed and documented to verify the participant's eligibility for the Extension Study. A urine pregnancy test will be performed for all women of child-bearing potential.

The following information obtained during the original RCT will be captured/reviewed and updated if necessary:

- Medical history
- Concomitant medications

Data obtained during the 26-week visit of the original RCT will be considered baseline data for the Extension study, including:

- HbA1c as described above
- Weight (and height if <21 years of age)

Screening procedures may last approximately 15 minutes.

Chapter 3: Study Procedures

3.1 Treatment Assignment

Treatment assignment will occur on the same day as the Screening visit.

- Participants who were assigned to the SAP group in the original RCT will be assigned to use CLC during the extension study

- Participants who were assigned to the CLC group in the original RCT will receive a randomized treatment assignment as detailed below

3.1.1 Randomization

Participants who were assigned to the CLC group in the original RCT will be randomly assigned to one of two treatment groups in a 1:1 ratio:

1. CLC Group
2. PLGS Group

The participant's randomization group assignment is determined by completing a Randomization 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 site 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 site in view of the relatively small number at each site.

3.2 Training for the Group Switching from SAP in the Original RCT to CLC (Control-IQ System)

Participants who were assigned to the SAP group in the original RCT will use CLC during the extension study. These participants will receive study system training on the Control-IQ system. This training sessions can occur on the same day or extend to up to one additional day if needed within 1-7 days from assignment; participants will not take the study system home until training has been completed.

For participants <18 years old, 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.

3.2.1 Control-IQ System Training Details

Participants will receive 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 may include any of the following refresher topics as needed:

- 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 may include any of the following refresher topics as needed:

- 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 current 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.

Upon completion of 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.

3.2.2 System Initiation and Home Use

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

Participants 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.

Participants 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 Control-IQ use should be temporarily discontinued.

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.

3.3 Training for the Group Switching from CLC in the Original RCT to PLGS (Basal-IQ System)

The participants who used CLC in the original RCT and who are assigned to the PLGS (Basal-IQ) group during the extension study will receive study system training on the Basal-IQ system. This training sessions can occur on the same day or extend to up to one additional day if needed within 1-7 days from assignment; participants will not take the study system home until training has been completed.

For participants <18 years old, 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.

3.3.1 Basal-IQ System Training Details

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

CGM training may include any of the following refresher topics as needed:

- 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 Basal-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 may include any of the following refresher topics as needed:

- 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 current 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 Basal-IQ Technology functions will include:

- How to turn on and off Basal-IQ technology.
- How to understand when Basal-IQ has suspended basal insulin delivery.
- What to do when exercising while using the system
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- The participant will be given a User Guide as a reference.

Upon completion of Basal-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.

3.3.2 System Initiation and Home Use

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

Participants will be instructed to use the system in accordance with the user documentation provided by study staff.

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.

3.4 Training for Group Continuing CLC Use After Using CLC in the Original Study

No additional system training is required for these participants. However, at the discretion of the investigator, refresher training may be provided using a subset of the topics described in section 3.2.1 above.

3.5 Blood Glucose and Ketone Testing

Participants will receive supplies for blood glucose and ketone testing as needed and will be provided Hypoglycemia, Hyperglycemia and Ketone Guidelines as detailed in section 4.2.

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.

3.6 Menstrual Cycle Data Collection

Participants who consent to participate in the collection of menstrual cycle data will be asked to install a Menstrual Cycle tracking app on their personal phones.

These participants will be given instructions on how to use the app to collect the desired menstrual cycle data information and will use the app to collect these data on an ongoing basis until the study Final Visit. The data collected will include details about contraception method and menses dates.

3.7 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings will occur at the following times:

- Screening
- At the 1- and 2-Week phone contacts for those participants participating in the Extension Phase who switched from SAP to CLC or from CLC to PLGS
- 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 sites.

3.8 Phone Contacts and Study Visits

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 study system components. Participants will be provided with sufficient study supplies to last until the 13-Week visit.

3.8.1 1- and 2-Week Phone Contacts

For those participants who switched from SAP in the original RCT to CLC in the Extension Study, or from CLC in the original RCT to PLGS in the Extension Study, study staff will perform a phone call with the participant within 7 (±3) days and at 14 (±3) days following group assignment.

If the participant cannot be reached, the participant's other contact methods will be utilized, including the emergency contact.

The following will occur during each contact:

- 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
- Optimization of pump settings, if indicated

At investigator discretion, either phone contact may be replaced by a clinic visit. Additional phone contacts or clinic visits may be performed as needed.

3.8.2 Data Uploads

Participants will be instructed to upload data from their study insulin pump prior to the 1- and 2-week phone contacts (if applicable) and at least every 4 weeks for the remainder of the study. Participants will be provided with any software and hardware needed to perform these data uploads.

If participating in the menstrual cycle data collection aspect of the study, participants may periodically be asked to transmit the collected data to the clinical site using the export functionality of the phone app that was used.

3.8.3 13-Week Visit

All participants will return to the clinic for a 13-Week (±7 days) 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
- Urine pregnancy test for all women of child-bearing potential
- Weight measurement
- 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)

All participants will be offered the opportunity to continue in the study, using the CLC system until such time that the system becomes commercially available.

- Participants who do not wish to continue in the study will transition back to personal insulin pump, or to resumption of MDI. The 13-Week visit will serve as the final study visit for these participants.
- Participants who agree to continue in the study will be provided with sufficient study supplies to last until the 26-Week visit
    - Participants who had been randomized to PLGS for the preceding 13-week period will be given a CLC pump and will receive refresher training on the CLC system at the discretion of the investigator, using a subset of the topics described in section 3.2.1 above.

3.8.4 26-Week Visit and Subsequent Visits Every 13 Weeks

Until the point that the CLC system is commercially available (but not longer than 15 months after study enrollment), participants will return to the clinic for a visit every 13 weeks (±7 days), beginning with a 26-Week visit (±7 days), during which the following will occur:

- HbA1c determination using the DCA Vantage or similar point of care device
- Completion of questionnaire (26-Week visit only)
- Urine pregnancy test for all women of child-bearing potential
- Weight measurement
- 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)

3.8.5 Final Visit

When the CLC system becomes commercially available from the manufacturer (or 15 months has elapsed since enrollment), participants will return to the clinic within a 6-week period for a final study visit. The 6-week transition period is intended to provide an opportunity for the participant to complete the logistics of obtaining the system commercially (insurance, etc.). The following will occur during the final visit:

- HbA1c determination using the DCA Vantage or similar point of care device (skipped if the prior 13-Week clinic visit occurred in the preceding 2-week period)
- Completion of questionnaires
- Weight measurement (skipped if the prior 13-Week clinic visit occurred in the preceding 2-week period)
- 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)
- If participating in the menstrual cycle data collection aspect of the study, participants will transmit the collected data to the clinical site using the export functionality of the phone app that was used
- Transition back to personal insulin pump, or to resumption of MDI; insulin parameters will be assessed by a qualified clinical study team member (e.g. MD, NP, CDE)
- Follow-up phone call with the participant within 7 (±3) days of transitioning back to personal insulin treatment regimen to assess safety of the treatment transition; will be instructed to also continue usual clinical care with their personal health care team

3.9 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.

3.10 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.

3.11 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 4: Study Devices

4.1 Description of the Investigational Device

4.1.1 Insulin Pump

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

4.1.2 Continuous Glucose Monitoring

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

4.1.3 Blood Glucose Meter and Strips

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

4.1.4 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.

4.1.5 Study Device Accountability Procedures

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

4.1.6 Blood Glucose Meter Testing

- Participants will be provided with instructions to perform QC testing per manufacturer guidelines.
- All study blood glucose meters will be QC tested with at least two different concentrations of 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 blood glucose measurements.
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

4.1.7 Blood Ketone Testing

- Participants to perform QC testing at home per manufacturer guidelines.
- All study blood ketone meters will be QC tested with at least two different concentrations of 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.

4.2 Safety Measures

4.2.1 CGM Calibration

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

4.2.2 Control-IQ 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.

4.2.3 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 60 mg/dL.

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

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

4.2.4 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 >0.6 mmol/L, take correction insulin, change insulin (pump) infusion site and contact study staff.
- If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours.

Chapter 5: Testing Procedures and Questionnaires

5.1 Laboratory Testing

1. HbA1c:
   - Performed locally at the 13-week visit and at subsequent study visits at 13-week intervals using the DCA Vantage or similar point of care device
   - A blood sample will be obtained and sent to central lab for HbA1c assessment at the 13-week visit.
2. Urine Pregnancy:
   - A urine pregnancy test will be performed locally for females of child-bearing potential at the Screening visit. The test will be repeated at the 13-week visit for participants continuing in the study, and will be repeated at subsequent clinic visits at 13-week intervals. A test will also be done anytime pregnancy is suspected.

5.2 Questionnaires

Questionnaires, described briefly below, are completed at various clinic visits detailed below. The procedures for administration are described in the study procedures manual.

The following questionnaire will be completed at the Screening visit:

- Technology Expectations Survey *(only for participants who had been assigned to SAP during the original 6-month RCT)*

The following questionnaires will be completed at the 13-week Visit:

- Clarke's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Hypoglycemia Confidence Scale
- Diabetes Distress Scale
- INSPIRE Survey
- Technology Acceptance Survey
- System Usability Scale (SUS)

The following questionnaires will be completed at the 26-week Visit:

- Control-IQ Patient-Reported Outcomes Questionnaire

The following questionnaire will be completed at the final clinic visit:

- System Usability Scale (SUS)
- Control-IQ Patient-Reported Outcomes Questionnaire

Clarke's Hypoglycemia Awareness Scale

The scale (28) 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.

Hypoglycemia Fear Survey (HFS-II)/Low Blood Sugar Survey

The Hypoglycemia Fear Survey-II (29) 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 above150 mg/dL, 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).

Administration time is approximately 10 minutes.

Hyperglycemia Avoidance Survey (HAS)/High Blood Sugar Survey

The HAS (30) reliably quantifies affective and behavioral aspects of hyperglycemia avoidance and is used to assess the extent of potentially problematic avoidant attitudes and behaviors regarding hyperglycemia in people with Type 1 diabetes (T1D).

Administration time is approximately 10 minutes.

Hypoglycemia Confidence Scale

The HCS (31) is a 9-item self-report scale that examines the degree to which people with diabetes feel able, secure, and comfortable regarding their ability to stay safe from hypoglycemic-related problems. It has been validated for use in adults with type 1 diabetes and insulin-using type 2 diabetes.

Administration time is approximately 5 minutes.

Diabetes Distress Scale

The Diabetes Distress Scale (32) is a measure of diabetes-related emotional distress and consists of a scale of 28 items. These include 7 items from each of four domains central to diabetes-

related emotional distress. Patients 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.

Technology Expectation and Technology Acceptance Surveys

The Technology Expectation and Technology Acceptance Surveys were developed for a Bionic Pancreas camp study (33). The 38 items in the Questionnaire were based on interviews conducted with individuals who had participated in previous Bionic Pancreas trials about their experience regarding the Bionic Pancreas. It was subsequently adapted to assess these same measures for the inControl closed-loop system. It assesses both positive and negative experiences with CLC, including blood glucose management, device burden, and overall satisfaction. Items were rated on a 5-point scale.

Administration time is approximately 10 minutes.

INSPIRE Survey

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 adult survey includes 31 items; the adolescent survey includes 28 items; and the parent survey includes 30 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.

System Usability Scale (SUS)

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

Administration time is approximately 5 minutes.

Control-IQ Patient-Reported Outcomes Questionnaire

This is a 10-item questionnaire that solicits information about frequency of use of the Control-IQ closed-loop feature, satisfaction with and trust in the system, impact on aspects of living with diabetes, and likelihood of recommending the system to others.

Administration time is approximately 5 minutes.

Chapter 6: Adverse Events, Device Issues, and Stopping Rules

6.1 Adverse Events

6.1.1 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 6.1.2 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, unless excluded from reporting as defined in section 6.2).

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

6.1.2 Reportable Adverse Events

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

1. An SAE
2. An ADE as defined in section 6.1.1, unless excluded from reporting in section 6.2
3. An AE as defined in section 6.1.1 occurring in association with a study procedure
4. An AE as defined in section 6.1.1 which leads to discontinuation of a study device for 2 or more hours
5. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
6. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemia or ketosis event meeting the criteria defined below

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

Pregnancy occurring during the study will be reported as an AE (see section 6.3).

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

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

6.1.2.2 Hyperglycemic/Ketotic Events

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 ≥1.0 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

6.1.3 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.

6.1.4 Intensity of Adverse Events

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.

6.1.5 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.

6.1.6 Outcome of Adverse Events

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

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).
- If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified UADEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the subject has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

6.2 Reportable Device Issues

All UADEs and ADEs as defined in section 6.1.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

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

- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion (including tubing and cartridge) not leading to ketosis ≥0.6 mmol/L or in the absence of checking for blood ketones, blood glucose >350 mg/dL; and not requiring an intervention other than replacing the tubing and/or cartridge
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to requiring system replacement or workaround/resolution not specified in user guide/manual
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

6.3 Pregnancy Reporting

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

6.4 Timing of Event Reporting

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

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 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 sites' IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must

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

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 site personnel, to be handled by its complaint management system.

6.5 Stopping Criteria

6.5.1 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 6.1.2.1

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

6.5.2 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 6.1.2), 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.

6.6 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.

6.7 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 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

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

7.2 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. This should not occur, since participants were required to use either lispro or aspast insulin during the preceding 6-month RCT.

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

7.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

A maximum of $200 will be paid for completing the entire study. Participants will be paid $100 for completing the screening visit and $100 for completing the 13-week visit. No additional payments will be provided for the subsequent clinic visits at 13-week intervals following the 13-week visit, or for unplanned visits to the research site.

- Screening Visit: $100
- 13-week Visit: $100

7.4 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

7.5 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 8: Statistical Consideration

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the first tabulation of data (i.e., for DSMB review).

8.1 Objectives

There are three objectives for this study:

- Objective 1: Among individuals who used CLC in the Main RCT, to compare continued use of CLC (t:slim X2 with Control-IQ Technology) for 3 months versus switching to a Predictive Low-Glucose Suspend (PLGS) system (t:slim X2 with Basal-IQ Technology) for 3 months.
    - RCT with 1:1 randomization to intervention with CLC vs. PLGS for 3 months. All analyses (treatment group comparisons) will be considered exploratory/hypothesis-generating. Consequently, there will not be an attempt to adjust for multiplicity. Time-in-range 70-180 mg/dL will be considered the primary exploratory outcome.
- Objective 2: Among individuals who used SAP in the Main RCT, to obtain additional safety data by initiating use of the Control-IQ system for 3 months.
    - Observational study of initiation and use of CLC for 3 months. Safety outcomes will be tabulated and certain exploratory analyses will be conducted, analyzing metrics as change from baseline (using SAP) to study period (using CLC).
- Objective 3: To obtain additional safety data by continuing use of the Control-IQ system until it becomes commercially available
    - Observational study of initiation and use of CLC for 3 months following use of PLGS for 3 months. Safety outcomes will be tabulated and certain exploratory analyses will be conducted, analyzing metrics as change from baseline (using PLGS) to study period (using CLC).

8.2 Sample Size

The sample size for Objectives 1 and 2 will depend on how many subjects will complete the prior 6-month Original RCT and consent to participate in the extension. However, it is expected that about 100 subjects will be enrolled and randomized for Objective 1 and 50 subjects enrolled for Objective 2.

As the sample size for objective 1 is determined by the preceding RCT and a variance estimate for both the group continuing CLC and the group switching to PLGS is not known (no prior data available to estimate), a power calculation has not been performed.

8.3 Outcome Measures

- *CGM Metrics*
    - Overall Control and Hyperglycemia

- CGM-measured % in range 70-180 mg/dL.
- CGM-measured % above 180 mg/dL
- CGM-measured mean glucose
- % >250 mg/dL
- % >300 mg/dL
- high blood glucose index
- % in range 70-140 mg/dL

- Hypoglycemia
  - % below 70 mg/dL
  - % below 54 mg/dL
  - % <60 mg/dL
  - low blood glucose index
  - hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)

- Glucose variability
  - Coefficient of variation (CV)
  - Standard deviation (SD)

The last 3 months of the Original RCT Study will be used to calculate baseline CGM metrics for the extension study. CGM data starting from randomization into the extension through the 3 month visit will be included in the calculation of each CGM metric. Each metric will be calculated giving equal weight to each CGM reading for each participant. CGM metrics will be computed overall and all for daytime (6am-12mn) and nighttime (12mn-6am) by time of day.

HbA1c

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

Questionnaires:

- Fear of Hypoglycemia Survey (HFS-II) – total score and 3 subscales:
  - Behavior (avoid)
  - Behavior (maintain high BG)
  - Worry
- Hyperglycemia Avoidance Scale – total score and 4 subscales:
  - Immediate action
  - Worry
  - Low BG preference
  - Avoid extremes
- Diabetes Distress Scale – total score and 4 subscales:
  - Emotional burden
  - Physician-related distress
  - Regimen-related distress
  - Interpersonal distress
- Hypoglycemia Confidence Scale – total score
- Clarke Hypoglycemia Awareness Scores
- INSPIRE survey scores
- System Usability Scale (SUS)
- Technology Acceptance Survey
- Control-IQ Patient-Reported Outcomes Questionnaire

Other

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

8.4 Objective 1 Analyses

8.4.1 Principles of Analyses

All analyses comparing the CLC arm with PLGS arm will follow the intention-to-treat (ITT) principle with each participant analyzed according to the treatment assigned by randomization. Safety outcomes will be reported for all enrolled participants.

If more than 5% of participants have fewer than 50% of post-randomization CGM data, the analyses will be replicated excluding such participants. In addition, analyses will be replicated including only those participants from the CLC and PLGS groups who used the system for >80% overall.

The analyses described below 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. The determination of a meaningful baseline imbalance will be based on clinical judgement and not a p-value.

With respect to 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 when using different methods. The following methods will be applied:

- Direct likelihood (analysis described below)
- Rubin's multiple imputation
- Available cases only

8.4.2 Analytic Methods

CGM Metrics

Summary statistics (mean ± SD or median (quartiles)) will be reported for each CGM metric and for differences from pre-randomization by treatment group.

The analyses will be done using direct likelihood. A longitudinal linear regression model will be fit with the metric at baseline and follow-up as the dependent variable. This model will adjust for age as fixed effect and site as a random effect. The analyses will report the point estimate, 95% confidence interval and p-value for the treatment group difference at follow-up. 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.

HbA1c

Summary statistics (mean ± SD or n(%)) will be reported for the central lab HbA1c (continuous variable) at 13-weeks and for differences from randomization by treatment group. A longitudinal

model will be fit using values at randomization and 13 weeks adjusting for age as fixed effect and site as a random effect. Missing data will be handled by direct likelihood in this longitudinal model. This model implicitly adjusts for baseline HbA1c by forcing the treatment groups to have the same mean value at baseline. Local HbA1c values measured at the site will be included as an auxiliary variable (analogous to imputing any missing lab values). Regression diagnostics will be employed as described earlier.

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.

Questionnaires and Other Outcomes

For questionnaires, insulin, weight, and BMI metrics comparisons between treatment arms will be made using similar methods as described above for the continuous HbA1c analysis.

8.4.3 Subgroup Analyses

In exploratory analyses, outcomes for which analyses suggest a treatment group difference 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. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous. If there is insufficient sample size in a given subgroup, the cutpoints for continuous measures may be adjusted per the observed distribution of values. Cutpoint selection for display purposes will be made masked to the outcome data.

- Baseline HbA1c
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Baseline CGM time 70-180 mg/dL
- Age
- Sex
- Race
- Clinical site
- Body mass index
- Income, education, and/or insurance status
- Baseline scores for quality of life, hypoglycemia awareness and fear questionnaires

8.5 Safety Analyses

The following will be summarized and tabulated by treatment group:

- Severe hypoglycemia
- Diabetic ketoacidosis

- Ketone events defined as a calendar day with ketone level >1.0 mmol/L
- CGM-measured hypoglycemic events (defined as at least 15 consecutive minutes <54 mg/dL)
- CGM-measured hyperglycemic events (defined as at least 120 consecutive minutes >300 mg/dL)
- Worsening of HbA1c from randomization to 13 weeks by >0.5%
- Serious adverse events with a possible or greater relationship to a study device (including anticipated and unanticipated adverse device effects)
- Other serious adverse events not related to a study device
- Adverse device effects (ADE) that do not meet criteria for SAE

- For the following, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group:
  - 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.

If there are at least 10 events across both treatment arms, the numbers will be compared between the two treatment arms using a robust Poisson regression and the percentage of subjects with at least one event will be compared using logistic regression. The regression will adjust for site as random effect. The amount of follow up will be included as an offset covariate to compare the rates.

8.6 Device Issues

Reported device issues will be tabulated by treatment group.

8.7 Protocol Adherence

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

- Listing of all protocol deviations
- Tabulation of protocol-specified visits and phone contacts completed in window, out of window and missed for each visit/phone contact
- Flow chart accounting for all enrolled participants
- Flow chart of all randomized participants at all scheduled visits and phone contacts to assess visit, and phone completion, and study completion rates

- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment (CLC or PLGS) and reasons

8.8 Other Tabulations

Baseline demographic and clinical characteristics will be tabulated by treatment group.

Individual listings of key data for each participant will be created.

The following tabulations and analyses will be performed by treatment group:

- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria)
- Sensor use –percent time of use overall and by month
- The daily frequency of downloaded BGM use - overall and by month
- % time CGM data were available to the system – overall and by month
- % time in different operational modes - overall and by month
- Rate of different failure events and alarms per 24 recorded by the system – overall and by month Among women who consent to collection of the menstrual information, an analysis that compares outcomes at different times during the menstrual cycle will be performed overall and by contraception type for selected CGM and insulin metrics.

8.9 Planned Interim Analyses

No interim efficacy analysis is planned.

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 6.5 of the protocol).

8.10 Objective 2 Analyses

All enrolled subjects will be included in the analyses. Although the primary objective is the collection of safety data, analyses will be conducted for the outcomes listed above for Objective 1 comparing baseline to follow up using paired t-tests unless the data are highly skewed in which case a transformation or a robust statistical method will be used instead.

Safety outcomes will be tabulated. Device issues, protocol adherence, and the other variables listed above for tabulation will be described or summarized as indicated.

8.11 Objective 3 Analyses

All enrolled subjects will be included in the analyses. Although the primary objective is the collection of safety data, analyses will be conducted for the outcomes listed above for Objective 1 comparing 3 months of PLGS baseline to 3 months of CLC follow up using paired t-tests unless the data are highly skewed in which case a transformation or a robust statistical method will be used instead.

Safety outcomes will be tabulated. Device issues, protocol adherence, and the other variables listed above for tabulation will be described or summarized as indicated.

Chapter 9: Data Collection and Monitoring

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

9.2 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.

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

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report

- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

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

9.4 Protocol Deviations

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

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

Chapter 10: Ethics/Protection of Human Participants

10.1 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.

10.2 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.

10.3 Informed Consent Process

10.3.1 Consent Procedures and Documentation

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

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

10.3.2 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 study site will permit access to such records.

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

Chapter 11: References

1. Kovatchev, B.P., Breton, M.D., Keith-Hynes, P.T., Patek, S.D. The Diabetes Assistant (DiAs) – Unified platform for monitoring and control of blood glucose levels in diabetic patients; PCT/US12/43910, 2012.
2. Keith Hynes, P., Guerlain, S., Mize, L.B., Hughes Karvetski, C., Khan, M., McElwee Malloy, M. & Kovatchev, B.P. DiAs user interface: A patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol, 7, 1416–1426 (2013). PMID: 24351168
3. Place, J., Robert, A., Ben Brahim, N., Keith Hynes, P., Farret, A., Pelletier, M.J., Buckingham, B., Breton, M., Kovatchev, B.P. & Renard, E. DiAs web monitoring: A real-time remote monitoring system designed for artificial pancreas outpatient trials. J Diabetes Sci Technol, 7, 1427–1435. (2013). PMID: 24351169
4. Keith-Hynes, P., Mize, B., Robert, A., Place, J. The Diabetes Assistant: A smartphone-based system for real-time control of blood glucose. Electronics 2014, 3, 609-623; doi:10.3390/electronics3040609
5. Kovatchev, B.P., Renard, E., Cobelli, C., Zisser, H., Keith-Hynes, P., Anderson, S.M. Brown, S.A. Chernavvsky, D.R., Breton, M.D., Farret, A., Pelletier, M.J., Place, J., Bruttomesso, D., Del Favero, S., Visentin, R., Filippi, A., Scotton, R., Avogaro, A. & Doyle III, F.J. Feasibility of outpatient fully integrated closed-loop control: First studies of wearable artificial pancreas. Diabetes Care, 36, 1851-1858 doi: 10.2337/dc12-1965 (2013). PMID: 23801798, PMCID: PMC3687268
6. Kovatchev, B.P., Renard, E., Cobelli, C., Zisser, H., Keith-Hynes, P., Anderson, S.M., Brown, S.A., Chernavvsky, D.R., Breton, M.D., Mize, L.B., Farret, A., Place, J., Bruttomesso, D., Del Favero, S., Boscari, F., Galasso, S., Avogaro, A., Magni, L., Di Palma, F., Toffanin, C., Messori, M., Dassay, E., Doyle, F. III. Safety of outpatient closed-loop control: First randomized crossover trials of a wearable artificial pancreas. Diabetes Care, 37, 1789-1796 doi: 10.2337/dc13-2076 (2014). PMID: 24929429, PMCID: PMC4067397
7. DeSalvo, D., Keith-Hynes, P., Peyser, T., Place, J., Caswell, K., Wilson, D., Harris, B., Clinton, P., Kovatchev, B.P., Buckingham, B.A. Remote glucose monitoring in camp setting reduces the risk of prolonged nocturnal hypoglycemia. Diabetes Technol Ther, 16, 1-7 doi:10.1089/dia.2013.0139 (2013). PMID: 24168317
8. Ly, T.T., Breton, M.D., Keith-Hynes, P., De Salvo, D., Clinton, P., Benassi, K., Mize, L.B., Chernavvsky, D.R., Place, J., Wilson, D.M., Kovatchev, B.P., Buckingham, B.A. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes Care, 37, doi: 10.2337/dc14-0147 (2014). PMID: 24879841, PMCID: PMC4179507
9. Kropff, J., Del Favero, S., Place, J., Toffanin, C., Visentin, R., Monaro, M., Messori, M., Di Palma, F., Lanzola, G., Farret, A., Boscari, F., Galasso, S., Magni, P., Avogaro, A., Keith-Hynes, P., Kovatchev, B.P., Bruttomesso, D., Cobelli, C., DeVries, J.H., Renard, E., Magni, L., for the AP@home consortium. 2 month evening and night closed-loop glucose control in patients with Type 1 Diabetes under free-living conditions: A randomised crossover trial. Lancet Diabetes Endocrinol, 3(12):939-47 dx.doi.org/10.1016/S2213-8587(15)00335-6 (2015).

10. Renard, E et al. Reduction of hyper- and hypoglycemia during two months with a wearable artificial pancreas from dinner to breakfast in patients with type 1 diabetes. 2015-A-3083-Diabetes. American Diabetes Association 75th Scientific Sessions, Boston, MA, poster 940-P.

11. Anderson, S et al. First New Year's Night on closed-loop control (CLC) at home: Case reports from a multi-center international trial of long-term 24/7 CLC. 2015-A-4763-Diabetes. American Diabetes Association 75th Scientific Sessions, Boston, MA, presentation 223–OR.

12. Kovatchev BP. JDRF Multi-Center 6-Month Trial of 24/7 Closed-Loop Control. Advanced Technologies and Treatments for Diabetes (ATTD), Plenary Session, Milan, Italy, 2016.

13. Kovatchev, B.P. Closed-loop control modalities in type 1 diabetes: Efficacy and system acceptance. Advanced Technologies and Treatments for Diabetes (ATTD), Paris, France, 2015.

14. Del Favero S. A multicenter randomized cross-over Italian pediatric summer camp: AP vs SAP in 5-8 year old children. Advanced Technologies and Treatments for Diabetes (ATTD), Plenary Session, Milan, Italy, 2016.

15. Cherñavvsky, D. et al. Closed-loop control during extended winter-sport exercise in youth with T1DM: Results from the first AP ski camp. ATTD Data Club Session, Milan, (2016).

16. Chernavvsky, D.R., DeBoer, M.D., Keith-Hynes, P., Mize, B., McElwee, M., Demartini, S., Dunsmore, S.F., Wakeman, C., Kovatchev, B.P., Breton, M.D. Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus. Pediatric Diabetes, doi:10.1111/pedi.12230 (2014). PMID: 25348683

17. Brown, S.A., Kovatchev, B.P., Breton, M.D., Anderson, S.M., Keith-Hynes, P., Patek, S.D., Jiang, B., Ben Brahim, N., Vereshchetin, P., Bruttomesso, D., Avogaro, A., Del Favero, S., Boscari, F., Galasso, S., Visentin, R., Monaro, M., Cobelli, C. Multinight "bedside" closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther 17(3), doi:10.1089/dia.2014.0259 (2015). PMID: 25594434, PMCID: PMC4346235

18. Kovatchev BP, Tamborlane WV, Cefalu WT, Cobelli C. The Artificial Pancreas in 2016: A Digital Treatment Ecosystem for Diabetes. Diabetes Care 2016; 39:1123-27. PMID: 27330124

19. Del Favero S, Boscari F, Messori M, Rabbone I, Bonfanti R, Sabbion A, IaFusco D, Schiaffini R, Visentin R, Calore R, Moncada YL, Galasso S, Galderisi A, Vallone V, Di Palma F, Losiouk E1, Lanzola G1, Tinti D, Rigamonti A, Marigliano M, Zanfardino A, Rapini N, Avogaro A, Chernavvsky D, Magni L, Cobelli C, Bruttomesso D. Randomized Summer Camp Crossover Trial in 5- to 9-Year-Old Children: Outpatient Wearable Artificial Pancreas Is Feasible and Safe. Diabetes Care. 2016;39:1180-5. PMID: 27208335

20. Renard E, Farret A, Kropff J, Bruttomesso D, Messori M, Place J, Visentin R, Calore R, Toffanin C, Di Palma F, Lanzola G, Galasso S, Avogaro A, Keith-Hynes P, Kovatchev BP, Del Favero S., Cobelli C, Magni L, DeVries HJ. AP@home Consortium. Day and night closed loop glucose control in patients with type 1 diabetes under free-living conditions: comparison of a single-arm, 1-month experience to results of a previously reported feasibility study of evening and night at home. Diabetes Care 2016; 39:1151-60. PMID: 27208331

21. Anderson SM, Raghinaru D, Pinsker JE, Boscari F, Renard E, Buckingham BA, Nimri R, Doyle FJ III, Brown SA, Keith-Hynes P, Breton MD, Chernavvsky D, Bevier WC, Bradley PK, Bruttomesso D, Del Favero S, Calore R, Cobelli C, Avogaro A, Farret A, Place J, Ly TT, Shanmugham S, Phillip M, Dassau E, Dasanayake IS, Kollman C, Lum JW, Beck RW, and Kovatchev BP. Multinational home use of closed-loop control is safe and effective. Diabetes Care 2016; 39:1143-1150. PMID: 27208316

22. DeBoer MD, Cherñavvsky DR, Topchyan K, Kovatchev BP, Francis GL, Breton MD. Heart rate informed artificial pancreas system enhances glycemic control during exercise in adolescents with T1D. Pediatr Diabetes. 2016; doi: 10.1111/pedi.12454. PMID: 27734563

23. Kovatchev BP, Cheng P, Anderson SM, Pinsker JE, Boscari F, Buckingham BA, Doyle FJ. III, Hood KK, Brown SA. Breton MD, Chernavvsky DR, Bevier WC, Bradley PK, Bruttomesso D, Del Favero S, Calore R, Cobelli C, Avogaro A, Ly TT, Shanmugham S, Dassau E, Kollman C, Lum JW, Beck RW, for the Control to Range Study Group. Feasibility of Long-Term Closed-Loop Control: A Multicenter 6-Month Trial of 24/7 Automated Insulin Delivery. Diabetes Technol Ther 2017; 19: 18-24. doi:10.1089/dia.2016.0333. PMID: 27982707

24. DeBoer MD, Breton MD, Wakeman CA, Schertz EM, Emory EG, Robic JL, Kollar LL, Kovatchev BP, Chernavvsky DR. Performance of an Artificial Pancreas System for Young Children with Type 1 Diabetes. Diabetes Technol Ther 2017; 19, DOI: 10.1089/dia.2016.0424. PMID: 28426239

25. Breton MD, Cherñavvsky DR, Forlenza GP, DeBoer MD, Robic J, Wadwa RP, Messer LH, Kovatchev BP, Maahs DM. Closed Loop Control During Intense Prolonged Outdoor Exercise in Adolescents With Type 1 Diabetes: The Artificial Pancreas Ski Study. Diabetes Care 2017 Aug; dc170883. https://doi.org/10.2337/dc17-0883

26. Gonder-Frederick L, Shepard J, Vajda K, Wakeman C, McElwee M, Kovatchev B: Personality traits and BG profile improvements with continuous glucose monitoring use. Diabetes 61 (Suppl 1):808-P, 2012

27. Jackson DN, Ashton MC, Tomes JL: The six-factor model of personality: Facets from the Big Five. Personality & Individual Differences 21:391-402, 1996

28. Clarke WL, Cox DJ, Gonder-Frederick L, Julian D, Schlundt D, Polonsky W: Reduced Awareness of Hypoglycemia in Adults With IDDM: A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 18:517-522, 1995

29. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, Cox DJ: Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care 34:801-806, 2011

30. Singh H, Gonder-Frederick L, Schmidt K, Ford D, Vajda K, Hawley J, Cox DJ: Assessing Hyperglycemia Avoidance in People with type 1 Diabetes. Diabetes Management 4:263-271, 2014

31. Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating Hypoglycemic Confidence in Type 1 and Type 2 Diabetes. Diabetes Technol Ther. 2017;19(2):131-6.

1666 32. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, Jackson RA: Assessing
1667 psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care
1668 28:626-631, 2005

1669 33. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L: Psychosocial Impact of the Bionic
1670 Pancreas During Summer Camp. J Diabetes Sci Technol, 2016