A Control-IQ 2.0 Feasibility Study in Adult and Adolescent Subjects

Study Sponsor:	Tandem Diabetes Care, Inc. 11075 Roselle Street San Diego, CA 92121
Study Number:	TP-0009170
Study Phase:	Feasibility
IDE Number:	G201146
Study Device:	t:slim X2 Insulin Pump with Control-IQ 2.0 technology
Protocol Chair:	Jordan Pinsker, MD
Date:	16 AUG 2021
Version:	03

Confidentiality Statement

Protocol Revision History

Version Number	Amendment Date	Brief Description of Changes
01	N/A	Initial Version
02	17 JUN 2021	• Added first 10 subjects will have remote monitoring in place with the Dexcom G6 app, sharing to their personal contact(s) and the study staff. After the first 10 subjects complete, the additional 20 subjects will be required to share in real-time with their personal contact only [2.2] •Added remote monitoring review criteria after the first 10 subjects to allow start of the next 20 subjects without real-time alerts to providers [4.5.2] •Added remote monitoring response plan for study staff for both hyper and hypoglycemia [7.9 and 7.10]

		•Added 48 hour (+/- 1 day) follow up phone call after each weekly feature update [4.5.2] and listed this in Table 1 [4.4] •Added required local personal contact to inclusion criteria [3.1.1] •Added personal contact training [4.4] •Added require pump download for review at end of phase 1 [4.5.1], and then weekly [4.5.2] •Clarified limit to no more than 1 episode of severe hypoglycemia or DKA for each participant during phase 1 [8.12] •Clarified temporary vs permanent participant stopping criteria due to illness [2] •Clarified number of severe hypoglycemic of DKA events for overall protocol stopping criteria [8.13] •Added additional exclusion criteria [3.1.2] •Moved remaining details of outpatient hyperglycemia treatment plan to appropriate section [7.9] •Clarified required threshold glycemic alert settings for outpatient hypoglycemia treatment plan [7.10] •Updated instructions for Control-IQ use after an insulin bolus is delivered by injection in the outpatient setting [7.9] •Updated subject instructions and download review for use of the eating soon feature [4.5.2]
03	16 AUG 2021	• Clarified up to 110 subjects may sign the consent form and be screened (40 subjects plus 70 local contacts), so a maximum of 90 subjects may be enrolled (30 subjects plus 60 local contacts) [2.2] • Updated screening and enrollment procedure to note that the subject will be considered enrolled when the investigator attests that the subject meets all eligibility criteria on the study enrollment CRF [4.2] • Moved signature page to the main protocol • Removed family history from screening visit [4.4]

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Terms, Acronyms, Abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
AP	Artificial Pancreas
AUC	(Glucose) Area under the curve
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
Control-IQ Pro	t:slim X2 insulin pump with a configurable version of software, used to enable evaluation of new features in this feasibility study
Control-IQ System	t:slim X2 insulin pump with Control-IQ technology
DKA	Diabetic Ketoacidosis
EC	Exclusionary Criteria
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	United States Food and Drug Administration
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed-loop
IC	Inclusionary Criteria
ICF	Informed Consent Form
ICR	Insulin to Carb Ratio
IDE	Investigational Device Exemption
ISF	Insulin Sensitivity Factor
SAP	Sensor-Augmented Pump
SD	Standard Deviation
t:connect	t:connect diabetes management system
T1D	Type 1 diabetes
TIR	Time in range

Site Principal Investigator Statement of Compliance

Protocol Identifying Number:	TP-0009170
Protocol Name:	A Control-IQ 2.0 Feasibility Study in Adult and Adolescent Subjects
Protocol Version/Date:	V 03 / 13 AUG 2021

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

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

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

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

Investigator Name: _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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PROTOCOL SYNOPSIS

Protocol Number	TP-0009170
Protocol Title	Control-IQ 2.0 Adult and Adolescent Feasibility Study
Device	t:slim X2 insulin pump with Control-IQ technology (Control-IQ System). Tandem developed a configurable version of software called Control-IQ Pro which will be used to enable evaluation of new features in this study.
Type of Protocol	Feasibility Study
Rationale	The purpose of this study is to obtain preliminary safety and performance data on planned improvements to Control-IQ. Based on data from algorithm simulations and historical customer outcomes on the current algorithm, several new algorithm features have been selected to include in this feasibility study. Outcomes of this study will allow for the determination of the optimal feature set to include in the subsequent clinical trials, and ultimately in the commercial version of Control-IQ 2.0.
Objectives	**Primary objective**: To demonstrate the safety of the Control-IQ Pro 2.0 System for the management of type 1 diabetes by assessing rates of AEs after using new features. **Secondary objective:** To further assess the safety of new features that potentially will be added to the current Control-IQ System; specifically, improved time in range (TIR) 70-180 mg/dL, improved time in the tight glycemic range 70-140 mg/dL, and lower median sensor glucose.
Study Endpoints	1) Primary Safety Endpoints: a. Significant hypoglycemia time <54 mg/dL b. Severe hypoglycemia (needing assistance) c. DKA d. Serious Adverse Events 2) Secondary Safety Endpoints: a. Time < 70 mg/dL b. Time > 250 mg/dL c. Overall TIR (70-140 mg/dL) d. Overall TIR (70-180 mg/dL) e. Post-prandial glycemic peak f. 4-hour post meal glucose AUC g. Sensor glucose median and interquartile range h. CGM metrics daytime vs. nighttime
Duration of Study	All subjects will be monitored for approximately 5 weeks after enrolling in the study.
Study Design	This feasibility study is a prospective, crossover study with a 48-hour supervised/transitional environment phase, followed by a 4-week home study with sequential interventions (new features) and remote monitoring. Up to 110 subjects may sign the consent form

	and be screened, so that a maximum of 90 subjects (up to 30 subjects to wear the study device, and up to 60 personal contacts) will be enrolled to participate in the study. Subjects wearing the study device will be both male and female, aged 14 and up, inclusive, who have used Control-IQ in closed-loop at least 80% of the 2-week time period before enrollment. Approximately 5 subjects will be enrolled in the initial 48-hr supervised phase. Approximately 25 additional subjects will be enrolled to participate in the at-home study. Each subject will use all features (current and new) and therefore will act as his/her own comparator. Remote real-time monitoring using the Dexcom G6 app will be required to be shared with their local contact(s) throughout the study, and with study staff for the first 10 subjects. After the first 10 subjects complete the study, required real-time alerts to study providers may be removed for future subjects after sponsor review and approval. Subjects will continue to share with their personal contacts.
Study Population	Adult male and female subjects aged 14 years and up who are current users of the t:slim X2 pump with Control-IQ technology.
Number of Subjects	Up to 110 subjects may sign the consent form and be screened, so that a maximum of 90 subjects (up to 30 subjects to wear the study device, and up to 60 personal contacts) can be enrolled.
Number of Sites	1 clinical site in the United States
Site Locations	University of Virginia
Main Criteria for Inclusion	Eligibility to enroll in the study will be assessed based on the following inclusion criteria: 1. Adult and adolescent male and female subjects ≥age 14 years 2. Clinical diagnosis of type 1 diabetes for at least one year 3. Experienced Control-IQ user for ≥3 months. 4. Use of Control-IQ in closed-loop at least 80% of the 2-week time period before the first visit timepoint. 5. Not pregnant or planning a pregnancy during the time period of the study 6. Using only Humalog or Novolog insulin 7. ICR and ISF optimized 8. Average time in range (70-180 mg/dL) at least 50% on Control-IQ 9. Has current glucagon product to treat severe hypoglycemia (injectable or nasal) at home (will provide prescription if they do not have one) 10. Willingness to follow study procedures and a signed informed consent form 11. Willingness to use the Dexcom G6 app on their personal phone throughout the study, and share real time CGM information with a local contact and study staff.

	12. Availability of a local contact who has access to the study participant, knows their whereabouts, and agrees to be promptly available if contacted by study staff. If the subject lives alone, the local contact must live within 30 minutes and have access to the subject overnight.
Main Criteria for Exclusion	Eligibility to enroll in the study will be assessed based on the following exclusion criteria: 1. Diabetic ketoacidosis (DKA) in the past 6 months and Severe hypoglycemia (needing assistance) in the past 6 months 2. Inpatient psychiatric treatment in the past 6 months 3. History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to screening or unwillingness to agree to abstain from illicit drugs throughout the study. 4. History of heart, lung or kidney disease determined by investigator to interfere with the study 5. Use of glucocorticoids, beta blockers or other medications determined by investigator to interfere with study 6. Use of long-acting insulin or any non-insulin glucose lowering agents (i.e. SGLT-2 inhibitor) other than Metformin 7. Febrile illness within 3 days of the start of the study 8. Subject is pregnant or lactating or intending to become pregnant before or during participation in this study. 9. For subjects >50 years old or with diabetes duration >20 years and who are exercising as part of the 48 hour study, abnormal electrocardiogram consistent with increased risk of arrhythmia, ischemia, or prolonged QTc interval (> 450 ms) 10. Significant chronic kidney disease (eGFR < 60) or hemodialysis 11. Significant liver disease 12. History of adrenal insufficiency 13. History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated
Procedures in Screening/Baseline Period	Baseline data will be collected. Mean/median sensor glucose, TIR and all glycemic outcomes will be recorded as baseline data from the use of Control-IQ in closed-loop at least 80% of the 2-week time period before the first visit timepoint.
Management of Adverse Events	Safety information will be collected weekly during study clinic visits. The event, date of onset, severity, seriousness, duration and relationship to the device will be documented. All reported device-related AEs will be followed until they are adequately resolved or stabilized, or until study completion/termination, whichever comes first.

Statistical Analysis	Descriptive statistics will be used to evaluate rates of AEs as well as glycemic outcomes after using existing Control-IQ system vs. new features. Each subject will use all features and therefore act as his/her own comparator.

The study will be conducted and documented in accordance with the US Federal and Local requirements for post-market human clinical studies, the protocol, and the stipulations of the clinical trial agreement.

1. Background

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 A_{1c} (HbA_{1c}) level of 7.0% for children and adults. These findings indicate the need for better approaches to type 1 diabetes management.

Recent estimates suggest that approximately 400,000 U.S. patients with type 1 diabetes (T1D) use insulin pumps. Adoption of pump therapy varies by geography and may be related to healthcare provider preference or patient characteristics and socioeconomic status. Use of insulin pumps is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education. Additionally, referrals from healthcare providers and insurance approvals are critical determinants for who becomes a pump user in the U.S.

1.2 Device background

The t:slim X2 insulin pump with Control-IQ technology is an advanced hybrid closed-loop (HCL) system, developed and manufactured by Tandem Diabetes Care, Inc. and cleared in the U.S. by the FDA. Control-IQ is integrated with the Dexcom G6 continuous glucose monitor (CGM) and uses CGM values to predict glucose values 30 minutes in the future. Based on the predicted glucose, Control-IQ modulates basal insulin delivery, and delivers automated correction boluses to mitigate impending hyperglycemia. The current Control-IQ system is FDA approved down to age 6 years old, and has been found to improve time in range (70-180 mg/dL) and decrease both time < 70 mg/dL and time >180 mg/dL (1,2). Control-IQ Pro 2.0 will incorporate several new features intended to improve time-in-range with no significant increase in hypoglycemia.

The new features are as follows:

1) Normal activity with lower target range 90-130 mg/dL
2) Control-IQ Pro v2.0 includes enhanced auto-bolus stacking protection, reducing the likelihood of bolus stacking
3) The ability to enable/disable automatic boluses during Normal and Exercise activity
4) "Eating soon" feature
5) "Late bolus" feature

Additional Features of Control-IQ 2.0 Pro:

a. Expanded ranges for user inputs
b. Temporary Rates
c. Automatic bolus minimum
d. Timed Exercise mode
e. Control-IQ High alert change

f. Additional overflow bolus reminder
g. Allow automatic bolus after bolus timeout
h. Configurability through PC-based application

Each of these new features are described in detail in the Study IDE, the Control-IQ Pro v2.0 User Guide and study training materials that will be reviewed with subjects as part of device training.

2. STUDY OBJECTIVES, DESIGNS AND ENDPOINTS

2.1 Study Objectives

Primary objective: To demonstrate the safety of the Control-IQ 2.0 System for the management of type 1 diabetes by assessing rates of AEs after using new features.

Secondary objective: To further assess the safety of new features that potentially will be added to the current Control-IQ System; specifically, improved time in range 70-180 mg/dL, improved time in the tight glycemic range 70-140 mg/dL, and lower median glucose, with no increase in time <54 mg/dL.

2.2 Study Design

This feasibility study is a prospective, crossover study with a 48-hour supervised hospital phase, followed by a 4-week home study with sequential interventions (new features) and remote monitoring. Up to 110 subjects may sign the consent form and be screened, so that a maximum of 90 subjects (up to 30 subjects to wear the study device, and up to 60 personal contacts) may be enrolled. Subjects wearing the device will be both male and female, aged 14 and up, inclusive, who have used Control-IQ in closed-loop at least 80% of the 2-week time period before enrollment. Approximately 5 subjects will be enrolled in the initial 48-hr hospital phase. Approximately 25 additional subjects will be enrolled to participate in the at-home study. Each subject will use all features (current and new) and therefore will act as his/her own comparator. Remote real-time monitoring using the Dexcom G6 app will be required to be shared with their local contact(s) throughout the study, and with study staff for the first 10 subjects. After the first 10 subjects complete the study, required real-time alerts to study providers may be removed for future subjects after sponsor review and approval. Subjects will continue to share with their personal contacts.

The data collected in this study will be directly entered into an electronic data capture system (EDC) using electronic case report forms (eCRFs) when possible. Paper source may also be used. Subject data will include demographics, focused medical history, therapy data, and baseline and follow-up measures.

2.3 Study Endpoints

1) Primary Safety Endpoints:
    a. Significant Hypoglycemia time <54 mg/dL
    b. Severe hypoglycemia (needing assistance)
    c. DKA
    d. Serious Adverse Events
2) Secondary Safety Endpoints:
    i. Time <70 mg/dL
    j. Time > 250 mg/dL
    k. Overall TIR (70-180 mg/dL)
    l. Overall TIR (70-140 mg/dL)
    m. Post-prandial glycemic peak

n. 4-hour post meal glucose AUC
o. Sensor glucose median and interquartile range
p. CGM metrics daytime vs. nighttime

3. SUBJECT SELECTION

3.1 Subject Population

3.1.1 Inclusion Criteria:

1) Adult and adolescent male and female subjects >age 14 years
2) Clinical diagnosis of Type 1 diabetes for at least one year
3) Experienced Control-IQ user for ≥3 months.
4) Use of Control-IQ in closed-loop at least 80% of the 2-week time period before the first visit timepoint.
5) Not pregnant or planning a pregnancy during the time period of the study
6) Using only Humalog or Novolog insulin
7) ICR and ISF optimized per investigator judgement
8) Time in range (70-180 mg/dL) at least 50% on Control-IQ
9) Has current glucagon product to treat severe hypoglycemia (injectable or nasal) at home (will provide prescription if they do not have one)
10) Willing to:
    a. Share Dexcom G6 data with study staff and Tandem
    b. Share t:connect data with Tandem
    c. Eat meals with known carbohydrate amounts
    d. Take meal boluses as directed (use of different options as scheduled and instructed)
    e. Follow study Glycemic Treatment Guidelines for hypo and hyperglycemia
    f. Keep food and exercise diary
    g. Set accurate sleep schedule on pump
    h. Exercise while using exercise activity in Control-IQ at least twice weekly
    i. Complete questionnaires before and after using investigational device
    j. Sign an informed consent form
11) Willingness to use the Dexcom G6 app on their personal phone throughout the study, and share real time CGM information with a local contact and study staff.
12) Availability of a local contact who has access to the study participant, knows their whereabouts, and agrees to be promptly available if contacted by study staff. If the subject lives alone, the local contact must live within 30 minutes and have access to the subject overnight.

3.1.2 Exclusion Criteria:

1) Diabetic ketoacidosis (DKA) in the past 6 months
2) Severe hypoglycemia (needing assistance) in the past 6 months
3) Inpatient psychiatric treatment in the past 6 months
4) History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to Screening or is unwilling to agree to abstain from illicit drugs throughout the study
5) History of heart, lung or kidney disease determined by the investigator to interfere with the study

6) Use of glucocorticoids, beta blockers or other medications determined by investigator to interfere with the study
7) Use of long-acting insulin or any non-insulin glucose lowering agents (i.e. SGLT-2 inhibitor) other than metformin
8) Use of Afrezza during the study period
9) Febrile illness within 3 days of the start of the study
10) Subject is pregnant or lactating or intending to become pregnant before or during participation in this study
11) For subjects >50 years old or with diabetes duration >20 years who will be exercising as part of the 48 hour study, abnormal electrocardiogram consistent with increased risk of arrhythmia, ischemia, or prolonged QTc interval (> 450 ms)
12) Significant chronic kidney disease (eGFR < 60) or hemodialysis
13) Significant liver disease
14) History of adrenal insufficiency
15) History of abnormal TSH consistent with hypothyroidism or hyperthyroidism that is not appropriately treated

3.2 Subject Withdrawal or Termination

Subjects are free to withdraw from the study at any time and will be withdrawn if they inform the study team that they no longer wish to participate. Data collected prior to the subject's withdrawal will remain part of the study record and will be included in the analyses.

4. TREATMENT OF SUBJECTS

4.1 The t:slim X2 insulin pump with Control-IQ technology

The Control-IQ System is a US FDA approved device indicated for the treatment of type 1 diabetes in people age 6 years and older. The Control-IQ System is integrated with the Dexcom G6 CGM and uses CGM values to adjust insulin delivery with the goal of improving glucose control (time in range of 70-180 mg/dL). For the current study, a configurable version of software (Control-IQ Pro v2.0) will be installed in the t:slim X2 pump. Control-IQ Pro v2.0 settings will be configured by the investigators with the specific features to be tested during the following study period. Glucose values and patterns will be monitored weekly and reviewed at each study visit by study staff, or with real time phone follow up and review online on the web with an investigator if subjects have questions or concerns. Pump and CGM data will be uploaded to the t:connect diabetes management system weekly during study visits. Dexcom Share data will be sent continuously to Dexcom Clarity. Subjects will have immediate real time access to their glucose values through the Dexcom App or the CGM screen on their pump.

4.2 Enrollment procedure:

The potential study subjects will be recruited by the clinical site from among their current users of the t:slim X2 pump with Control-IQ technology. After a description of the study is provided by the investigator, the subject will be asked to sign the informed consent form (ICF). Assent will be obtained from subjects <18 years of age. The subject's local contact(s) must also sign the "Personal Contact Consent". Eligibility to enroll in the study will be assessed based on the inclusion/exclusion criteria. Use of Control-IQ in closed-loop at least 80% of the 2-week time period before enrollment is required and must be confirmed during the screening process. Enrollment information will be entered into the EDC system. In addition, demographic and relevant medical history will be collected at this time and entered into the eCRFs. The subject will be considered enrolled when the investigator attests that the subject meets all eligibility criteria on the study enrollment CRF.

All subjects will be required to use the Dexcom G6 app if not using already, and enable real-time alerts to followers. Study staff will collect names and phone numbers for 1-2 local personal contacts in case a participant cannot be reached during the study period. If the participant lives alone, they must have a contact who lives within 30 minutes of them.

4.3 Duration of therapy and follow-up:

All enrolled subjects will be followed throughout the 5-week study period.

4.4 Measurements and Evaluations

Event Schedule: The eCRFs will be completed by the investigator (or an authorized member of the investigator's staff) and entered into the EDC database per the event schedule described below.

315 **Table 1.** Event Schedule.

Procedure	Screening	Study Period						End of Study/Early Termination
	Days (up to 21 days prior to Day 1)	Days -21 to 0	Day 1 (+/- 3 days)	Day 8 (+/- 3 days)	Day 15 (+/- 3 days)	Day 22 (+/- 3 days)	Day 29 (+/- 3 days)	Day 29 (+/- 3 days)
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographics and Medical History	X							
Physical Examination/EKG[1]	X							
Glycemic outcomes	X							
Blood or capillary point-of-care samples for HbA1c	X							
Pregnancy Test[2]	X							
Baseline on Standard Control-IQ v1.0		X						
Training on Control-IQ Pro v2.0 Study Pump[3]		X	X					
48 Hour Supervised Study (Selected Subjects)		X						
Testing with Control-IQ Pro v2.0 Study Pump/ Features Updated, with f/u phone call 48 hours (+/- 1 day) after feature update			X	X	X	X	X	
Site Visit[4] w/ CGM Download		X	X	X	X	X	X	X
User Experience Survey								X
Discharge from the Study								X
Monitor and/or Record Adverse Events	X	X	X	X	X	X	X	X

[1]Vital signs will be measured during the initial screening visit. EKG required for subjects >50 years old or with diabetes duration >20 years who will be exercising as part of the 48 hour study
[2]For female patients of childbearing potential, results must be negative before study enrollment.
[3]Device training may be completed as soon as screening and enrollment are complete.
[4]Sites visits may be remote if updating of pump firmware is not required at the visit, per investigator discretion.

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Baseline Data Collection: Only Control-IQ users demonstrating use of Control-IQ in closed-loop at least 80% of the time during the 2 weeks before enrollment are eligible for the study. Data from the 2-week period before enrollment will serve as the baseline pump and CGM data.

Subject Completion or Early Withdrawal: The subject completes the study approximately 5 weeks after enrollment, or when they choose to withdraw from the study, if earlier than 5 weeks.

Data Collection:

The data will be collected per the schedule outlined below:

Table 2. Data collection frequency.

Procedure/Assessment	Baseline*	Weekly	Final
Informed Consent	X		
Release of Medical Records	X		
Screening for eligibility	X		
Report of AEs		X	X
Glycemic outcomes	X	X	X
Device Download	X	X	X
User Experience			X

*Includes demographics, and frequency of AEs

Investigators will assign a de-identified number to each subject and will be required to keep any study paperwork or electronic files in a secure private area. Audits will be conducted to help ensure that data is secure and entered within reasonable limits.

Informed Consent Process: All subjects must sign the ICF approved by the IRB to be enrolled in the study. Subjects <18 years of age will also complete the assent form. The subject will receive study team contact information (email and telephone) and be given ample opportunities to ask questions about the procedures, required schedule of data collection, and the benefits and risks of participating in the study before signing the ICF. If requested, the subject will receive a copy of the ICF to keep for their records. Subjects will be informed of any revisions to the ICF and any revisions must be signed and kept in the subject study file. Acquisition of the informed consent, and any revisions will be documented in the subject's eCRF.

Demographics: The following demographic data will be obtained: date of birth, gender, race, ethnicity, educational level, socioeconomic status, residence, employment status, weight, height, and type of health insurance.

Medical History: Medical history, including existing comorbidities deemed clinically relevant (e.g. retinopathy, nephropathy, neuropathy, history of cardiovascular events) will be collected at baseline. In addition, details specific to type 1 diabetes, including age at diagnosis, duration of disease, previous therapy, most recent HbA1c within the past 3 months, frequency of SH and DKA will be collected from the study subject in the baseline questionnaire and documented in the subject's eCRF. A new hemoglobin A1c (point-of-care of central laboratory measurement) will also be obtained at the screening visit.

Pregnancy: In order to reduce the risk of pregnancy, subjects of childbearing potential must agree to use an effective method of birth control while participating in this study. Acceptable methods of birth control for use in this study are barrier methods, intrauterine devices, or oral contraceptive pills. The Investigator or study staff will discuss this with the subject.

Device Training: All subjects will complete study device training before starting use of the study device. Subjects will be trained using the study approved device training checklist, and will be given a copy of the Study Participant Instruction Sheet. In addition to device training, the Study Participant Instruction Sheet reviews procedures for checking ketones, and when to contact study staff for assistance. Subjects will be instructed that the commercial t:connect mobile app will not connect to their study pump and is not intended to be used in the study.

Study staff will also assure subjects have set up the Dexcom G6 app with required alerts sent to study staff for the first 10 subjects.

Study staff will review with the study subject's personal contact(s) the following safety procedures, either through remote or in person training:

1) How to disconnect the pump
2) How to give glucagon
3) How to set up the Dexcom Follow app, and expectations for responding to alerts or phone calls from study staff.

4.5 Study Procedures

4.5.1 Phase 1: 48-hr supervised study in-clinic/transitional environment:

Approximately 5 subjects will be enrolled in Phase 1 of the study. The purpose of Phase 1 is to determine the safety of the Control-IQ Pro v2.0 system with use of the new features in a medically supervised, observed setting: 1) Lower target normal activity overnight and receiving auto-correction boluses, 2) Exercise Activity without autocorrections, and 3) Adjustments to meal bolusing.

After enrollment and collection of baseline data (use of the current standard Control-IQ commercial system for 1-3 weeks) subjects will be admitted in the evening and will switch from their personal t:slim X2 insulin pump with Control-IQ technology to the t:slim X2 study pump with Control-IQ Pro v2.0. Subjects will receive training on all of the new features and the instructions for using them during the ~48-hours of the study.

During this phase of the study, subjects will be remotely monitored by the study team, including a study physician, 24 hr per day. Pump and CGM alerts will be set to annunciate throughout the study. The study team will intervene if 1) CGM <70 mg/dL overnight, or 2) if a Control-IQ Low Alert occurs (indicating that the glucose is predicted to fall below 70 mg/dL within 15 minutes). Meal boluses will be supervised by study staff to ensure that the correct number of carbohydrate grams are entered into the bolus calculator.

At least one member of the study medical staff (Physician, NP) from will be present on site at all times. Up to 5 subjects will be studied at one time during the supervised phase. The goal of this

phase is to evaluate the safety of the system with correct and incorrect use of new features of the system.

Day 1:

Arrival: Subjects will arrive at least 3 hours prior to the dinner meal. After training of the new features of the Control-IQ Pro v2.0 are complete, subjects will switch from their personal Control-IQ pump to the Control-IQ Pro v2.0 pump. The Control-IQ Pro v2.0 pump will be configured with the lower target normal activity enabled, auto-boluses enabled for normal activity but disabled for exercise, and all sleep schedules disabled. Subjects will activate the "Eating Soon" feature ~1 hour prior to dinner, as intended for use, with a control range of 80-100 mg/dL. Subjects will then consume a dinner with at least 30 grams of carbohydrate, giving the full meal bolus prior to the meal as per their normal bolus behavior.

Subjects will use continue to use the Normal Activity setting with lower target (90-130 mg/dL) and automated correction boluses enabled for the overnight portions of the hotel study.

Day 2:

Subjects will consume a normal breakfast (at least 15 grams carbohydrate) with a normal meal bolus.

In the late morning of day 2, subjects will perform a ~40 minute exercise session (either on a stationary bike or treadmill, or a brisk walk outside) with the Exercise Activity setting ON (increased glucose target range, no auto boluses). Subjects will be instructed to monitor CGM values during exercise, to have fast-acting carbohydrate available and to treat themselves appropriately during the session. Study staff will be available to intervene if necessary. Subjects make take additional carbohydrate as necessary per their usual exercise preparation routine. Exercise may be discontinued for multiple low fingerstick readings, as per investigator discretion.

For lunch, subjects will perform a "late bolus" using the late bolus feature after consuming at least 30 gram carbohydrates. The late bolus should occur at least 30 minutes after completing the lunchtime meal.

For dinner, subjects will enable the "Eating Soon" feature for just over 3 hours straight prior to dinner, (re-enabling it ~every 70 minutes for 3 times total) intentionally reactivating the feature multiple times so it stays active. This intentional re-enabling of the feature is intended to assess safety if a subject were to keep this feature active for many hours in a row prior to a meal. Subjects will then bolus for their meal in the usual manner, consuming at least 30 gram carbohydrates.

Subjects will use continue to use the Normal Activity setting with lower target (90-130 mg/dL) and automated correction boluses enabled for the overnight portions of the hotel study.

Day 3:

Subjects will consume a normal breakfast (at least 15 grams carbohydrate) with a normal meal bolus.

In the late morning of day 3, subjects will perform a ~40 minute exercise session (either on a stationary bike or treadmill, or a brisk walk outside) with the Exercise Activity setting ON (increased glucose target range, no auto boluses). Subjects will be instructed to monitor CGM values during exercise, to have fast-acting carbohydrate available and to treat themselves appropriately during the session. Study staff will be available to intervene if necessary. Subjects make take additional carbohydrate as necessary per their usual exercise preparation routine. Exercise may be discontinued for multiple low fingerstick readings, as per investigator discretion.

For lunch, subjects will consume at least 30 gram carbohydrates, but will skip their meal bolus (missed meal bolus scenario) with the goal of letting the system bring down their blood sugar after the meal.

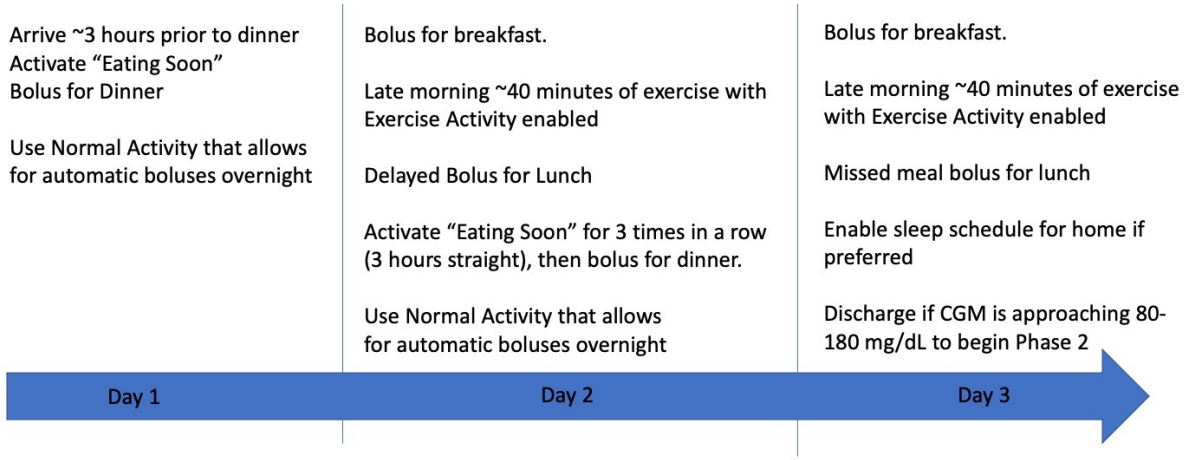
Subject will be asked to set-up/re-enable sleep schedules after lunch if they desire, or may continue to use the normal activity setting overnight with the required targets per each week of the study.

Subjects will be discharged home to begin Phase 2, as long as their CGM values are approaching 80-180 mg/dL at least 90 minutes after lunch, and remaining steady per investigator discretion.

Additional meals and snacks may be consumed by subjects as needed for satiety or treatment of hypoglycemia.

A schematic of the supervised challenges is shown below in Figure 1. The investigator on site may opt to give additional insulin boluses or carbohydrate treatments as necessary or end particular use of a feature, at their discretion for subject safety:

Figure 1. Schedule of supervised challenges.



During Phase 1, the following hyper and hypoglycemic treatment plan will be used:

Table 3. Hypoglycemia and Hyperglycemia Prevention and Treatment Plan during the supervised, 48 hour session.

Condition	Action Taken
CGM reading <70 mg/dL	A confirmatory fingerstick measurement will be performed. If fingerstick glucose ≥ 70 mg/dL, treatment may be initiated by the investigator (~4-16 g fast acting carbohydrate) per investigator discretion. Subjects will then perform a follow-up fingerstick measurement 15 minutes after treatment if CGM < 70 mg/dL. If fingerstick glucose < 70 mg/dL, treatment will be initiated by the investigator (~4-16 g fast acting carbohydrate) per investigator discretion. Subjects will then perform a follow-up fingerstick measurement 15 minutes after treatment if CGM < 70 mg/dL. This protocol will be repeated until the fingerstick is >70 mg/dL per standard clinical treatment for hypoglycemia.
Any time a subject has subjective symptoms of hypoglycemia	A fingerstick blood glucose measurement will be performed. Fast-acting carbohydrates may be given to any subject who is symptomatic or requests treatment.

CGM reading is >300 mg/dL for more than 1 hour	A confirmatory fingerstick measurement will be performed. If the subject's BG is confirmed to be >300 mg/dL, then ketones will be checked using the study-approved ketone meter.
BG confirmed >300 mg/dL for more than 1 hour and ketones are <0.6 mmol/L	A manual correction bolus may be delivered via the pump. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction dose given may be adjusted by the investigator. If BG fails to decrease by a minimum of 50 mg/dL in 1 hour, then study staff will replace the subject's infusion set with a new infusion set and the correction bolus will be repeated per the investigator's discretion.
BG confirmed >300 mg/dL for more than 1 hour and ketones are ≥0.6 mmol/L	A manual correction bolus may be delivered via injection to assure proper absorption in the setting of likely infusion set failure. Fingerstick BG and ketone measurements will be repeated after 1 hour. The correction dose given may be adjusted by the investigator. The study staff will replace the subject's infusion set with a new infusion set and the correction bolus will be repeated per the investigator's discretion. Control-IQ will be disabled by the investigator for the next 2-4 hours and until BG has returned to < 180 mg/dL.
Subject loses consciousness or has a seizure, or subject is unable to take oral carbohydrates	1 mg of IM glucagon or 3 mg nasal glucagon will be administered and 911 will be called. The study will be stopped immediately until sponsor conducts a full investigation to determine the root cause for the compromised system performance and is able to address all issues. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators.
No heart rate, no blood pressure	Perform resuscitation, call 911, and transfer subject to ER. Sponsor will conducts a full investigation to determine the root cause for the compromised system performance. Sponsor will also communicate the results of this root cause investigation to FDA and to study investigators.

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To allow subjects to continue using the study pump at discharge and proceed with further use of the study device in additional subjects, the study pump must be downloaded by study staff and the device download reviewed by the study PI and Tandem staff. The following success criteria must be met for continuation into the outpatient phase of the study:

1) No serious adverse events related to the study device or procedures.
2) No unanticipated adverse device effects.
3) Subject will be reminded to schedule a sleep activity setting if preferred for home use.
4) Subject must be able to complete system-related use tasks independently to be eligible to continue in the study as per the device training checklist.
5) Subjects must show understanding of the outpatient study safety plan, as described below in Phase 2: At-home study, as well as in sections 7.9 and 7.10, to include continued real-time sharing of glycemic data with the Dexcom G6 app and responding to calls from the study team that may result from sharing alerts.

4.5.2 Phase 2: At-home study

After enrollment and collection of baseline data, subjects will switch from their personal t:slim X2 insulin pump with Control-IQ technology to the t:slim X2 study pump with Control-IQ Pro v2.0. Subjects will receive training on all of the new features and the instructions for using them during the following week of the study. Subjects will keep a log of their use of the required features of the new pump for the week. Subjects will be required to attend the study site visit each week (+/- 3 days), during which time their pump and CGM data will be downloaded and they will receive instructions for the following week.

Remote real-time monitoring using the Dexcom G6 app will be required to be shared by subjects with their local contact(s) throughout the study, and with study staff for the first 10 subjects. After the first 10 subjects complete the study, required real-time alerts to study providers may be removed for future subjects after sponsor review and approval. This review will certify that:

1) No severe hypoglycemia events related to algorithm delivered automated insulin dosing occur that required study staff intervention because the subject was not aware/treating appropriately in the first 10 subjects.
2) No severe hyperglycemic events related to algorithm delivered automated insulin dosing occurred that required study staff intervention because the subject was not aware/treating appropriately in the first 10 subjects.

During the weekly required visit, the Control-IQ software in their pump will be reconfigured to support the following week's features. The configuration tool will be run by clinical staff from an approved study laptop, using Bluetooth to reconfigure the pump. If a software update to the pump is not required at the weekly visit, and the subject is able to download their pump remotely, the visit may be performed remotely per investigator discretion.

After each weekly download, staff will review the download to document correct use of each feature, and document this on the study CRF. If a subject is using a feature not per the study instructions (for example, using eating soon not just prior to meals), subjects will be re-educated

on the relevant instructions and this will be documented in the study CRF. All subjects will receive a phone call 48 hours (+/- 1 day) after each weekly feature update to review any new questions that may arise.

The feature use will be randomized per subject. The feature schedule is outlined below in **Table 4**:

Table 4: Schedule of prescribed use of standard vs. new features.

Participants will be sorted into cohorts. Each cohort will be randomly assigned the order in which they complete weeks A-D.

Study Period	Normal Activity Setting	Exercise Setting	Eating Soon	Late Meal Bolus
Baseline	Standard	Standard	N/A	N/A
2-day Supervised/Hotel Study	Lower Target Auto-bolus on Use while sleeping	Auto-Bolus Off x 2 required exercise sessions	Use once ~1 hour to meal Use once for 3 consecutive hours prior to a meal	One time
Week A	Lower Target Auto-bolus on	Auto-bolus off	40-60 minutes before every meal	Directed not to use
Week B	Lower Target Auto-bolus off	Auto-bolus off	40-60 minutes before every meal	Directed not to use
Week C	Lower Target Auto-bolus on	Auto-bolus off	As needed	As needed
Week D	Standard Target Auto-bolus on	Auto-bolus off	As needed	As needed

Prior to sending any subject home with the study device, study staff will assure the following safety instructions are reviewed with subjects as part of device training:

1) Completion of the study device training form, reviewing the new features of Control-IQ 2.0 and their required use.
2) Study subjects will be given a logbook to record use of the late bolus feature, to record the time they ate their meal relative to pressing the late bolus feature button, as well as to record start and end of exercise.

3) Subject will be asked to set-up/re-enable sleep schedules after lunch if they desire, or may continue to use the normal activity setting overnight with the required targets per each week of the study.
4) Study staff will collect names and phone numbers for 1-2 local personal contacts in case a participant cannot be reached during the study period. If the participant lives alone, they must have a contact who lives within 30 minutes of them.
5) Staff will review the outpatient hyper- and hypoglycemia treatment plans (Section 7.9 and 7.10) and expectations for real-time monitoring with each subject.

Observation and Recording of Adverse Events: Subjects will be required to report AEs. Open-ended questions and questions specific to SH and DKA will be included in all subject visits. An AE form will be completed for every adverse event reported by a subject. Any medical management of an event and the resolution of the event must be recorded in source documentation and on the appropriate eCRF using medical terminology.

4.6 Early Termination Visit (If Applicable)

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

4.7 Unscheduled Visits

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

4.8 Final Visit

Subjects will return all study supplies and complete the system usability scale survey. All study devices (glucose meter, ketone meter, insulin pump and CGM) will be downloaded. Participants will be permitted to keep the blood glucometer, blood ketone meter and any remaining CGM sensors at the end of the study, but will need to return all other devices, including insulin pump and related supplies.

5. STATISTICAL CONSIDERATIONS

5.1 Statistical Analysis:

This feasibility study is a prospective, crossover 5-week home study with sequential interventions (new features). Each subject will use all features (current and new) and therefore will act as his/her own comparator (paired data points). The study is designed to obtain a primary safety profile on new feature configuration

Descriptive statistics of the rates of significant hypoglycemia (< 54 mg/dl), severe hypoglycemia, DKA, and serious adverse events will be reported for baseline and each intervention configuration. Additionally, descriptive statistics of glycemic outcomes will for baseline and each intervention configuration will be provided. The statistics will include:

- % time < 54 mg/dl median and interquartile range
- Number of events of severe hypoglycemia (needing assistance) and percent of individuals experiencing at least one event of severe hypoglycemia.
- Number of events of DKA and percent of individuals experiencing at least one DKA event.
- Rate of serious adverse events per 100 patient years.
- % time < 70 mg/d median and interquartile range
- % time > 250 mg/dl median and interquartile range
- % time between 70-180 mg/dl median and interquartile range
- % time between 70-140 mg/dL median and interquartile range
- Post-prandial glycemic peak median and interquartile range
- 4-hour post-meal glucose AUC median and interquartile range
- Median sensor glucose and interquartile range
- % time in automation median and interquartile range

These statistics will be calculated at the patient-level, and a sub-analysis of daytime vs. nighttime statistics will be provided.

Additionally, the distributions of glycemic outcomes for baseline and each intervention configuration will be depicted using boxplots. The individual-level difference between each intervention configuration and baseline will also be depicted using boxplots.

Success Criteria / Goal: The 48 hour observed session will be considered useful for data analysis if the subject has at least 75% CGM availability during the session.

6. Risks and Benefits

6.1 Potential Risks and Benefits of the Device

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with T1D and participants will be monitored for this.

6.2 Venipuncture Risks

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

6.3 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood glucose and sometimes Hemoglobin A1c (HbA1c) or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

6.4 Subcutaneous Catheter Risks (CGM)

With CGM use participants are at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours, it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

On rare occasions, the CGM may break and leave a small portion of the sensor probe under the skin that may cause redness, swelling or pain at the insertion site. The participant will be instructed to notify the study coordinator immediately if this occurs.

6.5 Risk of Hypoglycemia

As with any person having T1D and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

6.6 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. In this study, subjects will take full insulin boluses for all their meals. All subjects will be issued a ketone meter and ketone strips to use to carefully monitor for hyperglycemia and be given instructions on how to mitigate hyperglycemia should it occur.

6.7 Risk of Device Reuse

All devices will be used by a single study participant only. There will be no device re-use.

6.8 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or from tape to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore, participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, and the home glucose and ketone meter will be collected for the study as measures of diabetes self-management behaviors. The downloaded data from the subject's home pump will include data from prior to the date of the screening visit. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

6.9 Known Potential Benefits

By using these improvements to Control-IQ technology, we expect to see a reduction in the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control. Hyperglycemia will likely be reduced as well.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control glucose levels. The individual participant may or may not benefit from study participation.

6.10 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, (4) rapid reversal of hypoglycemia and

hyperglycemia can be achieved, and (5) the Control algorithm (Control-IQ) is already FDA approved since early 2020 and has shown significant (10+%) TIR improvements in individuals with type 1 diabetes, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes with the new features added to Control-IQ.

6.11 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

7. Description of the Study Devices and Use

All study supplies will be provided by Tandem Diabetes Care, Inc.

7.1 Insulin Pump

The study system will include the Tandem t:slim X2 insulin pump (K201214, Tandem Diabetes Care, San Diego, CA).

7.2 Continuous Glucose Monitoring

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

7.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the study-assigned blood glucose meter (glucometer) and the CGM device will be calibrated if needed using the study glucometer and strips in accordance with the manufacturer's labeling. (Contour NEXT or Contour NEXT ONE, Ascensia Diabetes Care US, Inc., 5 Wood Hollow Rd, Parsippany, NJ 07054 USA)

7.4 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meter and strips in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra device will not be used. (Abbott Diabetes Care Inc., 1360 South Loop Road, Alameda, CA 94502 USA)

7.5 Study Device Accountability Procedures

Device accountability and inventory will be documented in each subject's study chart, to include detailed inventory records of the study glucose meter, study ketone meter, study CGM supplies, and Tandem insulin pump system.

7.6 Blood Glucose Meter Testing

- QC testing will be performed before issuing the blood glucose meter to a subject. Additional QC testing may be performed per manufacturer guidelines.
- A tested meter will not be used in a study if it does not read within the target range concentration per manufacturer labeling.
- Participants will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements.
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labelling of the study CGM device.

7.7 Blood Ketone Testing

- QC testing will be performed before issuing the blood ketone meter to a subject. Additional QC testing may be performed per manufacturer guidelines.

- A tested meter will not be used in a study if it does not read within the target range concentration per manufacturer labeling.
- Participants will be instructed on how to perform blood ketone testing.
- Participants will be given guidelines for treatment of elevated blood ketones.

7.8 CGM Calibration

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

7.9 Hyperglycemia Safety Protocol

In Phase 2, for outpatient use of the study device, study staff will:

1) Provide emphasis on having a low threshold of suspicion to changing out the infusion set, and emphasizing that "when in doubt, change it out." Participants should be told that sufficient supplies are available so that they should not hesitate to change out the infusion set if they have any doubt that it is working well.
2) Participants will receive local alerts on their phone from their Dexcom G6 app if CGM reading is >300 mg/dL, and if this continues for 60 minutes, or if CGM is greater than 400 mg/dL at any time, the participant will be instructed to take the following steps:
   a. Perform a blood glucose meter check.
   b. If the blood glucose is >300 mg/dL, check for blood ketones with the study meter
   c. If the ketone level is >0.6 mmol/L or blood glucose remains elevated above 300 mg/dL for one hour after a correction dose and is not decreasing substantially, or ketones > 2.5 mmol/L at any time, take correction insulin by injection, change insulin (pump) infusion site and contact study staff for additional instructions, to include turning off Control-IQ for the next 2-4 hours and until and until BG has returned to <180 mg/dL.
3) For the first 10 subjects who are required to have real-time CGM remote alerts sent to study staff active through the Dexcom G6 app, providers will receive remote alerts for CGM > 300 mg/dL, and if this does not resolve after 1 hour, or CGM rises to > 400 mg/dL, providers must call subjects and/or their personal contact(s) to implement the study safety plan of checking ketones and take corrective action.
4) If the subject needs to give an injection of insulin by syringe, Control- IQ will be disabled for the next 2- 4 hours and until BG has returned to <180 mg/dL.
5) When a subject contact is made about the hyperglycemia safety plan, they must speak directly to a Certified Diabetes Care and Education Specialist, Physician's Assistant, Registered Nurse, Nurse Practitioner, or Physician to assure this safety plan is being followed per protocol.
6) If ketones are >2.5 mmol/L, or >0.6 mmol/L for more than 60 minutes, and glucose values are not decreasing an hour after an injection of insulin, the Site PI must be informed within one hour if he/she is not already aware of the event (if the site PI will not be available, then the site PI should designate another investigator for the period he/she will not be available so that it is clear who has this responsibility). Study staff must attempt to ascertain whether the participant has the capacity to care adequately for themselves with guidance based on current symptoms and rate of resolution, or if their

personal contact is able to assist to the necessary degree. If based on their experience and judgement, they believe the participant may not be adequately able to care for themselves without assistance, or the subject's personal contact is not providing adequate assistance for the situation, then they must either directly communicate with someone on the scene whom they judge to have that capacity, or call 911, or both.

7) If study staff conclude that the participant needs emergency care, the participant/personal contact should be told to go to an emergency department. Study staff should determine which emergency department (ED) the participant will be taken to and follow up within 15 minutes of the expected arrival time to make sure the participant arrived.
8) If the study staff calls 911, they should remain on the telephone with the participant/personal contact until the ambulance arrives and speak to the Emergency Medical Technician to provide history and determine where the participant will be taken.
9) When a participant is sent to the ED, a study staff member should speak with a member of the medical staff (e.g., physician, PA, NP, nurse) at the ED to confirm arrival and provide information about the reason for referral to the ED.
10) If there is serious concern for the well-being of the participant and the participant cannot be reached, then study staff should attempt to reach the study participant's personal contact(s). If no contacts are available or their contacts do not succeed in reaching them, then 911 should be called immediately and a well-being check should be requested. Study staff must follow up on and document the results of the well-being check.

7.10 Hypoglycemia Safety Protocol

In Phase 2, for outpatient use of the study device, hypoglycemia low threshold alerts will be set to 70 mg/dL, and if a participant's CGM reading is <70 mg/dL, subjects will be instructed to treat with ~15 grams of carbohydrate, and perform fingerstick testing as necessary per CGM manufacturer instructions.

In phase 2, all subjects will be using the Dexcom G6 app to share real-time CGM data with their local contact(s). In addition, the first 10 subjects in the study will share real-time CGM data with the study staff at all times. Study providers will be notified of CGM predictive low alerts below 55 mg/dL in real-time (urgent low soon alert – notifies when sensor glucose will be at or below 55 mg/dL within 20 minutes). If the event does not resolve in 15 minutes showing a rising CGM value, providers will call the subjects and/or care partner(s) to assure adequate carbohydrate intake or other intervention was given.

8. Adverse Events, Device Issues, and Stopping Rules

8.1 Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (see section 8.2 for reportable adverse events for this protocol).

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

Results in death.

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

Requires inpatient hospitalization or prolongation of existing hospitalization.

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

Is a congenital anomaly or birth defect.

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

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

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

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

8.2 Reportable Adverse Events

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

1. A serious adverse event
2. An Adverse Device Effect as defined in section, unless excluded from reporting in section 8.9
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

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

Pregnancy occurring during the study will be recorded.

8.3 Hypoglycemic Events

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

8.4 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥0.6 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥2.5 mmol/L, even if there was no communication with a health care provider

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

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

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

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

Treatment provided in a health care facility

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

8.5 Relationship of Adverse Event to Study Device

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

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

Yes

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

No

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

8.6 Intensity of Adverse Event

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

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

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

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

8.7 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The investigator's assessment will be recorded.

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

8.8 Outcome of Adverse Event

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

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

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

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

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

An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.

The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

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

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

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will

be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

8.9 Reportable Device Issues

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

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

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

8.10 Pregnancy Reporting

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

8.11 Timing of Event Reporting

SAEs and UADEs must be recorded within 24 hours via completion of the serious adverse event form and sponsor notification.

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

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

Upon receipt of a UADE report, the study principal investigators will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the Sponsor (Tandem Diabetes Care) within ten working days of becoming aware of the UADE per 21CFR 812.46(b)(2). The Sponsor must determine if the UADE presents an unreasonable risk to participants. If so, all investigations, or parts of investigations presenting that risk, will be 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.

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

8.12 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

1) 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*
2) The participant requests that the treatment be stopped
3) Participant pregnancy
   If pregnancy occurs, the participant will be discontinued from the study entirely. Otherwise, even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.
4) During phase 1, one episode of severe hypoglycemia (as defined in section 8.3) or DKA (as defined in section 8.4)
5) During phase 2, two distinct episodes of DKA as defined in section 8.4
6) During phase 2, two distinct episodes of severe hypoglycemia as defined in section 8.3
7) The investigator may have a subject temporarily stop use of Control-IQ 2.0 during minor illness, such as temperature > 101.5 for one night, or rapid resolution of an allergic reaction. The investigator will permanently discontinue use of the study device if the subject experiences a period of significant illness, prolonged fever with temperature >101.5 more than one day, use of oral or injectable glucocorticoids, use of epinephrine for the emergency treatment of a severe allergic reaction or asthma attack with potential continued symptoms, or if a subject is admitted to the hospital for any reason.

8.13 Criteria for Suspending or Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in sections 8.3 and 8.4), use of the study device system will be suspended while the problem is diagnosed.

Study activities will also be stopped for 3 or more episodes of severe hypoglycemia (as defined in sections 8.3) or 3 or more episodes of DKA (as defined in sections 8.4), regardless of the underlying cause.

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

The Sponsor (Tandem Diabetes Care) will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The Sponsor will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

8.14 Independent Safety Oversight

This is a single site, short-term feasibility study. The clinical site principal investigator will review all reported adverse events and adverse device effects, and report them to the sponsor as required.

8.15 Risks

The potential risks associated with use of the study device are described in section 6.1

Additional risks are minor and/or infrequent and include:

1) Pain, bruising, redness, or infection from fingersticks or blood draws
2) Loss of confidentiality

9. Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

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

9.2 Prohibited Medications, Treatments, and Procedures

Participants using other insulins at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

Treatment with any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas and naturaceuticals) or Afrezza will not be permitted during the trial.

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

9.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

10. Data Collection and Monitoring

10.1 Case Report Forms and Device Data

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

When data are directly collected in electronically, this will be considered the source data. The clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

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

10.2 Study Records Retention

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

10.3 Protocol Deviations

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

10.4 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.

10.5 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.

10.6 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.

10.7 Participant and Data Confidentiality

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or authorized representatives from the clinical site(s) or Tandem Diabetes Care, Inc., may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted from the clinical site(s) and sent to and stored at Tandem Diabetes Care. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the clinical site(s). Permission to transmit data will be included in the informed consent

10.8 Participant Withdrawal

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

10.9 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be securely stored at the clinical site. De-identified participant information may also be provided to the Sponsor consistent with these guidelines.

11. References

1. Brown SA, Kovatchev BP, Raghinaru D, Lum JW et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. New England Journal of Medicine Oct 2019, DOI: 10.1056/NEJMoa1907863.
2. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L et al. A randomized trial of closed-loop control in children with type 1 diabetes. New England Journal of Medicine August 2020, DOI: 10.1056/NEJMoa2004736