Signature Page

Control-IQ 2.0 Feasibility Study #2: Use of Control-IQ Technology 2.0 in Adults, Children, and Preschoolers with Type 1 Diabetes

Protocol Identifying Number: TP-0011713

IDE Number: G220181

IDE Sponsor: Tandem Diabetes Care, Inc.

Version Number: v 3.0

20 SEP 2022

Medical Monitor and Protocol Chair	
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Protocol Revision History

Version Number	Amendment Date	Brief Description of Changes
1.0	16 MAY 2022	Initial Version Submitted to FDA
2.0	27 JUL 2022	Initial Version Approved by FDA
3.0	20 SEP 2022	Updated for consistency between sections and figures: • Study schematic figure updated to note Sleep Activity is required • Synopsis and Section 3.4 updated to add day 1 contact to match tables • Section 2.3.1 and 3.3: Clarified pregnancy test is for females "of childbearing potential" • Section 3.3: Clarified target is 112.5 mg/dL to be consistent with rest of protocol • Section 3.:4 Corrected visit numbers 10 and 14, and updated reference to section 3.4.1 Section 6.24: Clarified when a hyperglycemia/ketotic event qualifies as an AE, or as a SAE, an adverse event form should be completed.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
AID	Automated Insulin Dosing
BGM	Blood Glucose Meter
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
DCCT	Diabetes Control & Complications Trial
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ICF	Informed consent form
ICH	International Conference of Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
RBM	Risk-Based Monitoring
SAE	Serious Adverse Event
T1D	Type 1 Diabetes
UADE	Unanticipated Adverse Device Effect

Site Principal Investigator Statement of Compliance

Protocol Identifying Number:	TP-0011713
Protocol Name:	Control-IQ 2.0 Feasibility Study #2: Use of Control-IQ Technology 2.0 in Adults, Children, and Preschoolers with Type 1 Diabetes
Protocol Version / Date:	3.0 / 20 SEP 2022

The Principal Investigators (undersigned) hereby declare that they have read this protocol and agree to its contents.

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

By written consent to this protocol, the investigators agree to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation, including source data, by authorized individuals representing Tandem Diabetes Care, Inc., IRBs and/or by the US Federal, State and local regulatory authorities.

Investigator Name: _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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PROTOCOL SUMMARY

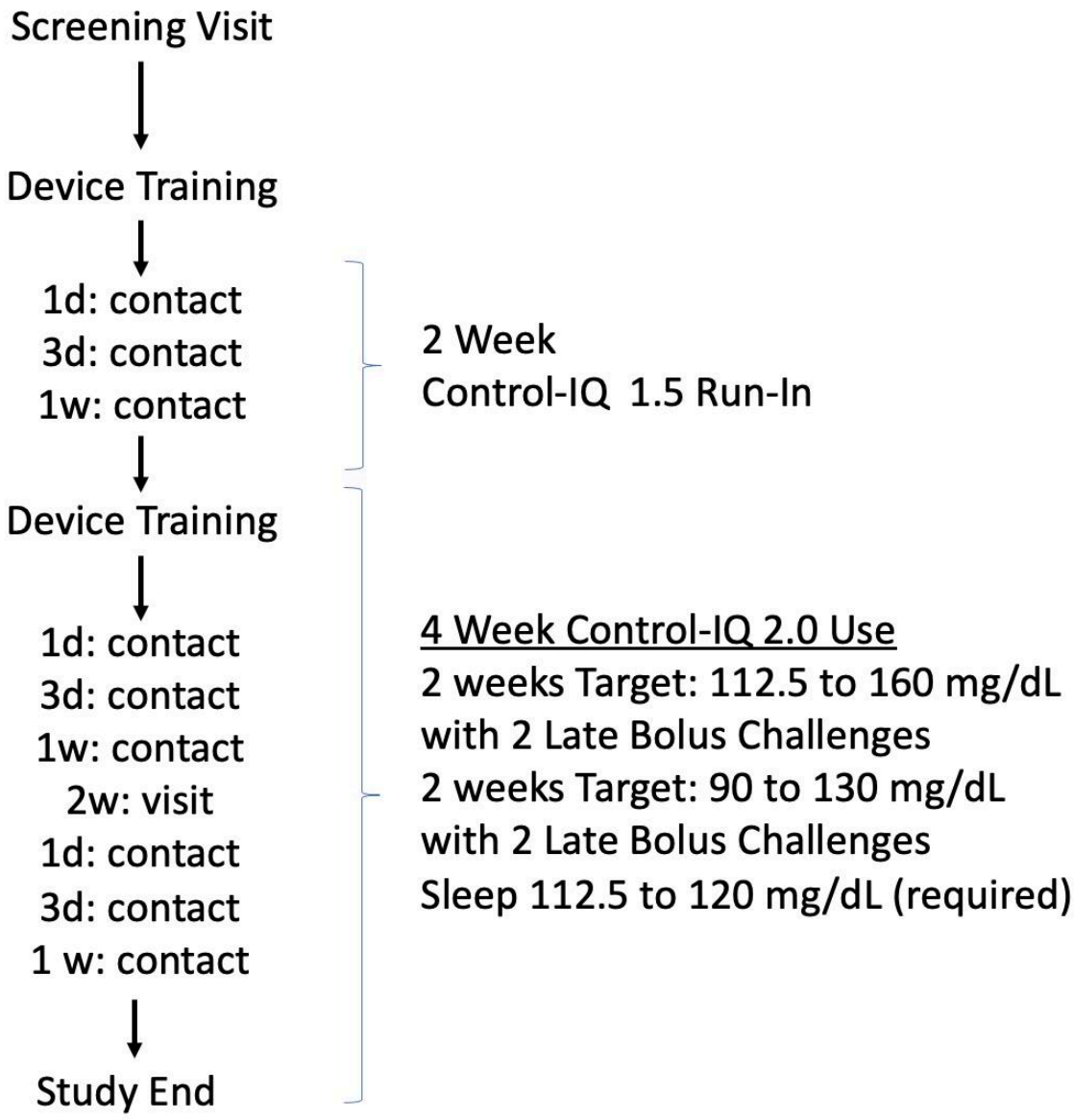
Study Sponsor	Tandem Diabetes Care, Inc.
Protocol Number	TP-0011713
Protocol Title	Control-IQ 2.0 Feasibility Study #2: Use of Control-IQ Technology 2.0 in Adults, Children, and Preschoolers with Type 1 Diabetes
Précis	This feasibility study is a prospective, randomized, two-period crossover multi-center study of 2 weeks of home use of Control-IQ 1.5 technology (run-in period), followed by 2 weeks of home use of Control-IQ 2.0 technology at one target, followed by 2 weeks of home use of Control-IQ 2.0 at another target. This automated insulin dosing (AID) system will be evaluated in multiple age groups, with late bolus meal challenges.
Products	t:slim X2 insulin pump with Control-IQ technology 1.5 (Run-In Period) t:slim X2 insulin pump with Control-IQ technology 2.0 (Treatment Periods)
Objectives	The objectives of the study are to assess safety of and explore glycemic outcomes with Control-IQ technology 2.0 in adults, children and preschoolers with type 1 diabetes using different targets and after late bolus meal challenges.
Number of Sites	Up to 6 clinical sites in the US.
Study Design	Randomized sequence, prospective safety study
Number of Participants	Up to 100 participants signing consent to use the study devices, so that at least 72 complete the study (at least 30 participants age 14+, at least 30 participants age 6-13, and at least 12 participants age 2-5), plus local contacts for adult participants. Enrollment goal is at least 50% of all participants in each age group have an HbA1c at baseline of ≥ 7.5%.
Participant Population:	**Eligibility to enroll in the study will be assessed based on the following inclusion criteria:** 1. Age 2 to ≤ 81 years 2. Diagnosis of type 1 diabetes for at least 1 year, or at least 6 months for age 2-5 years at enrollment 3. Prior Dexcom CGM user, with at least 11 of the prior 14 days of CGM use available for download at the screening visit to confirm eligibility 4. Total Daily Insulin Dose (TDD) at least 2 units/day 5. Weight ≥ 20 lbs 6. HbA1c ≤ 10.5% 7. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia, present with the participant during and for 5 hours (3 hours for participants age 2-5) after the meal challenges, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study. 8. For participants ≥18 years old, availability of a local contact who has access to the study participant, knows their whereabouts, can be available to assist during the late bolus meal challenges, agrees to be promptly available if contacted by study staff, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study. If the participant lives alone, the local contact must live within 30 minutes and have access to the subject overnight. 9. Investigator has confidence that the participant and/or parent/guardian can successfully operate all study devices and is capable of adhering to the protocol. 10. Willing to use only aspart (novolog) or lispro (humalog) insulin with the study devices, with no use of long-acting basal insulin injections, or inhaled insulin with the study devices. 11. Have current glucagon product to treat severe hypoglycemia (injectable or nasal) at home (site will provide prescription if they do not have one)

	12. Willing and able to perform the study late bolus meal challenges. **Eligibility to enroll in the study will be assessed based on the following exclusion criteria:** 1. More than 1 episode of diabetic ketoacidosis (DKA) in the past 6 months 2. More than 1 episode of severe hypoglycemia (needing assistance) in the past 6 months 3. Inpatient psychiatric treatment in the past 6 months 4. For Female: Currently pregnant or planning to become pregnant during the time period of study participation a. *A negative pregnancy test will be required for all females of child-bearing potential* *b. Counseling on appropriate birth control options will be provided to all females of child-bearing potential* 5. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 6. Hemophilia or any other bleeding disorder 7. Hemoglobinopathy 8. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study 9. History of allergic reaction to Humalog or Novolog 10. Use of any medications determined by investigator to interfere with study 11. Significant chronic kidney disease (which could impact CGM accuracy in investigator's judgment) or hemodialysis 12. Concurrent use of any medication that could interfere with the study CGM, such as hydroxyurea 13. History of adrenal insufficiency 14. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated 15. History of gastroparesis 16. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk 17. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation 18. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial
Participant Duration	Approximately 6-12 weeks

Study Endpoints	The adult, pediatric and preschool populations will be combined for the analysis of primary and secondary endpoints. Separate analyses also will be performed for the adult, pediatric and preschool cohorts for the primary and secondary endpoints. CGM data collected during the challenge periods will not contribute to overall analysis of CGM metrics. The three study time periods are the Run-In period with Control-IQ technology 1.5, treatment period with Control-IQ technology 2.0 at the standard target, and treatment period with Control-IQ technology 2.0 at the lower target, where the order of treatment periods will be randomized. Primary Endpoints: 1. Severe hypoglycemia (with cognitive impairment such that assistance of another individual is needed for treatment) during study compared with data on severe hypoglycemic events reported by T1D Exchange clinic registry over a 3-month time period 2. Diabetic ketoacidosis during study compared with data on DKA events reported by T1D Exchange clinic registry over a 3-month time period 3. Number of unanticipated adverse device effects 4. Number of other serious device-related adverse events Secondary Endpoints: 1. All device-related adverse events 2. CGM hypoglycemia outcomes, compared between the three study time periods a. Overall % time <54 mg/dL b. Overall % time <70 mg/dL 3. Times in ranges-overall (70-180 mg/dL, >180 mg/dL, >250 mg/dL, 70-140 mg/dL) compared between the three study time periods 4. Mean glucose compared between the three study time periods 5. Overall variability (CV and SD) compared between the three study time periods 6. Secondary endpoints 2 – 5 compared during daytime and nighttime, across the three study time periods 7. Secondary endpoints 2 - 5 as well as adverse events, during the study meal challenge periods, for late bolus feature use compared to normal bolus in the meal challenges. 8. Time to intervention for hypo- or hyperglycemia during the study meal challenge periods, for late bolus feature use compared to normal bolus in the meal challenges. 9. Number of interventions for hypo- or hyperglycemia during the study meal challenge periods for late bolus feature use compared to normal bolus in the meal challenges. 10. Subgroup Analysis for all metrics by age cohort, baseline HbA1c cohort, and target activity use (standard target, lower target, sleep activity, exercise activity)
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. <u>Run-In Period</u>: Participants will return to clinic to undergo device training with the study CGM and a Control-IQ technology 1.5 pump. Training for both devices may be combined, or depending on comfort level of investigator and participant, participants may return for a second session to complete device training and begin the Control-IQ 1.5 run in period. The run-in period will end after 2 weeks of Control-IQ technology 1.5 use. Participants will have a phone follow up phone call at 1 day, 3 days and 1 week after starting Control-IQ technology 1.5 use, and will return to clinic at two weeks to commence Control-IQ technology 2.0 training. <u>Treatment Periods</u>: Participants will then use the study pump with Control-IQ technology 2.0 for 4 weeks during the study period (2 weeks with a lower target of 90-130 mg/dL, and 2 weeks with a standard target of 112.5-160 mg/dL, in random order). Participants will have a follow up contact at 1

	day, 3 days and 1 week into Control-IQ 2.0 use, a follow-up visit at 2 weeks to switch targets, a follow up contact 3 days later and 1 week after switching targets, and a follow up visit at 4 weeks to end the study. Participants will use the t:slim X2 insulin pump with Control-IQ technology 2.0 turned on. It is acceptable to use manual mode when there is a loss of CGM data. Each participant will perform 2 late bolus meal challenges in each two-week period, contacting the study clinical site before and after each challenge. An assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events, and their underlying cause and relationship to the study device or other parts of the system (such as the infusion set), will occur at all visits/contacts. <u>Study Safety Plan</u>: Participants will be given a blood glucose and ketone meter to use throughout the study, and will be trained on their use by qualified staff. BGM readings will be performed in accordance with the participant instruction sheet and per CGM manufacturer instructions. Ketone readings will be performed per the participant instruction sheet. Site investigators may adjust insulin delivery profile settings as needed throughout the study in accordance with their clinical practice. Real-time CGM alerts will be sent to study staff providers (MD, DO, NP, PA) for the first ten 6-13 year old participants to begin use of the lower target (90-130 mg/dL) for the first week of Control-IQ 2.0 use at that target. In addition, real-time CGM alerts will be sent to study staff providers for all 2-5 year old participants throughout their use of Control-IQ 2.0 technology (all 4 weeks).

SCHEMATIC OF STUDY DESIGN



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SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	UV
		Run-In Period				Treatment Period									
	Screening Visit	Control-IQ 1.5 Training Visit	Control-IQ 1.5 Run-In Period			Control-IQ 2.0 Training	Control-IQ 2.0 Treatment Period 1				Control-IQ 2.0 Treatment Period 2				
		Up to 2 weeks after screening	1d	3d	1w	2w	1d	3d	1w	2w	1d	3d	1w	2w (Final Visit)	UV
Visit (V) or Contact (C)	V	V	C	C	C	V	C	C	C	V	C	C	C	V	V/C
Informed Consent	X														
Eligibility Assessment	X														
Medical history/ physical exam	X														
Height, weight, blood pressure and pulse	X														
HbAlc (POC or local lab)	X														
Pregnancy test (females of child-bearing potential)	X	X[2]				X									
Questionnaires						X				X				X	
Assessment of Device Use	X					X									
Study system training		X				X				X					
Late Meal Bolus Challenges[1]								X				X			
AE/Device Issue Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X
Upload and Review Study Device Data			X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Late meal bolus challenges will occur throughout Control-IQ 2.0 use in the treatment period, with 2 challenges in each 2 week period.

[2]Pregnancy test at Control-IQ 1.5 device training does not need to be repeated if screening and Control-IQ 1.5 training visits are performed on the same day.

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Chapter 1: Background Information

1.1 Introduction

1.1.1 Disease Background

Type 1 diabetes affects 1.25 million people in the United States. Approximately 70% of individuals with type 1 diabetes report poor metabolic control, and do not meet the American Diabetes Association's recommended goal of hemoglobin A1c (HbA1c) level of 7.0%. These findings indicate the need for better approaches to type 1 diabetes management.

1.1.2 Tandem X2 Insulin Pump with Control-IQ Technology

The Tandem X2 insulin pump with Control-IQ technology is an FDA-approved closed-loop control (CLC) system based on the control algorithm developed and initially tested in the University of Virginia's DiAs system and then implemented in the inControl system (TypeZero, Technologies, Inc.). Use of the Control-IQ system has been extensively tested in adults and children with type 1 diabetes (T1D), demonstrating its efficacy and safety when used with insulin lispro (Humalog) or insulin aspart (Novolog).[1,2] The system is currently approved for ages 6 years and older and its use in younger children is currently being studied (clinical trials.gov NCT04796779). There are over 150,000 users of the system since it became commercially available in 2020. A recent evaluation of real-world use of the system in 9,451 users age $\geq$6 years with at least 12 months of system use found results comparable to those found in the randomized trials.[3]

Since the initial approval of the system, modifications have been made in the software, which is referred to as version 1.5. These modifications include modest usability improvements and other enhancements intended to further reduce risk. The Control-IQ 1.5 system also allows for a wider range of inputs to weight and total daily insulin, allowing it to be used by a broader group of individuals with diabetes, and has been evaluated in numerous clinical trials (NCT04796779, NCT05111301, NCT05403502).

Control-IQ technology 2.0 incorporates all the changes in version 1.5, and adds several new features intended to improve time-in-range with no significant increase in hypoglycemia. These changes also include features to improve safety around exercise, and to make bolusing for meals safer. Control-IQ technology 2.0 was recently studied in 30 adults and adolescents age 14+, with over 20,000 hours of use, and showed improvements in time in range without increases in hypoglycemia (NCT05014789).

1.2 Rationale

The objective of this randomized, prospective, two-period crossover study conducted in three age cohorts is to assess safety and explore glycemic outcomes associated with use of Control-IQ technology 2.0 including Adults and Adolescents age 14+ years old, children age 6-13 years old, and preschool children age 2-5 years old. Participants will evaluate Control-IQ 2.0 technology using different glycemic targets, as well as perform late bolus meal challenges.

1.3 Potential Risks and Benefits

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these events.

1.3.1 Known Potential Risks

1.3.1.1 Blood Draw

A venipuncture and/or fingerstick will be performed to obtain blood for HbA1c measurement. Venipuncture can cause 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. A fingerstick frequently causes transient pain and there may be a small, localized bruise, which may be followed by a small scar that may persist for several weeks. The risk of local infection is less than 1 in 1000 with either venipuncture or fingerstick.

1.3.1.2 CGM and Pump Catheter Risks

There is a small risk of bleeding where the sensor or infusion set is inserted. There is a small risk for developing a local skin infection at the site of CGM sensor placement of pump infusion set placement. This may be associated with swelling, redness and pain; and may require antibiotic therapy. Rarely, a CGM sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site.

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.

1.3.1.3 Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having 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. 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. The study meal challenges, requiring boluses to be delivered late, could increase the risk of hypoglycemia.

1.3.1.4 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. The study meal challenges, requiring boluses to be delivered late, could increase the risk of hyperglycemia.

1.3.1.5 Risk of Device Reuse

All devices will be used by a single study participant only. There will be no device reuse.

1.3.1.6 Potential Risks of the CLC System

Even though the study system has been tested prior to this study, there is still a risk that parts of the system may not function properly. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery system;

- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin.

1.3.1.7 Other Risks

Data downloaded from the CGM, pump, and the home glucose and ketone meter will be collected for the study. The downloaded data from the participant's home devices at the screening visit may include data from the period beyond the last 2 weeks prior to screening. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

1.3.2 Benefits

Participants may achieve better glucose control than they are currently achieving using their home insulin pump.

The individual participant may not benefit from study participation.

1.3.3 Risk Assessment

Based on the facts that (1) individuals with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2), 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 (3) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the Sponsor that this protocol is an investigation involving a minor increase over minimal risk. In addition, it is the belief of the Sponsor 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 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).

In accordance with 21 CFR 812.66, the protocol is considered a significant risk device study, due to the fact that the intervention is investigational. 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 Lead-in Period

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of having up to 100 subjects screened, so that at least 72 complete closed loop use (at least 30 participants age 14+, at least 30 participants age 6-13, and at least 12 participants age 2-5), plus local contacts for adult participants.

Enrollment will be staged, so that at least ten 6-13 year olds will complete the trial before enrolling any 2-5 year olds. A trial level safety review with the study coordinating center, sponsor and the site primary investigators will be performed, summarizing the data after the first ten 6-13 year olds who complete this trial. Criteria to begin enrolling 2-5 years will include 1) No UADE's affecting participant safety, 2) Study Stopping Criteria have not been met overall (total AE's related to DKA or severe hypoglycemia), 3) No safety concerns from all parties and approval from all parties to continue the study. This review will be documented in the trial master file.

An enrollment goal is to have at least 50% of all participants in each age group have an HbA1c at baseline of ≥ 7.5%, and to have at least 6 participants age 14-17 years old.

Study participants will be recruited from up to 6 clinical centers in the United States without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal.

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 or electronic informed consent will be obtained.

For potential study participants, 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 participants less than 18 years of age, a parent/legal guardian will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Assent will be obtained from subjects 7 to <18 years of age. A legally authorized representative (parent/guardian) must sign the consent form for all participants less than 18 years of age, and agree to the CGM monitoring requirements of the study.

A copy of the consent/assent form will be provided to the participant and if the participant is a minor, his/her parent/guardian, 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 and/or parent/guardian, questions will be answered about the details regarding authorization.

A local contact is required for all participants > 18 years of age. Each local contact must sign the local contact consent form, and agree to the CGM monitoring requirements of the study.

A participant is considered enrolled when the informed consent form has been signed.

2.2 Participant Eligibility Criteria

2.2.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age 2 to ≤ 81 years
2. Diagnosis of type 1 diabetes for at least 1 year, or at least 6 months for age 2-5 years at enrollment
3. Prior Dexcom CGM user, with at least 11 of the prior 14 days of CGM use available for download at the screening visit to confirm eligibility
4. Total Daily Insulin Dose (TDD) at least 2 units/day
5. Weight ≥ 20 lbs
6. HbA1c < 10.5%
7. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia, present with the participant during and for 5 hours (3 hours for participants age 2-5) after the meal challenges, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study.
8. For participants ≥18 years old, availability of a local contact who has access to the study participant, knows their whereabouts, can be available to assist during the late bolus meal challenges, agrees to be promptly available if contacted by study staff, and willing to use the Dexcom Follow app (with push notifications turned on) for the duration of the study. If the participant lives alone, the local contact must live within 30 minutes and have access to the subject overnight.
9. Investigator has confidence that the participant and/or parent/guardian can successfully operate all study devices and is capable of adhering to the protocol.
10. Willing to use only aspart (novolog) or lispro (humalog) insulin with the study devices, with no use of long-acting basal insulin injections, or inhaled insulin with the study devices.
11. Have current glucagon product to treat severe hypoglycemia (injectable or nasal) at home (will provide prescription if they do not have one).
12. Willing and able to perform the study late bolus meal challenges.

2.2.2 Exclusion Criteria

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

1. More than 1 episode of diabetic ketoacidosis (DKA) in the past 6 months
2. More than 1 episode of severe hypoglycemia (needing assistance) in the past 6 months
3. Inpatient psychiatric treatment in the past 6 months
4. For Female: Currently pregnant or planning to become pregnant during the time period of study participation
    - *A negative pregnancy test will be required for all females of child-bearing potential*

- *Counseling on appropriate birth control options will be provided to all females of child-bearing potential*

5. Concurrent use of any non-insulin glucose-lowering agent, other than metformin (for example, GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).
6. Hemophilia or any other bleeding disorder
7. Hemoglobinopathy
8. History of heart, liver, lung or kidney disease determined by investigator to interfere with the study
9. History of allergic reaction to Humalog or Novolog
10. Use of any medications determined by investigator to interfere with study
11. Significant chronic kidney disease (which could impact CGM accuracy in investigator's judgment) or hemodialysis
12. Concurrent use of any medication that could interfere with the study CGM, such as hydroxyurea
13. History of adrenal insufficiency
14. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated
15. History of gastroparesis
16. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk
17. Participation in another pharmaceutical or device trial at the time of enrollment or anticipated for during the time period of study participation
18. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

2.3 Visit 1: Screening Visit

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

2.3.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant). Height, weight and vital signs may be recorded by appropriately delegated office staff.

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

- Inclusion and exclusion criteria assessed
- Demographics (age or year and month of birth for preschool participants, sex, race and ethnicity and socioeconomic information)
- Subject initials to verify eCRF entry is associated with the correct individual

- Contact information (retained at the site and not entered into study database)
- Medical history
- Concomitant medications
- Physical examination to include:
    - Weight, height
    - Vital signs including measurement of blood pressure and pulse
- Blood draw (venipuncture or fingerstick) for local HbA1c measurement
- Urine pregnancy test for all females of childbearing potential who are premenopausal and not surgically sterile
- Current device download, to include insulin pump and CGM device data, for up to the last two weeks of data if available

Screening procedures will last approximately 1-2 hours. The screening visit must occur in clinic and cannot be performed remotely.

2.4 Screen Failures

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

Chapter 3: Device Training and Study Visits

3.1 Visit 2: Control-IQ 1.5 Training Visit

After screening, participants will have a clinic visit at which they will undergo CGM and Control-IQ 1.5 technology pump device training.

The device training visit should be completed within 2 weeks of screening, and may be performed the same day as the screening visit. If not completed within 2 weeks of screening, re-review of screening results by the investigator should be performed, who may ask for repeated testing as per investigator judgement. The device training visit may be extended over the course of more than 1 session if needed. The device training visit must occur in clinic and cannot be performed remotely.

A urine pregnancy test for all females of childbearing potential (postmenarchal) who are premenopausal and not surgically sterile will be completed.

Participants will receive supplies for blood glucose and ketone testing. Quality Control (QC) testing will be performed on the meters before they are dispensed.

All participants will use study supplied Control-IQ technology 1.5 pumps during the study run-in phase, even if they are current Control-IQ technology users. Pump settings may be transferred over from the participant's prior pump, or for current multiple daily injection users, can be started per the guidance on the device training checklist.

3.1.1 Training on System Use

All participants will receive study system training from qualified staff, to include CGM and Control-IQ training.

At a minimum training will include the following:

- Calibration of the CGM in accordance with manufacturer labeling
- Procedures for treating severe hypoglycemia
- Procedures for identifying potential infusion set failure and steps to take including the checking of the blood ketone level and changing the infusion set
- Use of the security PIN on the insulin pump will be required for anyone who is not entirely responsible for their own diabetes care, to include all 2-5 year olds, and those 6 years of age or older who may be only partially responsible for their own diabetes management.

The participant will be given a User Guide as a reference as well as Hypoglycemia and Hyperglycemia Treatment Guidelines as part of the Study Participant Instruction Sheet. The device training checklist for CGM and the Control-IQ 1.5 pump will be completed by qualified study staff.

Participants will be instructed to download the study device prior to each phone contact or office visit.

The participant will be instructed to use the system in closed-loop mode except 1) when no calibrated CGM sensor is available or 2) if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, participant will be instructed to turn off Control-IQ for the next four hour and until CGM glucose is < 180 mg/dL.

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

glucocorticoids is needed to determine if and for how long closed-loop use should be temporarily discontinued. Given the short period of use of each aspect of the system, participants may be asked to end participation in the study if the investigator judges Control-IQ technology use must be stopped for more than a few days.

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 the system. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties.

Participants may use available manufacturer-provided CGM 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. The t:connect mobile app from Tandem Diabetes Care will not be available for use during the trial, and will not pair to the study pumps.

Study staff will discuss with the participant that routine contact is required as per the study visit schedule and will make arrangements with the participant for the contacts.

Participants may complete the device training visit in more than 1 session if necessary.

3.1.2 Training on Management of Hypoglycemia

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). Participants will be permitted to change the CGM low glucose threshold alert setting on their device (or Dexcom mobile app), but will be instructed to choose a value no less than 70 mg/dL.

If the participant receives a Control-IQ Low Alert, a message appears on the user interface 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 participant. The user is prompted to test blood glucose and treat with carbohydrate.

The participant (and /or parent/guardian) will be instructed that if severe hypoglycemia occurs, the study pump's insulin delivery should be suspended and glucagon administered if the participant is unable to consume carbohydrate.

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.

3.1.3 Training on Management of Hyperglycemia

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. 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.

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

If a participant's CGM reading is >300 mg/dL for more than 60 minutes or is ≥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 (or ≥ 2.5 mmol\L at any time), take correction insulin, change insulin (pump) infusion site and contact study staff. Continue to monitor their glucose and blood ketone levels until they return to normoglycemia and ketones are < 0.6 mmol/l.
    - If ketones are <0.6 mmol/l, participants will be advised to continue to monitor their glucose until it returns to normoglycemia and to repeat the ketone measurement in 90 minutes if necessary
- If correction insulin is administered via insulin syringe, turn Control-IQ off for four hours and until glucose level has returned to <180 mg/dL.

3.2 Visits 3, 4 and 5: Control-IQ 1.5 follow up contacts

Following the Control-IQ 1.5 Training Visit, participants will use the study Control-IQ 1.5 pump and study CGM for ~2 weeks during the study Run-In Period. A contact will occur at 1 day (+12 hours), 3 days (±1 day) to review adverse events as well as discuss infusion set care, and another phone call at 7 days (±2 days). Participants will then return to clinic in approximately 2 weeks (±3 days).

3.3 Visit 6: Control-IQ 2.0 Training Visit

After participants complete the run-in, they will return for the Control-IQ 2.0 training visit, and switch to the Control-IQ 2.0 study pump after training by qualified staff.

Control-IQ 2.0 allow for selection of different glycemic targets, as well as toggling autoboluses in standard and exercise activity. The late bolus feature will also be available.

Participants will be randomized to use either a daytime 30-min predictive glucose target of 90-130 mg/dL or 112.5 to 160 mg/dL for the first two-week period, then switch to the other target after 2 weeks.

In the training visit, participants will:

1) Select the appropriate target in clinic on their study pump per the randomization, and will be instructed by study staff to use the assigned glycemic target during each two week period.
2) Be instructed that autoboluses will default to on during normal activity, and off during exercise activity.
3) Be reminded again that use of the security PIN on the insulin pump will be required for anyone who is not entirely responsible for their own diabetes care, to include all 2-5 year olds, and those 6 years of age or older who may be only partially responsible for their own diabetes management.
4) Be instructed that sleep activity will be required during Control-IQ 2.0 use. A sleep schedule should be programmed into the pump for use each night. Participants will be instructed to disable sleep or adjust the schedule on the nights of the late bolus meal challenges, then re-enable sleep activity as soon as the challenges are over, so it is used the rest of the night.
5) Review prior training guidelines from the Control-IQ technology 1.5 training visit, and be taught how the new features are different in Control-IQ technology 2.0.
6) Review the study meal late bolus challenges, to be performed twice in each two week period. Participants may also use late bolus as desired outside of the challenges.

The participant will be given a User Guide as a reference as well as review the Hypoglycemia and Hyperglycemia Treatment Guidelines as part of the Study Participant Instruction Sheet. The study device training form will be completed.

Participants will be instructed to download the study device prior to each phone contact or office visit.

Participants may use available manufacturer-provided CGM 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. The t:connect mobile app from Tandem Diabetes Care will not be available for use during the trial, and will not pair to the study pump.

The device training checklist for the Control-IQ 2.0 pump will be completed by qualified study staff.

A urine pregnancy test for all females of childbearing potential who are premenopausal and not surgically sterile will be performed.

Study staff will discuss with the participant that routine contact is required as per the study visit schedule and will make arrangements with the participant for the contacts.

Clinical staff will verify with participants at each contact that the correct glycemic targets are being used.

Contacts for the study meal challenges will occur throughout the study Treatment Period.

Baseline INSPIRE questionnaire for pediatric participants age 8-17, for adult participants age 18+, and for parents of pediatric participants age 2-17 will be completed.

3.4 Study Contacts in the Treatment Period with Control-IQ 2.0 Technology

Participants will have a phone (or video-conference) follow-up visit at 1 day, 3 days and 1 week, a clinic follow-up visit at 2 weeks, a phone follow-up visit at 3 days and 1 week after switching glycemic targets, and a final clinic visit at 2 weeks after switching glycemic targets, within the windows specified below.

TARGET DAY/WEEK	VISIT OR PHONE	TARGET WINDOW (AROUND TARGET DAY/WEEK)
Visit 6: Control-IQ 2.0 Training Visit	V	2 weeks (±3 days) after Visit 2
Visit 7: 1 days after visit 6	P	±12 hours
Visit 8: 3 days after visit 6	P	±1 day
Visit 9: 1 week after visit 6	P	±2 days
Visit 10: 2 weeks after visit 6 (switch targets)	V	±3 days
Visit 11: 1 day after visit 10	P	±12 hours
Visit 12: 3 days after visit 10	P	±1 days
Visit 13: 1 week after visit 10	P	±2 days
Visit14: 2 weeks after visit 10	V	±3 days

If necessary, visits should be completed out-of-window rather than missed. A visit is not considered missed until the next visit/phone window opens.

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances or due to changes in contact precautions that may be needed during the evolving COVID-19 pandemic) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only (Visits 1, 2 and 6) as an alternative to withdrawal from the study. Remote (phone) visits will still be performed as scheduled. When a participant is placed into this status, remote visits for visits 10 and 14 will not be recorded as protocol deviations.

Additional phone and office visits may occur as needed.

For the in clinic visits at the end of each two week treatment period, if a clinical site believes these visits need to be performed remotely, the following approvals must be obtained prior to conducting the visit remotely:

- Sponsor approval for the reason the visit cannot be performed in person
- Investigator approval at the site level for the reason the visit cannot be performed in person

In addition, all study procedures listed in section 3.4.1 are to be completed, including upload of the study device and review of the device data. If the final visit is performed remotely, participant will mail in their study devices, and investigators will remotely supervise transition back to their home diabetes treatment plan.

3.4.1 Procedures at all Study Visits

The following procedures will be performed at each visit, unless otherwise specified:

- Review of study device data
- Assessment of compliance with study device use by review of any available device data
- Assessment of device issues that have occurred
- Assessment of adverse events, using open ended questions to capture hyperglycemic and hypoglycemic events, and their underlying cause and relationship to the study device or other parts of the system (such as the infusion set).
- Review of ongoing study late bolus meal challenges when in the treatment period
- Baseline INSPIRE questionnaire for pediatric participants age 8-17, for adult participants age 18+, and for parents of pediatric participants age 2-17 will be completed at visit 6
- Post Assessment INSPIRE questionnaire for pediatric participants age 8-17, for adult participants age 18+, and for parents of pediatric participants age 2-17 will be completed at visits 10 and 14
- SUS Scale will be completed at visits 10 and 14
- Study Specific Questionnaire will be completed at visits 10 and 14

At the final visit (or at subject withdrawal), the study staff will then supervise the participants transition back to their standard of care therapy as follows:

- Study staff will re-evaluate the subject's baseline therapy doses, noting changes in basal rates, carbohydrate ratios, and correction factors in use at the end of the trial. For prior CSII users, the study investigator will supervise and confirm the entry of settings in the insulin delivery profile of the participant's home pump at the end of the study.
- For those subjects using basal insulin, doses will be adjusted to best match the current daily insulin requirements from CSII use, typically = (total daily dose + 20%)/2, with further modification as per clinical site usual practice.
- Participants must have two CGM or fingerstick BG values, separated by at least 15 minutes, that must be above 80 mg/dL prior to discharge from the clinic for the final visit. In addition, CGM trend arrow must not be going down at the time of discharge.
- Study staff will confirm subjects have carbohydrates on hand for their drive back home, and instruct subjects to check their glucose levels when they arrive at home, prior to bedtime, and at least one time overnight on the first night to monitor for hypoglycemia, reminding subjects that insulin on board can be active for the next few hours even after stopping their pump.

3.5 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.

3.6 Late Bolus Meal Challenges

Participants will complete two late bolus meal challenges during each two week treatment period. Procedures are described in section 5.1.

3.7 Adjustments in Insulin Pump Settings

Insulin and glucose data from the screening visit, as well as follow up visits, will be reviewed and the site investigator may adjust insulin delivery profile settings as needed in accordance with their clinical practice.

3.8 Early Discontinuation of Study Device

If the participant cannot be reached for scheduled study contacts, the participant's other contact methods will be utilized. Participants who are not compliant with the arranged contacts on two separate occasions may be discontinued at the discretion of the investigator. Participants who discontinue the study device prior to the final visit, either by choice or by investigator decision, will be asked to come for an end of study visit and then will be dropped from the study.

3.9 Remote Monitoring

Real-time CGM alerts will be sent to study staff providers (MD, DO, NP, PA) for the first ten 6-13 year old participants to begin use of the lower target (90-130 mg/dL) for the first week of Control-IQ 2.0 use at that target. This requirement will only be removed for future participants in this age group after the first ten participants finish the first week of use of the lower target, and no safety concerns arise, where:

1) No severe hypoglycemia events related to algorithm delivered automated insulin dosing occur that required study staff intervention because the participant was not aware/treating appropriately.
2) No severe hyperglycemic events related to algorithm delivered automated insulin dosing occurred that required study staff intervention because the participant was not aware/treating appropriately.

In addition, real-time CGM alerts will be sent to study staff providers (MD, DO, NP, PA) for all 2-5 year old participants throughout their use of Control-IQ 2.0 technology (all 4 weeks).

Chapter 4: Study Devices and Drugs

4.1 Study Devices

4.1.1 Insulin Pump

For the run in period, participants will use a study provided Tandem t:slim X2 with Control-IQ 1.5 technology (Investigational Device). For the treatment period, participants will use a study provided Tandem t:slim X2 with Control-IQ 2.0 technology (Investigational Device).

4.1.2 Continuous Glucose Monitoring

The study CGM is the commercial version of the Dexcom G6, which includes a transmitter and sensors. The CGM sensor will be replaced at least once every 10 days.

4.1.3 Blood Glucose Meter

The study blood glucose meter is the Contour® NEXT (Ascencia Diabetes Care).

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.

4.1.4 Ketone Meter

The study blood ketone meter is the Precision Xtra Blood Glucose and Ketone Monitoring System (Abbott Diabetes Care).

Blood ketone levels will be measured when needed to evaluate prolonged hyperglycemia. The blood glucose meter component of the Precision Xtra device will not be used.

4.2 Study Device and Drug Accountability Procedures

Device accountability and inventory will be documented to include detailed inventory records of the study CGM supplies, and Tandem insulin pump system.

4.3 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 5: Testing Procedures and Questionnaires

5.1 General Challenge Guidelines

All study participants will complete two late bolus meal challenges during each two week treatment period. Participants will be instructed to wait at least 48 hours after switching targets in the treatment period to perform the next set of challenges.

A minimum of 48 hours will occur between all challenges for each participant.

A paper logbook will be provided to participants that includes a page to record details about each challenge and procedural instructions about how participants will conduct these challenges. This material will be reviewed with each participant, and will be used for source verification for the eCRF database.

Before starting each challenge, participants (or parent/guardian if the participant is < 18 years of age) must assure the participant has a working CGM and Control-IQ is active. For pediatric participants, the participant's parent or guardian must remain with the child at all times and monitor CGM readings frequently during and through meal completion plus 5 hours (3 hours for participants age 2-5). Snacks and glucagon must be available for use during and after each challenge.

Participants will be instructed to communicate with study staff within one day prior to each challenge to review procedures and to have a contact with study staff no more than 1 day after the completion of each challenge. The participant or parent/guardian must have an on-call phone number for the study team prior to initiation of each challenge.

Hyperglycemia and Hypoglycemia treatment guidelines (sections 3.1.3 and 3.1.2) remain in effect for the challenges, and will be reviewed with participants prior to each challenge.

Site staff will directly contact the participant if they do not receive a follow up contact from participants when 24 hours have passed since the time of completion of the planned challenge.

5.1.1 Late Bolus Meal Challenges

All challenges will be performed with the last meal of the day (dinner) and participants will be instructed not to snack after dinner on days they are performing meal challenges, unless it is to treat hypoglycemia.

Participants will also be instructed not to use sleep activity for at least 5 hours (3 hours for participants age 2-5) once starting the meal challenge. Participants will be reminded to disable sleep activity if it is inadvertently activated during the challenge, and to re-enable it at the end of the challenge.

Time zero (start of the challenge) is at the first bite of food for the study meal.

During each two week treatment period with Control-IQ technology 2.0 use, the two meal challenges will consist of:

- Full bolus for the given carbohydrates and calculated correction, given 45 minutes after starting the meal, based on calculated bolus dose using the bolus calculator (with full amount of carbohydrates entered).
- Full bolus for the given carbohydrates and calculated correction, given 45 minutes after starting the meal, based on calculated bolus dose using the bolus calculator (with full amount of carbohydrates entered) **AND enabling the late bolus feature to 45 minutes later.**

For each meal challenge, participants will:

1. Be in a fasting state for two hours prior to consuming the last meal of the day, with the last manual insulin bolus more than two hours prior to the meal.

2. For participants age 6+, only begin the meal challenge if CGM glucose is between 70 mg/dL and 200 mg/dL, and CGM trend arrow is not down.

   For participants age 2-5, only begin the meal challenge if CGM glucose is between 70 mg/dL and 250 mg/dL, and CGM trend arrow is not down.

   Subjects with hyperglycemia > 200mg/dL will reschedule their challenge for another time. If < 70 mg/dL, carbohydrate treatment can be given, after which the meal challenge can continue.

3. Pediatric participants age 2-5 should have a meal with at least 20 grams of carbohydrates. Participants age 6-13 should have a meal with at least 35 grams of carbohydrates. All other participants should have at least 50 grams of carbohydrates for the study meal challenges. *Each participant should use the same meal for all of their meal challenges in the study. Participants will be encouraged to use the same frozen entrée of their choice for consistency.*
4. Do their best to complete the meal within 30 minutes of starting to eat.
5. Write down the start and end time of eating the meal, as well as the meal content (to include amount of carbohydrate, protein and fat) on the study provided logbook.
6. Bolus for the meal 45 minutes after starting to eat, entering the full carbohydrate amount and using the recommended dose from the bolus calculator. For one of the two challenges during a single treatment period, use the bolus calculator but do not change the bolus time. For the other challenge during the same treatment period, use the bolus calculator but change the bolus time to 45 minutes late.
7. Not give an additional bolus during 5 hours (3 hours for participants age 2-5) after the start of meal challenge (i.e., after start of meal), unless BG is above 300 mg/dL for more than 1 hour, or symptoms of hyperglycemia develop.
8. Not take additional carbohydrates during 5 hours (3 hours for participants age 2-5) after the start of meal challenge (i.e., after start of meal), unless BG is < 70 mg/dL, or symptoms of hypoglycemia develop.
9. Not exercise for 5 hours (3 hours for participants age 2-5) after the meal challenge begins.
10. Make sure sleep activity is not active for the 5 hours (3 hours for participants age 2-5) after the meal challenge begins (start of meal).
11. Notify the site within 24 hours after completion of each meal challenge.

5.2 Laboratory Testing

5.2.1 HbA1c

HbA1c measurement will be performed locally at the Screening visit.

5.2.2 Urine Pregnancy

Urine pregnancy testing performed locally at clinical site for females of child-bearing potential at the screening visit, at the start of study device use (for both device training visits), and anytime pregnancy is suspected.

5.2.3 Patient Reported Outcomes

The following patient reported outcomes/questionnaires and study specific outcomes will be assessed during the trial as per the study visit schedule.

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.

Study Specific Questionnaire

A study-specific questionnaire will be used to assess experiences and views around the different target ranges, late bolus challenges, freedom to eat and adjust meals, and general thoughts about the trial.

Administration time is approximately 5 minutes.

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

6.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center and Sponsor on an eCRF all unanticipated problems meeting the criteria below. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

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

The Coordinating Center will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at another participating entity such as a pharmacy or laboratory. These instances must be reported to the study IRB within seven calendar days of recognition. The Sponsor will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting.

6.2 Adverse Events

6.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic in a study participant, including any comparator used, irrespective of the relationship between the adverse event and the device(s) under investigation (referred to as *Adverse Reaction* when caused by a drug).

Serious Adverse Event (SAE): Any untoward medical occurrence that meets at least one of the following:

- 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 Issues Form, unless excluded from reporting as defined in section 6.2.2).

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

Device Complaints and Malfunctions: A device malfunction 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.

Use Error: User action or lack of user action while using the medical device (3.34) that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

6.2.2 Reportable Adverse Events

A reportable adverse event includes all events meeting the definition of an adverse event, except for the following:

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

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

6.2.3 Hypoglycemic Events

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

- a hypoglycemic event occurred meeting the following definition of severe hypoglycemia: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia

When a severe hypoglycemia event occurs (as defined above), an Adverse Event Form should be completed. Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 6.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.4 Hyperglycemic/Ketotic Events

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

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- blood ketone level ≥1.0 mmol/L, even if there was no communication with a health care provider at the time of the event

Hyperglycemic events are classified as DKA if all of the following are present, or judged likely to have been present based on available data:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO2) <15; and
- Treatment provided in a health care facility

When a hyperglycemia/ketotic event qualifies as an AE, or as a SAE as defined in section 6.2.1, an Adverse Event Form should be completed. Events meeting DKA criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria

for DKA generally will not be considered as serious adverse events unless one of the SAE criteria in section 6.2.1 is met.

When a hyperglycemia/DKA event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 6.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

6.2.5 Relationship of Adverse Event to Study Investigational Device

The study investigator will assess the relationship of any adverse event to the study device or study drug. The Medical Monitor also will make this assessment, which may or may not agree with that of the study investigator. Reporting requirements will be based on the Medical Monitor's assessment.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guidelines when determining whether an adverse event is related to a study device or study drug:

Unrelated: The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.

Unlikely Related: The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.

Possibly Related: The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.

Probably Related: The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.

Definitely Related: The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Events determined to be *Possibly Related*, *Probably Related*, or *Definitely Related* will be considered 'Related' with respect to any required IRB and FDA reporting.

6.2.6 Severity (Intensity) of Adverse Events

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

MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.

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

6.2.7 Expectedness

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

6.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary.

6.2.9 Outcome of Adverse Events

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

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

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

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

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as UADEs or related SAEs or SUSARs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

6.3 Reportable Device Issues

All UADEs and ADEs as defined in section 6.2.1 will be reported as both 'device issues' and adverse events, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

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

- CGM sensor lasting fewer days than expected per manufacturer
- CGM tape adherence issues
- Pump infusion set insertion lasting fewer days than expected per manufacturer
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication

- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

6.4 Timing of Event Reporting

SAEs possibly related to a study device, study drug, or study participation and UADEs must be reported by the site to the Sponsor within 1 working day of the site becoming aware of the event. This can occur via phone or email, or by completion of the appropriate eCRFs as applicable. If the form(s) are not initially completed, they 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 eCRF(s) within 7 days of the site becoming aware of the event.

The Sponsor will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 working days after the Sponsor 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 qualifying event, the Sponsor will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b). The Sponsor must determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after first receipt notice of the UADE.

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

6.5 Safety Oversight

The study Sponsor's Medical Director will serve as Medical Monitor, and will review all reported adverse events, including all cases of severe hypoglycemia and DKA, and adverse device effects that are reported during the study. SAEs typically will be reviewed within 1 working day of reporting. Other AEs typically will be reviewed on a weekly basis.

The Medical Monitor will determine if the events require expedited reporting to FDA, IRB and/or all participating sites. In addition, the Medical Monitor will confirm the MedDRA code assigned and adjudicate events as specified in the safety management plan for relatedness to the study procedure and investigational device, assess seriousness and severity, and determine if the event the event is anticipated or unanticipated. Both the investigator's and Medical Monitor's assessments will be recorded, however, the adjudication decision of the Medical Monitor will be used for the final classification of events, including relatedness to the study procedures and/or the investigational device, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations.

6.6 Stopping Criteria

6.6.1 Participant Discontinuation of Study Device

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA event (or a malfunction that could have led to severe hypoglycemia or DKA), use of the study device will be suspended for that participant while the problem is diagnosed. The UADE will be reported to the IRB and FDA. After assessment of the problem and any correction, use of the study device will not be restarted until approval is received from the IRB and FDA.

In the absence of a device malfunction, use of the study device by a participant will be discontinued if any of the following occur:

- 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 distinct episodes of DKA in the study treatment period as defined in section 6.2.4
- One distinct severe hypoglycemia events in the study treatment period as defined in section 6.2.3

Each DKA or severe hypoglycemia event will be reviewed by the Medical Monitor with respect to determination of cause and whether the occurrence of the event can be attributed to use of the study device or study drug.

6.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of device use due to a UADE as described in section 6.6.1, 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.

Closed-loop system use will also be suspended if there are five or more cases of severe hypoglycemia or five or more cases of DKA across the entire study in participants who have initiated Control-IQ technology 2.0 use. The IRBs and FDA will be notified. After assessment of the problem and any corrections are implemented, use of the closed-loop system may be restarted if approval is received from the IRBs and FDA.

Chapter 7: Miscellaneous Considerations

7.1 Drugs Used as Part of the Protocol

Subjects will use their own Humalog (insulin lispro) or Novolog (insulin aspart) during the Run In and Treatment Period with the study devices.

7.2 Collection of Medical Conditions and Medications

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

Medical Conditions Developing During the Study: Medical conditions developing during the study will be reviewed by the investigator for their relationship to the study device.

Medications: All medications in use at the time of screening or added during the course of the study will be recorded. Nutraceuticals and preventative treatment also will be recorded. Medications only taken as needed either can be recorded when prescribed or only recorded if used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

7.3 Prohibited Medications, Devices, Treatments, and Procedures

Treatment with any insulin other than Humalog or Novolog insulin with the study pumps is not permitted. Treatment with a non-insulin glucose -lowering agent, other than metformin, is not permitted, including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas.

The investigational study devices (t:slim X2 insulin pump with Control-IQ technology 1.5 or 2.0) and study sensor and transmitter (Dexcom CGM sensor and transmitter) 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 above.

7.4 Rescue Medications, Treatments, and Procedures

Each participant will be required to have a glucagon preparation for rescue therapy for severe hypoglycemia.

7.5 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven days and to the IRB as an Unanticipated Problem within seven calendar days.

7.6 Participant Compensation

Participant compensation will be specified in the informed consent form.

7.7 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.

Chapter 8: Statistical Considerations

8.1 General Statistical Considerations

Summary statistics will be generated for all relevant variables. In the comparison of continuous variables, distributions will be tested for the normality assumption. If standard parametric techniques are found to be inadequate, an appropriate non-parametric technique will be used. Categorical variables will be presented using frequencies and percentages and compared using differences in proportions unless stated otherwise. For safety/adverse event reporting, both the number of overall events and the number of subjects experiencing that event will be tabulated. No corrections will be made for multiple testing procedures. All analyses will be conducted using SAS® version 9.4 or higher. Although this study features a crossover design, it will be assumed for the exploratory purposes of this analysis that there are no residual period effects and no carryover effects present. The correlated nature of data collected by the same subject across multiple conditions will be accounted for in the statistical modeling, such as using a paired t-test for comparing continuous outcomes.

8.2 Statistical Hypotheses

The primary objective of the study is assessment of safety. Therefore, there are no formal statistical hypotheses associated with any of the endpoints. Safety endpoints for SH and DKA will be compared to historical published data. Efficacy endpoints will be compared across study periods with the run-in period designated as the comparator study period. P-values for differences between study periods on both safety and efficacy endpoints will be calculated, however, will not be used for formal statistical inference due to the exploratory nature of the study objectives and the lack of correction for multiple testing.

8.3 Sample Size

The sample size of at least 30 adults and adolescents age 14+ years old, 30 children age 6-13 years old, and 12 preschool participants age 2-5 years of age who will complete the trial was selected to have a reasonable time period of use in each age cohort to establish safety, with each subject completing 2 weeks of Control-IQ 1.5 technology use, 2 weeks of Control-IQ 2.0 technology use with the target of 112.5 to 160 mg/dL, and 2 weeks of Control-IQ 2.0 technology use with the target of 90-130 mg/dL. The choice of sample size is not based on statistical principles. In addition, the sample size assures a reasonable number of late bolus meal challenges completed.

There is a further enrollment goal of at least half of all participants in each age group have an HbA1c at baseline of ≥ 7.5%, and have at least 6 participants age 14-17.

8.4 Outcome Measures

Primary Endpoints

1. Severe hypoglycemia (with cognitive impairment such that assistance of another individual is needed for treatment) during study compared with data on severe hypoglycemic events reported by T1D Exchange clinic registry over a 3-month time period
2. Diabetic ketoacidosis during study compared with data on DKA events
3. Number of unanticipated adverse device effects
4. Number of other serious device-related adverse events

Secondary Endpoints

1. All device-related adverse events

2. CGM hypoglycemia outcomes, compared between the three study time periods
    a. Overall % time <54 mg/dL
    b. Overall % time <70 mg/dL
3. Times in ranges-overall (70-180 mg/dL, >180 mg/dL, >250 mg/dL, 70-140 mg/dL) compared between the three study time periods
4. Mean glucose compared between the three study time periods.
5. Overall variability (CV and SD) compared between the three study time periods
6. Secondary endpoints 2 - 5 compared during daytime and nighttime, across the three study time periods
7. Secondary endpoints 2 - 5 as well as adverse events, during the study meal challenge periods, for late bolus feature use compared to normal bolus in the meal challenges.
8. Time to intervention for hypo- or hyperglycemia during the study meal challenge periods, for late bolus feature use compared to normal bolus in the meal challenges.
9. Number of interventions for hypo- or hyperglycemia during the study meal challenge periods for late bolus feature use compared to normal bolus in the meal challenges.
10. Subgroup Analysis for all metrics by age cohort, baseline HbA1c cohort (HbA1c at baseline of ≥ 7.5%, yes/no), and target activity use (standard target, lower target, sleep activity, exercise activity).

8.5 Analysis Datasets

Safety analysis set: All participants who initiate the Treatment Period and use the study device at least one time (including training).

CGM analysis set: Any member of the Safety Analysis Set who has at least 24 hours of CGM data during either Treatment Period. CGM data occurring within the meal challenge windows (from time of start of meal up to 5 hours afterwards [3 hours for age 2-5]) will not be used to determine whether a subject is included in CGM analysis set or not.

Late bolus meal challenge set: Any member of the Safety Analysis Set who has at least 24 hours of CGM data during the Treatment Period, and who has at least 3 hours of CGM data for at least one meal challenge.

8.6 Analysis of Endpoints

8.6.1 Analysis of the Safety Event Endpoints

Safety events (not including CGM defined events defined in sections 6.2.2, 6.2.3, and 6.2.4) will be based on Safety analysis set, and tabulated for each primary endpoint as the number of events per participant, the number of participants with ≥ 1 event, and the rate of events per 100 person-years. A 95% confidence interval will be calculated for the rate of events per 100 person-years.

Since study eligibility excluded participants with 2 or more severe hypoglycemia or DKA events in the prior 6 months, an unbiased comparison of the event rate during the Treatment Period with the pre-study event rate is not possible. Therefore, the severe hypoglycemia and DKA event rates will be compared with the T1D Exchange data,[4] which reported the frequency of 1 or more severe hypoglycemia and DKA events in the prior 3 months. The proportion of participants with events during the Treatment Period (each

period separately) will be compared with the run-in period as well as with the T1D Exchange frequency. Differences in proportions across the three study periods (two active treatments and the run in) will be estimated in a pairwise fashion, and statistical significance will be assessed using a normal approximation to a binomial distribution.

8.6.2 Analysis of Other Safety Endpoints

Safety summaries will be based on Safety analysis set. All adverse events reported over the course of the study will be summarized by study period for run-in and both treatment periods separately and overall. Adverse events will be tabulated by System Organ Class and Preferred Term based on MedDRA version 22.0. Adverse events will also be summarized by seriousness, severity, and relationship to study procedures and the investigational device. Except where indicated, a subject reporting the same adverse event more than once will be counted once when calculating the number and percent of subjects with that particular event.

Adverse events leading to death or to discontinuation from the study will be listed separately. A listing of all adverse events will be provided.

8.6.3 Analysis of CGM Endpoints

CGM metrics will be assessed in CGM analysis set, and computed for the Run-In and both Treatment Periods separately. CGM metrics will be computed per subject over 24 hours, during daytime (6am-11:59pm), and during nighttime (12am-5:59am), as well as by age cohort (adults/adolescents, children 6 – 13, and preschool), baseline HbA1c cohort (HbA1c at baseline of $\geq$ 7.5%,yes/no), and target activity use as specified by the device (standard target, lower target, sleep activity, and exercise activity).

The main statistical comparison will be made between the three 2-week periods (Run In, Treatment Period at standard target, Treatment Period at lower target). The comparison will be pairwise – Run-in vs standard targe, Ru-in vs lower target, and standard vs lower target. The percent time in glycemic ranges will be calculated as the number of measurements in the specified range divided by the total number of measurements for which it can be determined whether or not the measurement was in specified range. The "Low" and "High" CGM readings will be included in all analyses. Percent time will be compared using a paired t-test assuming sufficient normality assumptions hold, otherwise an appropriate non-parametric method will be utilized.

8.6.4 Analysis of Late Bolus Meal Challenges

All analyses in section 8.6.4 will be conducted in the late bolus meal challenge analysis set. Data included in these analyses will be restricted to data during the meal challenge window (start of meal through 5 hours from meal imitation [3 hours for age 2-5]). The subgroups assessed will be the same as sections 8.6.1 – 8.6.3 (age cohort, baseline HbA1c cohort (HbA1c at baseline of $\geq$ 7.5%. yes/no), etc.)

8.6.4.1 Late Bolus Meal Challenge Safety and CGM Subgroup Analysis

Two challenges are expected per subjects per treatment period for a total of four challenges, therefore agreement of outcomes will need to be assessed. For continuous outcomes, two sets of Pearson's correlation coefficients will be calculated to measure concordance: one restricted to each treatment period (higher range target and lower range target), and a single coefficient for all four challenges. For categorical outcomes, a Cohen's kappa statistic for agreement or a similarly appropriate statistic will be calculated and presented to describe agreement/dependence of outcomes by individual subjects. Results will be compared by treatment period and across treatment periods.

The analyses described in sections 8.6.1, 8.6.2, and 8.6.3 will be repeated for subjects included in the late bolus meal challenge set. For the CGM outcomes, the mean of the CGM metrics for the two late meal

bolus challenges within study period will be used to account for within-subject non-independence (i.e. one data value per subject per study period).

8.6.4.2 Time to Intervention Analysis

Time to intervention for both hypo- or hyperglycemia during the study meal challenge periods will be summarized. Time to intervention is defined as the time (in minutes) from start of meal until the first treatment is given as defined in Section 6.2. If multiple interventions are needed to treat hypo- or hyperglycemia during the meal challenge, only time to the earliest intervention will be summarized. The results will be presented using general summary statistics, as well as utilizing Kaplan-Meier time-to-event analysis where subjects who complete the meal challenge without requiring any intervention will be right-censored. A cox proportional hazards model will be fit comparing time to intervention between the two active treatment periods. A p-value from the log-rank test will be used to evaluate whether there is evidence of a difference between the two target ranges with respect to time to intervention. Results will be compared by treatment period and across treatment periods.

8.6.4.3 Number of interventions analysis

Number of interventions for hypo- or hyperglycemia during the study meal challenge periods will be summarized both overall and by type. The results will be presented using general summary statistics.

Type of intervention may include timing of intervention (during meal, less than one hour after starting meal, greater than one hour after meal start), the number of carbs administered (grouped in increments of 10 grams), and the timing of carb administration (less than 15 minutes per administration vs 15 minutes or more). The categories and groupings utilized for intervention type will be expanded or decreased based on the types of interventions that actually occur in the study. Results will be compared by treatment period and across treatment periods.

Type of intervention will be reviewed and assessed by the study Medical Monitor prior to analysis to define the logic that can be applied across all subjects (e.g., an intervention that occurred more than 15 minutes after the previous intervention will count as new intervention). Different logic may be applied to different age cohorts. This logic will be fully detailed in the final clinical study report.

8.7 Intervention Adherence

The following tabulations will be performed:

- Sensor use – percent time of use as a function of overall treatment period
    - Sensor use is defined as percent of time CGM is recorded as active (to include warmup) vs total study time.
- Closed loop system use – percent time of use as a function of overall treatment period
    - Closed loop system use is defined as percent of time closed-loop is recorded as active (to include pinning in sensor warmup) vs total study time.
- Percent time in different operational modes as a function of overall treatment period
    - The investigational device allows for the following operational modes: standard target, lower target, sleep activity, and exercise activity.

For intervention adherence, overall treatment period is calculated from the start of the treatment period to the end of the treatment period where any gaps in CGM data are ignored.

8.8 Protocol Adherence and Retention

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

- Number of protocol deviations by site and by type, and number of unique subjects with each type of protocol deviation
- Disposition summary (e.g., chart, table) accounting for all enrolled participants at each scheduled visit
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who were enrolled but did not enter the Treatment Period and reasons
- Number of participants who stopped treatment and reasons

8.9 Baseline Descriptive Statistics

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

- Age
- Sex
- Race
- Ethnicity
- Socio-economic factors (income, education, and/or insurance status)
- Diabetes duration
- HbA1c
- BMI
- Total daily insulin
- Prior severe hypoglycemia and DKA events in the last 6 months

8.10 Additional Tabulations and Analyses

The following data will be tabulated at baseline, for the run-in period, and for the two treatment periods.

- Insulin metrics (units/kg): total daily insulin, total daily basal insulin, total daily bolus insulin (plus total daily manual bolus, total daily automated bolus)

8.11 Device Issues

The following tabulations will be performed with respect to device issues:

- Number of device issues by type, and number of unique subjects with each type of device issue

8.12 Planned Interim Analyses

No formal interim analyses are planned.

8.13 Subgroup Analyses

Results will be tabulated according to age cohort, baseline HbA1c category, and target activity use (standard target, lower target, sleep activity, exercise activity). There is an enrollment goal of at least half of all participants in each age group have an HbA1c at baseline of ≥ 7.5%, and all participants meeting that criteria will be analyzed as a subgroup.

8.14 Multiple Comparison/Multiplicity

There are no adjustments performed for multiple comparisons.

8.15 Handling of Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. All analyses will be based on available data only; no imputation for missing data is planned.

8.16 General Statistical Considerations

Up to six sites in the US will enroll subjects into the study. For the purposes of statistical analyses and data summaries, data from all study centers will be pooled. Not official assessment of poolability will be performed.

Unless otherwise specified, continuous variables will be summarizing using count, mean, median, standard deviation, and range. 95% confidence intervals, and/or first and third quartile may be presented were appropriate. Categorical variables will be summarized using count and percent of each level of categorical variable. Any statistical testing will be performed at a two-sided significance level of 5% with no adjustment for multiple testing. If the observed data are found not to follow a normal distribution, non-parametric methods may be employed (such as Wilcoxon rank sum test as appropriate).

The statistical software package SAS® 9.3 or later will be used for all data derivations, summaries, listings, and statistical analyses. Additional statistical software may be used for graphics or validation purposes as appropriate.

Chapter 9: Data Collection and Monitoring

9.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF, data collected in the electronic medical record, study specific source worksheets, etc.), the original source documentation will be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF.

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

9.2 Study Records Retention

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

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

9.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and 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, GCP and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A monitoring plan will be developed and revised as needed during the course of the study. Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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

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

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

9.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall be developed by the site and implemented promptly.

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

Chapter 10: Ethics/Protection of Human Participants

10.1 Ethical 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

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

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Coordinating Center. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Coordinating Center.

10.3.3 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Coordinating Center. After the study is completed, a dataset will be provided to the study Sponsor.

No biologic specimens will be stored.

Chapter 11: References

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2. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E, Schoelwer M, Ruedy KJ, Jost E, Carria L, Emory E, Hsu LJ, Oliveri M, Kollman CC, Dokken BB, Weinzimer SA, DeBoer MD, Buckingham BA, Cherñavvsky D, Wadwa RP; iDCL Trial Research Group. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med. 2020; 383:836-845.
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4. Foster et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019; 21:66-72.