Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin

Participating Institutions

University of Virginia Center for Diabetes Technology

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KEY ROLES

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed Loop
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
NIH	National Institutes of Health
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SAP	Sensor-Augmented Pump
SD	Standard Deviation
TDI	Total Daily Insulin
UI	User Interface

Signature Page

Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin

Protocol Identifying Number: Winter-Study-2019

IDE Sponsor: Marc Breton, PhD

Version Number: v1.4

2/7/2019

Protocol Chair/Director	
Name, degree	Marc Breton, PhD
Signature / Date	

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin

Protocol Version/Date: v1.4/07FEB2019

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 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: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin
Investigational Device	Control-IQ Artificial Pancreas System with MyTDI
Objectives	The objective of the study is to assess the safety and efficacy of using the Control-IQ artificial pancreas system using MyTDI in a randomized controlled trial.
Study Design	Up to 25 participants may be consented. Up to 20 participants will complete a 5-day at-home data collection period prior to coming to the Ski Admission where they will be randomized in a 1:1 fashion. Half of participants will initiate on the Control-IQ AP with their usual parameters while half will be initiated on the Control-IQ with MyTDI AP system. Participants will continue study treatment for an additional 5 days at home following the end of the Ski Admission.
Number of Sites	1
Endpoint	The primary outcome for the first phase is time in target range 70-180 mg/dL measured by CGM in Control-IQ group vs Control-IQ with MyTDI group over approximately 2 weeks.
Population	**Key Exclusion Criteria** - Age 12-18 - Clinical diagnosis of Type 1 Diabetes **Key Exclusion Criteria** - History of DKA in the past 6 months - History of hypoglycemic seizure or loss of consciousness in the past 6 months
Sample Size	20 participants (up to 25 may be consented)
Treatment Groups	**Group 1 (HCL – Hybrid Closed Loop):** • Control-IQ with usual parameters **Group 2 (MyTDI):** • Control-IQ with MyTDI
Participant Duration	3 weeks
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants will be screened and enter the data collection period for approximately 5 days at home. Participants will then be randomized 1:1 to the use of Control-IQ vs. Control-IQ with MyTDI during a 72 hours ski admission. Following the admission, participants will continue the randomized treatment for approximately 5 days at home.

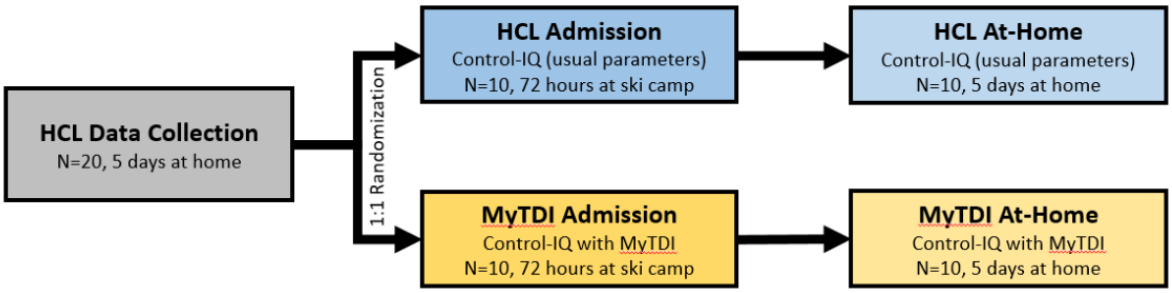

Figure 1: Study Design

Following a 5-day at-home data collection period, participants will be randomized 1:1 to use the Control-IQ system with their usual parameters or the Control-IQ system based on his/her total daily insulin. This treatment will continue through the Ski Admission and for 5 days at home.

Table 1. Schedule of Study Visits and Procedures

	Screening	Post-Training Data Collection	Ski Admission	Post-Admission Data Collection	End of Study
Location	**Clinic**	**Home**	**Ski Lodge**	**Home**	**Home**
Comment	**Screen / Enroll**	**5 Days**	**72 Hours**	**5 Days**	**15-60 min**
Informed Consent	**X**				
Eligibility Assessment	**X**				
Medical History	**X**				
HbA1c	**X**				
Randomization			**X**		
Pregnancy test (if applicable)	**X**		**X**		
Physical Exam	**X**		**X**		
Vital Signs (including height/weight)	**X**		**X**		
Device Data download(s)			**X**		**X**
Wear Study CGM, Insulin Pump, & Activity Tracker		**X**	**X**	**X**	
Group 1: - Control-IQ AP (usual parameters)			**X**		
Group 2: - Control-IQ AP with myTDI			**X**		
Review diabetes management and AEs	**X**	**X**	**X**	**X**	**X**

Chapter 1: Background Information

1.1 Introduction

The Tandem t:slim X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system. The CLC is an "artificial pancreas" (AP) that uses algorithms to automatically manage insulin delivery for people with diabetes based on their blood sugar and calculated insulin needs. This system retains the same control algorithm that was initially tested by UVA's 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 peer-reviewed papers in References). This control algorithm has been implemented in two mobile platforms (DiAs and inControl) and has been tested in over 30 clinical trials by hundreds of adults and children with type 1 diabetes in the United States and overseas

This trial will expand on a number of clinical trials that have extensively tested the AP system in over 350,000 hours of outpatient human use and in several centers in the U.S. and abroad. The italicized IDEs are currently using the t:slim X2 with Control-IQ Technology system proposed in this trial:

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#G160181: Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued; 10/26/2017

19. IDE#150240/S008: A long-term home use study, enrolling 18-70 years old TID participants since January 2018; this study is expected to be completed April 2019; 02/02/18;

20. IDE#G18053 : "The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas - A Pivotal Study of t:slim X2 with Control-IQ Technology"; randomized controlled trial of 6 month at home closed loop system vs. sensor-augmented pump with a 3 month extension phase ; 04/13/18 ;

21. IDE #G180174: "The VRIF Trial: Hypoglycemia Reduction with Automated-Insulin Delivery System"; 08/29/18.

22. IDE#G180053/S007 :"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 ;"A 3-month extension study for participants who completed the prior 6-month randomized controlled trial (RCT) of a closed loop system (Control-IQ) vs. sensor-augmented pump (SAP); [PENDING REVIEW BY AGENCY]

23. IDE#G180053/S008 : "The International Diabetes Closed Loop (iDCL) Trial: Clinical Acceptance of the Artificial Pancreas in Pediatrics - A Pivotal Study of t:slim X2 with Control-IQ Technology"; 4-month parallel group randomized clinical trial with 3:1 randomization to intervention with the closed loop system vs. standard of care (SC); [PENDING REVIEW BY AGENCY]

This trial will test the closed-loop AP system both under home conditions as well as during a stress situation of ski camp while utilizing a new feature, MyTDI, which will be described in more detail in the next section.

1.2 Rationale

The closed-loop AP system works by modulating subcutaneous insulin infusion based on computed real-time needs. Studies have shown that use of an AP system results in increased time in the euglycemic range (70-180 mg/dL), particularly overnight. Challenges persist during times of rapid blood sugar fluctuations, such as following meals or during exercise. Significantly improved glycemic control and fewer hypoglycemic events have been previously demonstrated in pediatric patients using the AP system in summer and winter camp settings. Studies to date have run the system using the foundation of the subject's home insulin parameters, which are often complicated and involve fluctuating basal rates, carbohydrate ratios, and correction factors depending on the time of the day and might not be reflective of his/her true insulin needs. The CLC system allows the user to receive feedback on his/her average total daily insulin needs with a report of Total Daily Insulin (TDI). Clinicians can in turn use TDI to easily determine insulin pump parameters using standard formulas to calculate the optimal basal rate, carbohydrate ratio, and correction factor as follows:

- Basal rate = TDI/48 (half of the daily insulin needs are delivered in the form of basal insulin)
- Correction factor (CF) = 1650/TDI
- Carb ratio (CR) = 450/TDI (to be used for lunch and dinner)
- Carb ratio for breakfast: to achieve a 20% increase in insulin we will use the following carb ratio: CR_{bkfst}=CR/1.2 (to account for increased insulin needs in the morning)

The system can then modify the insulin to keep blood glucose in range as necessary.

This trial aims to demonstrate the safety and feasibility of using MyTDI to determine insulin parameters on the CLC AP system t:slim X2 with Control-IQ technology for use both at ski camp and at home in adolescent patients with type 1 diabetes.

Primary Specific Aim:

To assess the safety and feasibility of using insulin parameters as determined by MyTDI during normal outpatient conditions in the t:slim X2 with Control-IQ Technology AP system.

Secondary Specific Aims:

To assess the safety and feasibility of using insulin parameters as determined by MyTDI during intense exercise outpatient conditions in the t:slim X2 with Control-IQ Technology AP system.

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

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, only one person can use each device as there are rare risks that bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

1.3.1.7 Risk of Injury during Ski/Snowboarding

Bruising, dislocations, sprains, and fractures of the leg and shoulders are very common while participating in these activities.

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 in relation to performing a winter sport exercise (skiing/snowboarding).

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. The individual participant may not benefit from study participation.

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 proceed with the goal of having 20 participants, age 12-18 years, enter the randomized trial, with the expectation that 20 participants will complete the randomized trial. A maximum of 25 individuals may be enrolled into screening for the study in order to achieve this goal.

Participants will be recruited at the University of Virginia.

2.1.1 Informed Consent and Authorization Procedures

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

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.

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.

- Criteria for documented hyperglycemia (at least 1 must be met):
    - Clinical diagnosis of type 1 diabetes (C-peptide levels and antibody determinations are not required)
    - Diagnosis of type 1 diabetes is based on the investigator's judgement
- Criteria for requiring insulin at diagnosis (both criteria must be met):
    - Daily insulin therapy for ≥ 6 months
    - Insulin pump therapy for ≥ 3 months

- Age 12-18 years
- Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra). If using glulisine, subject must be willing to switch to lispro or aspart.
- Treatment with any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas, and naturaceuticals) is permitted if stable on current dose for at least 3 months.
- Willingness to wear a continuous glucose sensor and physiological monitor for the duration of the study.
- For females, not pregnant or breastfeeding. Female subjects who are sexually active should agree to use birth control during the study.

2.3 Participant Exclusion Criteria

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

- Diabetic ketoacidosis in the past 6 months
- Hypoglycemic seizure or loss of consciousness in the past 6 months
- History of seizure disorder
- History of any heart disease including coronary artery disease, heart failure, or arrhythmias
- History of altitude sickness
- Chronic pulmonary conditions that could impair oxygenation
- Cystic fibrosis
- Current use of oral glucocorticoids, beta-blockers or other medications, which in the judgement of the investigator, would be a contraindication to participation in the study.
- History of ongoing renal disease (other than microalbuminuria).
- Subjects requiring intermediate or long-acting insulin (such as NPH, Detemir, or Glargine).
- Pregnancy
- Presence of a febrile illness within 24 hours of the Ski Admission.

- Medical or psychiatric conditions that in the judgement of the investigator might interfere with the completion of the protocol such as:
    - Inpatient psychiatric treatment in the past 6 months
    - Uncontrolled adrenal insufficiency
    - Alcohol abuse

2.4 Screening Procedures

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

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

2.4.1 Eligibility and Baseline Procedures at Screening

The following procedures and testing will be performed to ensure eligibility:

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information
- Medical history
- Concomitant medications and supplements
- Pregnancy Test for women of child-bearing potential (urine)
- Blood draw
- Hemoglobin A1c measured using the DCA2000 or comparable point of care device or local lab; a lab result within 3 months of enrollment may be used at the investigator's discretion
- Physical examination including height, weight, and vital signs (physical exam from the last 12 months may be used at the investigator's discretion)

Chapter 3: Study System Training

3.1 Study Equipment Training

This phase may begin immediately after enrollment is complete. Participants will be trained and begin using the Control-IQ system to manage their glucose levels and insulin delivery at the conclusion of the training session. Participants will discontinue the use of their existing CGM and insulin pump, if applicable. Training on use of the activity tracker (i.e. Fitbit) will also occur. Participants will use the study equipment (study insulin pump, study CGM, study activity tracker) to collect data for approximately 5 days prior to the Ski Admission. During this at-home portion of the study, participants will be remotely monitored by at least one of their parents or care providers, using the Dexcom or Tandem app.

3.1.1 Initiation of CGM

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

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

3.1.2 Initiation of Study Pump

Participants will complete training on the study pump as detailed below.

- The participant will be fully instructed on the study insulin pump. A qualified system trainer (i.e. Certified Diabetes Educator) 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 are not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

3.1.3 Initiation of Activity Tracker

Participants will receive a commercially available activity tracker to collect additional information about movement and heart rate. The activity tracker can be removed during bathing.

3.1.4 Blood Glucose and Ketone Testing

Participants will receive supplies for blood glucose and ketone testing.

- Blood glucose testing
  - Participants will be provided with a study blood glucose meter and test strips.
  - 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.
  - Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.
  - Participants will be given guidelines for treatment of low or high blood glucose.
- Blood ketone testing
  - Participants will be provided with a study blood ketone meter and test strips.
  - 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.
  - Participants will be instructed to perform blood ketone testing as described in section 6.2.4
  - Participants will be given guidelines for treatment of elevated blood ketones
- Participants will be required to have a home glucagon emergency kit. Participants who currently do not have one will be given a prescription for the glucagon emergency kit

3.1.5 Post-Training Check In

The study team will contact the participants approximately 48-72 hours after initiation of the study equipment to discuss:

- Questions or concerns about the study and/or equipment
- Ensure proper use of study equipment
- Ask about the occurrence of any events, including adverse events

Members of the study team are available 24 hours a day to address questions or concerns from the participants. Participants will have the contact information of multiple team members. If there is a medical emergency that requires immediate medical attention, participants will be instructed to call emergency medical services (e.g. 911).

Chapter 4: Ski Admission Procedures

4.1 Admission Check-In Procedures

4.1.1 Participant Check-In & Verification

At time of check-in, participants will undergo the following procedures/tests:

- Vital signs measured
- A fever or had a significant illness within 24-hours of admission will disqualify participant from study
- A fingerstick blood glucose and fingerstick ketone measurement will be obtained
- Female subjects of childbearing potential will be required to complete a urine pregnancy test. If positive, participant will be discontinued from the study.
- Study devices and insertion sites will be inspected
- Confirm that the participant brought his/her personal insulin, study supplies, and regular medications.
- Participants will be asked to perform a blood ketone fingerstick. If ketones >1.5 mmol/L, study staff should treat with oral hydration and, if needed, the Glycemic Treatment Guidelines will be followed; ketones will be re-checked every hour until ≤1.5 mmol/L. The participant will be able to begin participation in the winter sport activities once the CGM reads between 80-300 mg/dL and ketones are ≤1.5 mmol/L.
- Data from the participant's insulin pumps will be reviewed and/or downloaded for a review of pump settings and average of daily insulin delivery.

4.1.2 Randomization

After participants have successfully checked in and are deemed eligible to continue participation in the study, they may be randomized. Using a randomized block design, the participants will be assessed and put in blocks of two according to age and HbA1c. If an identical match is not possible, the closest in age and HbA1c value will be paired and then randomized – one member of each block randomly assigned to each of the two treatment groups.

Participants who randomize to Group 1 Hybrid Closed Loop (HCL) will have no modifications to their insulin pump parameters other than the standard 20% reduction in insulin to account for increased exercise while at ski camp. Participants who randomize to Group 2 (MyTDI) will have modifications to their insulin pump parameters to take into consideration his/her total daily insulin along with the 20% reduction in insulin during ski camp.

The MyTDI adjustments will be as follows:

- A single basal rate equal to TDI/48 will be implemented across the whole day
- A single correction factor of 1650/TDI will be implemented across the whole day

- Carbohydrate ratios will be set at:
    - 0000-04:00 CR=450/TDI
    - 0400-1100 CR=450/TDI)/1.2
    - 1100-0000 CR=450/TDI

TDI will be reduced by 20% of the internal Control-IQ estimation total daily dose; if not available, total daily dose over the last 5 days will be used.

Aside from the insulin pump settings, all other study procedures are identical in the two treatment groups during the Admission and the second at-home portion of the study.

4.2 Main Admission Activities and Procedures

4.2.1 General Admission Overview

During the entire admission, participants will be monitored remotely by the study team. Study team members trained in all protocol interventions (including the hypo and hyperglycemia safety protocols) will be skiing with the participants, with each member remotely connected to the participants CGM data. In addition, a study team member trained in all protocol and glycemic treatment guidelines procedures will be available at a central location in the resort.

All recreational activities will be managed by *'Riding on Insulin'* with study staff supervision.

During the overnight hours, study staff will be actively monitoring real-time CGM data for all participants from a dedicated room in the ski resort with direct access to the participants.

4.2.2 Device Procedures for the Participants

All participants will continue to wear the CGM and insulin pump that was provided to them at the Screening Visit throughout the Admission, with the only difference between the randomized groups being the insulin regimen settings in the AP system.

Participants will have all equipment with them at all times, including a cell phone (personal or study-provided) with the Dexcom Follow App. Participants will be asked to respond to both hypoglycemia and hyperglycemia alarms. If they do not respond to the alarms within 10 minutes, study personnel will assist the subject as per the Glycemic Treatment Guidelines. Participants may be re-educated as needed by the study staff, who will be available at all times to assure proper use of all study equipment.

4.2.3 Participants' Admission Itinerary

Participants will generally follow the below schedule during the Admission:

<u>Evening of Check-in</u>

1500-1900: Check-In & Randomization. Participants will undergo the check-in procedures outlined in section 4.1. Study team will download the study equipment.

1900-2000: Dinner. The study CGM will be used to determine the pre-meal bolus.

2000-2300: Evening Activity.

Day 1

0800-0900: Breakfast. The study CGM will be used to determine the pre-meal bolus.

0900-1200: Morning Ski Activity. Participants will begin the morning ski session if his/her CGM reads >100 mg/dL. If ≤ 100 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1200-1300: Lunch. The study CGM will be used to determine the pre-meal bolus.

1300-1600: Afternoon Ski Activity. Participants will begin the afternoon ski session if his/her CGM reads >100 mg/dL. If ≤ 100 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1600-1800: Quiet time

1800-2000: Dinner. The study CGM will be used to determine the pre-meal bolus.

2200: Bedtime Snack. The study CGM will be used to determine the pre-meal bolus.

2030-2300: Evening Activity.

Day 2

0800-0900: Breakfast. The study CGM will be used to determine the pre-meal bolus.

0900-1200: Morning Ski Activity. Participants will begin the morning ski session if his/her CGM reads >100 mg/dL. If ≤ 100 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1200-1300: Lunch. The study CGM will be used to determine the pre-meal bolus.

1300-1600: Afternoon Ski Activity. Participants will begin the afternoon ski session if his/her CGM reads >100 mg/dL. If ≤ 100 mg/dL, the Glycemic Treatment Guidelines will be followed until cleared to begin activity.

1600-1800: Quiet time

1800-2000: Dinner. The study CGM will be used to determine the pre-meal bolus.

2200: Bedtime Snack. The study CGM will be used to determine the pre-meal bolus.

2030-2300: Evening Activity.

Day 3

0800-0900: Breakfast. The study CGM will be used to determine the pre-meal bolus.

0900-1200: Checkout and discharge to parents. The study staff will adjust all participants' insulin pumps to remove the 20% rate reduction with the cessation of ski activity and in anticipation of the at-home treatment period. Participants will be discharged if appropriate and in accordance with the Glycemic Treatment Guidelines. Participants will be discharged with the study equipment and any supplies needed for the at-home treatment period.

Chapter 5: At-Home Treatment & Study Completion

5.1 At-Home Treatment Continuation

Participants discharged from the Ski Admission will continue the randomized treatment for approximately 5 days at home. Participants are free to engage in their normal daily activities and diets during this time. Participants will receive and be instructed to follow the Glycemic Treatment Guidelines during this time. During the at-home continuation portion of the study, participants will be remotely monitored by at least one of their parents or care providers, using the Dexcom or Tandem app.

5.1.1 Post Admission Follow-up Phone Call

The study team will contact the participants approximately 24-48 hours after they are discharged from the Ski Admission to discuss:

- Questions or concerns about the study and/or equipment
- Ensure proper use of study equipment
- Ask about the occurrence of any events, including adverse events

Members of the study team are available 24 hours a day to address questions or concerns from the participants. Participants will have the contact information of multiple team members. If there is a medical emergency that requires immediate medical attention, participants will be instructed to call emergency medical services (e.g. 911).

5.2 Final Study Visit

The final study visit may be performed remotely (phone) or in-person. After approximately 5 days of at-home use of the study-assigned treatment, participants will be instructed to turn off the Control-IQ system and remove the study equipment. If this visit is performed in person, the participant will return the study equipment to the study team. If this visit is performed remotely, the participant will return the study equipment by mailing it. At this visit, participants will be asked about any existing adverse events and any new adverse events that have not been reported to the study team.

5.3 Early Termination Visit (If Applicable)

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

5.4 Unscheduled Visits

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

5.5 Participant Access to Study Device at Study Closure

Participant will return all investigational study devices and supplies (insulin pump, CGM, activity tracker, 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 after the study team has downloaded all data from the devices.

Chapter 6: Study Devices

6.1 Description of the Investigational Device

6.1.1 Insulin Pump

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

6.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors when using the Tandem t:slim X2 with Control-IQ technology. The CGM sensor will be replaced at least once every 10 days.

6.1.3 Blood Glucose Meter and Strips

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

6.1.3.1 Blood Glucose Meter Testing

- 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.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements.

6.1.3.2 Blood Glucose Meter Supplies

- Participants will be provided all necessary supplies during the study.
- Participants will permitted to keep these devices at the conclusion of the study.

6.1.4 Blood Ketone Meter and Strips

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

6.1.4.1 Blood Ketone Testing

- 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.
- Participants will be instructed on how to perform blood ketone testing.
- Participants will be given guidelines for treatment of elevated blood ketones.

6.1.4.2 Blood Ketone Meter Supplies

- Participants will be provided all necessary supplies during the study.
- Participants will permitted to keep these devices at the conclusion of the study.

6.1.5 Activity Tracker

- Participants will be trained on the study activity tracker that will be used to collect additional information about movement and heart rate.
- Participants will be asked to wear the device during the entire study. The monitor can be removed during bathing.

6.1.6 Study Device Accountability Procedures

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

6.1.7 Blood Ketone Testing

- 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.
- Participants will be instructed on how to perform blood ketone testing.
- Participants will be given guidelines for treatment of elevated blood ketones.

6.2 Safety Measures

6.2.1 CGM Calibration

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

6.2.2 System Failure

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

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

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

6.2.3 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 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.

If a participant's CGM reading is <80 mg/dL, the Glycemic Treatment Guidelines will be followed.

6.2.4 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 Glycemic Treatment Guidelines will be followed.

Chapter 7: Point-of-Care Testing

7.1 Point-of-Care Samples

1. HbA1c:

- Performed locally at the Screening visit or a lab result that was completed within 2 weeks prior to the Screening visit.

2. Urine Pregnancy:

- Performed locally for females of child-bearing potential at the Screening visit and prior to the start of the Ski Admission.

Chapter 8: Adverse Events, Device Issues, and Stopping Rules

8.1 Adverse Events

8.1.1 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 8.1.2 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.

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.

8.1.2 Reportable Adverse Events

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

1. A serious adverse event
2. An Adverse Device Effect as defined in section 8.1.1, unless excluded from reporting in section 8.
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

Pregnancy occurring during the study will not be considered an adverse event.

8.1.2.1 Hypoglycemic Events

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

8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

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

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.5 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

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

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

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

8.1.3 Relationship of Adverse Event to Study Device

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

8.1.4 Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

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

8.1.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

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

8.1.6 Outcome of Adverse Event

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

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

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

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

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

8.2 Reportable Device Issues

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

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

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication

- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

8.3 Pregnancy Reporting

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

8.4 Timing of Event Reporting

SAEs must be reported to the IRB per IRB reporting guidelines for this protocol.

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

Upon knowledge of an UADE, the investigator will investigate the UADE and if indicated, report the results of the investigation to the IRB, and the FDA within ten working days of the investigator 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.

8.5 Stopping Criteria

8.5.1 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
- One episode of DKA
- One severe hypoglycemia event as defined in section 8.1.2.1

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

8.5.2 Criteria for Suspending or Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 8.1.2.2), use of the study device system will be suspended while the problem is diagnosed.

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

The study medical monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. 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.

8.6 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

Chapter 9: Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

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

9.2 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.

Treatment with any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals) will be reviewed by the study team. Use of these agents must be approved by the investigator prior to initiation of study equipment.

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

9.3 Participant Compensation

Participants will not receive compensation or reimbursement for his/her participation in this study.

9.4 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.

9.5 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. De-identified participant information may also be provided to Tandem for system evaluation purposes.

Chapter 10: Statistical Consideration

10.1 Statistical and Analytical Plans

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

10.2 Statistical Hypotheses

The hypotheses for the primary outcome are:

a. *Null Hypothesis*: the use of MyTDI results in a decreased percentage of the time spent between 70-180mg/dL during home use

b. *Alternative Hypothesis* : the use of MyTDI does not results in a decreased percentage of the time spent between 70-180mg/dL during home use

All outcomes will be analyzed using repeated measure ANOVA between baseline and the studied period, using within-between factors.

We will compute all outcome for baseline, camp, and the final home segment. Outcomes will be further refined to focus on daytime (7am-11pm), nighttime (11pm-7am), and for the Ski Admission, ski time (9am-noon & 1:30pm-4:30)

10.3 Sample Size

We set the study to detect an effect size of 0.25 using repeated measure ANOVA and a within-between comparison (baseline – home, grouped by treatment), assuming 0.75 correlation between measurements. With N=20 we expect to reach 85% power, allowing for up to 2 participants (10%) to fail to complete the study.

10.4 Outcome Measures

10.4.1 Primary Efficacy Endpoint

The primary outcome for this study is the percent of time spent between 70mg/dL and 180mg/dL as computed by the number of CGM values falling in this interval divided by the total number of available CGM values. CGM gaps inferior to 3 hours will be linearly interpolated

10.4.2 Secondary Efficacy Endpoints

Additional CGM outcomes will include:

- Percent CGM below 50mg/dL
- Percent CGM below 54mg/dL
- Percent below 60mg/dL
- Percent CGM below 70mg/dL

- Percent CGM above 180mg/dL
- Percent CGM above 250mg/dL
- Percent CGM above 300mg/dL:
- Average CGM
- CGM coefficient of variation
- CGM based LBGI & HBGI

Furthermore, we will compute

- Total amount of insulin used
- Number of Hypoglycemic episodes as defined by contiguous CGM below 70mg/dL
- Number of rescue CHO
- Total amount of rescues CHO

10.4.2.1 Safety Analyses

All randomized participants will be included in these analyses and the circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Other serious adverse events and serious adverse device events
- Unanticipated adverse device effects

10.5 Device Issues

The following tabulations and analyses will be performed by treatment group to assess device issues:

- Device malfunctions requiring study team contact and other reported device issues
- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- % time CGM data available - overall and by month

The following tabulations will be performed for the CLC arm only:

- Performance metrics, describing the Control-IQ system and its components like:
  - % time CGM data were available to the Control-IQ system – overall and by month

- % time in different operational modes per week - overall and by month
- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by month

Chapter 11: Data Collection and Monitoring

11.1 Case Report Forms and Device Data

The main study data are collected through a combination of 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.

11.2 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.

11.3 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.

Chapter 12: Ethics/Protection of Human Participants

12.1 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.

12.2 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.

12.3 Informed Consent Process

12.3.1 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. 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.

12.3.2 Participant and Data Confidentiality

The medical 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 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.

Chapter 13: References

1. Anderson SM, Raghinaru D, Pinsker JE, et al. Multinational Home Use of Closed-Loop Control Is Safe and Effective. Diabetes Care 2016;39:1143-50.

2. Breton MD, Brown SA, Karvetski CH, et al. Adding heart rate signal to a control-to-range artificial pancreas system improves the protection against hypoglycemia during exercise in type 1 diabetes. Diabetes Technol Ther 2014;16:506-11.

3. Breton MD, Chernavvsky DR, Forlenza GP, et al. Closed-Loop Control During Intense Prolonged Outdoor Exercise in Adolescents With Type 1 Diabetes: The Artificial Pancreas Ski Study. Diabetes Care 2017;40:1644-50.

4. Breton MD, Patek SD, Lv D, et al. Continuous Glucose Monitoring and Insulin Informed Advisory System with Automated Titration and Dosing of Insulin Reduces Glucose Variability in Type 1 Diabetes Mellitus. Diabetes Technol Ther 2018;20:531-40.

5. Chernavvsky DR, DeBoer MD, Keith-Hynes P, et al. Use of an artificial pancreas among adolescents for a missed snack bolus and an underestimated meal bolus. Pediatr Diabetes 2016;17:28-35.

6. Cobelli C, Renard E, Kovatchev BP, et al. Pilot Studies of Wearable Outpatient Artificial Pancreas in Type 1 Diabetes. Diabetes Care 2012;35:e65-e7.

7. DeBoer MD, Breton MD, Wakeman C, et al. Performance of an Artificial Pancreas System for Young Children with Type 1 Diabetes. Diabetes Technol Ther 2017;19:293-8.

8. DeBoer MD, Chernavvsky 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 2017;18:540-6.

9. Del Favero S, Boscari F, Messori M, et al. 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.

10. Gildersleeve R, Riggs SL, Chernavvsky DR, Breton MD, DeBoer MD. Improving the Safety and Functionality of an Artificial Pancreas System for Use in Younger Children: Input from Parents and Physicians. Diabetes Technol Ther 2017;19:660-74.

11. Keith-Hynes P, Guerlain S, Mize B, et al. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol 2013;7:1416-26.

12. 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.

13. Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36:1851-8.

14. Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 2014;37:1789-96.

15. Kovatchev B, Cheng P, Anderson SM, et al. 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.

16. Ly TT, Buckingham BA, DeSalvo DJ, et al. Day-and-Night Closed-Loop Control Using the Unified Safety System in Adolescents With Type 1 Diabetes at Camp. Diabetes Care. United States2016:e106-7.

17. Place J, Robert A, Ben Brahim N, et al. DiAs web monitoring: a real-time remote monitoring system designed for artificial pancreas outpatient trials. J Diabetes Sci Technol 2013;7:1427-35.

18. Sanchez-Pena R, Colmegna P, Garelli F, et al. Artificial Pancreas: Clinical Study in Latin America Without Premeal Insulin Boluses. J Diabetes Sci Technol 2018;12:914-25.

19. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795-805.

20. Troncone A, Bonfanti R, Iafusco D, et al. Evaluating the Experience of Children With Type 1 Diabetes and Their Parents Taking Part in an Artificial Pancreas Clinical Trial Over Multiple Days in a Diabetes Camp Setting. Diabetes Care 2016;39:2158-64.

21. Zisser H, Renard E, Kovatchev B, et al. Multicenter closed-loop insulin delivery study points to challenges for keeping blood glucose in a safe range by a control algorithm in adults and adolescents with type 1 diabetes from various sites. Diabetes Technol Ther 2014;16:613-22