UNIVERSITY of VIRGINIA HEALTH SYSTEM | School of Medicine

UVA CENTER FOR DIABETES TECHNOLOGY

SGLT2 Inhibitor Adjunctive Therapy to Closed Loop Control in Type 1 Diabetes Mellitus

Protocol Chair

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KEY ROLES

Protocol Principal Investigator	
Name, degree	Ananda Basu, MD
Institution Name	University of Virginia Center for Diabetes Technology

PROTOCOL VERSION HISTORY

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0				Original Protocol
1.1	Mary Oliveri	Mary Oliveri	24-Oct-2019	FDA Review: • Modified Figure 1: Study Diagram to include extra check in visit post CiQ training • Added to Inclusion Criteria (section 4.4): insulin pump use for six months • Modified Exclusion Criteria (section 4.5): eGFR lab value from below 45 to below 60 mL/min/1.73 m2 • Added to Ketoacidosis Management (section 6.3): ketone measurement will be obtained any symptoms, change of conditions, and as described in Glycemic Treatment Guidelines • Added to Empagliflozin Treatment Group (section 9.1.1): Participant will meet the following criteria to continue study participation after the completion of the Run-In phase during the Main Study: ○ Adherence to study protocol ○ Ketone testing at least 2 times daily, preferably 4 times, with monitored values not greater than 0.6/mmol on at least two successive occasions ○ No adverse events relating to perineal infections, symptomatic postural hypotension, no evidence of significant hypoglycemia (< 54 mg/dl) or any other listed adverse effects of medication. • Added to Check In visits (section 9.4): Two visits will occur after the Control-IQ Training Visit. • Added to Ketoacidosis Management (section 10.5): If ketones > 0.6 mmol/L, participants will be advised to stop the drug and then recheck ketones in 3-4 hours. Participants may restart the use

				of Empagliflozin after the ketone measurement if <0.6 mmol/L. All ketosis events should be recorded and evaluated in participants who are taking the study drug. • Added to Empagliflozin Adverse Reactions (section 12.2.1): Participates will also be advised that a majority of infections can be prevented by maintaining attention to basic hygiene include regular washing after urination. • Added to Stopping Rules (section 13.9.2): In the event that two subjects experience urosepsis, AKI, fournier's gangrene, severe genital mycotic infections and hypotension requiring hospitalization, the study will be paused to discuss events with the DSMB.
1.2	Mary Oliveri	Mary Oliveri	27-Oct-2019	FDA Review: • Added sentence for clarification (Chapter 6): Participants will download the study equipment approximately one time per week or as frequently as needed. • Added sentence for clarification (section 9.5): Participants will be instructed to download the study devices (i.e. insulin pumps, CGM, ketone meters, activity tracker, etc…) each week, or as needed, to secure data collection, except the ketone meter which will assess ketosis events). • Added to Ketoacidosis Management (section 10.5): Experimental participants will be advised to check ketones if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. Added to Adverse Event (section 13.1.1): now includes study drug in definition. Modified sentence (section 13.2.2): Ketosis as defined by symptoms and ketones regardless of treatment provided in a health care facility. Modified participants' stopping rules (section 13.9.1):

				○ Two distinct episodes of DKA that are not attributable to the study drug ○ One distinct episode of DKA directly attributable to the study drug
1.3	Mary Oliveri	Mary Oliveri	30-Oct-2019	FDA Review: • Inserted that study drug is not approved for use in T1DM patients (section 1.2). • Inserted User Manual language regarding the pumps response to missing CGM data (section 9.6).
1.4	Mary Oliveri	Mary Oliveri	01-Nov-2019	IRB Pre Review Comments from 04-Oct-2019. • Added that Equipment training in the Pilot Study is intended to begin immediately after screening eligibility has been met (section Chapter 6). • Clarified sentence to read that staff & participants will be at the hotel admission (section 7.1).
1.5	Laura Kollar	Mary Oliveri	24-Mar-2020	Study Team Modifications: • DSMB reduced Empagliflozin from 10 mg/daily to 5 mg/daily post-pilot study review. • Empagliflozin dosage instructions (section 3.3). • The study physician will determined screening test(s) needed for pilot participants to proceed to the Main Study. (section 4.1). • Corrections to the Glycemic Treatment Guidelines (section 7.5). • Virtual study visits may take the place of in-person study visits (Chapter 9). • Participants will be asked to record two days of baseline ketone values before initiating the use of the study drug (section 9.1.1). • Ketone meters will no longer be downloaded each week (section 9.5).

				• Study participants will log daily ketone values in an online resource for ongoing assessment purposes (section 9.5). • Blood glucose check in section 10.3 conflicts with section 7.4. • Clarified that Pregnancy will not be considered an adverse event (section 13.1.1). • A Data and Safety Monitoring Board (DSMB) will review compiled safety data after the completion of 10 Main Study participants. As a safety measure, the Board will review if the rate of mild ketosis greater than 40% (B-OH-B level > 0.6 mmol), 20% significant ketosis (B-OH-B > 1.5 mmol) and more than 5% DKA (B-OH-B > 3 mmol) to be considered significant to stop the study (section 8.3). • Other miscellaneous corrections throughout document.
1.6	Mary Oliveri	Ralf Nass; Laura Kollar	06-Apr-2020	Response to FDA questions 03-Apr-2020: • Clarified the Pilot participants lab work needed to proceed into Main Study: Pilot participants may enroll the Main Study. The study physician may request repeat laboratory values if values are greater than 6 weeks from Pilot screening laboratory values. A current urine/blood pregnancy test will be required prior to enrolling into the Main Study (section 4.1). • Added for clarification: Main Study participants who did not participate in the Pilot Study may use historical lab results that are dated within 2 weeks of the screening appointment (section 4.6). • The study physician has the discretion to exclude a study participant if concerned about

				their safety in this trial (section 4.6).
1.7	Mary Oliveri		10-Apr-2020	Response to FDA questions 07-Apr-2020: • Added: Empagliflozin is available only in 10 mg and 25 mg film coated unscored tablets. For this study, the participants will be provided 10 mg tablets and a pill splitter. They will be instructed to split only 1 tablet at a time and take each half tablet (5mg each) on subsequent days. Participants will be cautioned against spitting more than one tablet at a time (section 3.3). • A Data and Safety Monitoring Board (DSMB) will review compiled safety data after 10 participants complete 4 weeks of the Main Study. Absence of serious adverse events related to Empaglifozin, the participants will continue with study participation pending DSMB review (section 8.3). • Added: The study team will download the ketone meter whenever the study subject attends an in-clinic visit (section 9.5).
1.8	Mary Oliveri		19-Apr-2021	Study Team Modifications: • Remove exclusion criteria of 'Having a family member(s) 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

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: SGLT2 Inhibitor Adjunctive Therapy to Closed Loop Control in Type 1 Diabetes Mellitus

Protocol Version: v1.8

Protocol Date: 19-Apr-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. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

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

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

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

Investigator's Signature _____Date: _____ / _____ / _____

Investigator's Name: _____

Site Name: University of Virginia

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADRR	Average Daily Risk Range
AP	Artificial Pancreas
BiQ	Tandem t:slim X2 Insulin Pump with Basal-IQ Technology
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CiQ	Tandem t:slim X2 Insulin Pump with Control-IQ Technology
CSII	Continuous Subcutaneous Insulin Injection
DKA	Diabetic Ketoacidosis
DSMB	Data Safety Monitoring Board
EMPA	Empagliflozin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBGI	High Blood Glucose Index
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
JDRF	Juvenile Diabetes Research Foundation
LBGI	Low Blood Glucose Index
NIH	National Institutes of Health
POC	Point-of-Care
SAP	Sensor-Augmented Insulin Pump
SGLT2	Sodium-Glucose Cotransporter 2
SGLT2-i	Sodium-Glucose Cotransporter 2-inhibitor
QC	Quality Control
UI	User Interface

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	SGLT2 Inhibitor Adjunctive Therapy to Closed Loop Control in T1D
Investigational Device	Tandem Control-IQ with G6 Continuous Glucose Monitor (CiQ)
Investigational Medication	Empagliflozin 5 mg daily
Objectives	To evaluate the safety and efficacy of combining SGLT2 inhibitors with closed loop control
Study Design	The study is a randomized control trial where approximately 60 participants will be in the trial for approximately 10 weeks. A Pilot Study with approximately five (5) participants will use the Basal-IQ insulin therapy + Empagliflozin 10 mg daily. These participants will participate in an estimated 36-48 hour hotel admission to initiate use of Closed Loop Control (CLC) with the Tandem t:slim X2 with Control-IQ Technology (CiQ) with Empagliflozin (CiQ-EMPA). The safety data from the hotel admission will be presented to the DSMB for review. Upon DSMB approval, up to 40 participants will be randomized 1:1 to (a) CiQ x 4 weeks with or without Empagliflozin 5 mg daily (CiQ-EMPA vs. CiQ-NO EMPA) then Basal-IQ x 2 weeks with or without Empagliflozin 5 mg daily (BiQ-EMPA vs. BiQ-NO EMPA) or (b) Basal-IQ x 2 weeks with or without Empagliflozin (BiQ-EMPA vs. BiQ-NO EMPA) then CiQ x 4 weeks with or without Empagliflozin (CiQ-EMPA vs. CiQ-NO EMPA)
Number of Sites	1
Endpoint	To demonstrate the efficacy of Empagliflozin as adjuvant therapy with Basal-IQ therapy vs a closed loop artificial pancreas system (CiQ-EMPA) in patients with T1DM. The primary efficacy outcome variable will be time in range (70-180 mg/dl).
Population	Key Inclusion Criteria • Age 18-65 • Diagnosis of Type 1 Diabetes Key Exclusion Criteria • Hemoglobin A1c > 9%
Sample Size	• Enrollment for the Pilot Study will proceed with the goal of completing approximately 5 participants in the trial. • Enrollment for the Main Study will proceed with the goal of completing approximately 40 subjects, 10 subjects in each group.
Treatment Groups	With Empagliflozin 5 mg daily: • CiQ x 4 weeks (CiQ-EMPA) then Basal-IQ x 2 weeks (BiQ-EMPA) • Basal-IQ x 2 weeks (BiQ-EMPA) then CiQ x 4 weeks (CiQ-EMPA) Without Empagliflozin: • CiQ x 4 weeks (CiQ-NO EMPA) then Basal-IQ x 2 weeks (BiQ-NO EMPA) • Basal-IQ x 2 weeks (BiQ-NO EMPA) then CiQ x 4 weeks (CiQ-NO EMPA)
Participant Duration	Approximately 10 weeks
Protocol Overview/Synopsis	Up to five participants will participate in a Pilot Study. These participants will wear the Basal-IQ insulin pump, continuous glucose monitor, and take one tab daily of Empagliflozin 10 mg for about 2-3 weeks at home. They will then participate in a 36-48 hour hotel admission to begin the use of Control-IQ System with Empagliflozin. After DSMB review of safety data, up to 40 participants will be enrolled to begin the Main Study where, in a crossover design, participants will use the Control-IQ for 4 weeks and then Basal-IQ for 2 weeks, with the drug given at the dosage of 5mg per day or without drug.

STUDY VISITS AND PROCEDURES SCHEDULE

	Screening	Hotel Admission	Randomization & Equipment Training	Control-IQ Use	Equipment Training	Basal-IQ Use	Equipment Training	Follow-Up
Location	Clinic/Virtual	about 36-48 hours	Clinic/Virtual	Home x 4 weeks	Clinic/Virtual	Home x 2 weeks	Clinic/Virtual	Home
Informed Consent	X							
Eligibility Assessment	X							
Medical History	X							
HbA1c	X							
Blood Testing: TSH, CMP (additional labs as necessary)	X							
Pregnancy test (if applicable)	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X							
Physical Exam	X							
Vital Signs (including height/weight)	X							
Randomization			X					
Questionnaires			X	Post Use		Post Use		X
Review diabetes management and AEs	X	X		X		X		X

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Chapter 1: Background

1.1 Introduction

Current automated insulin delivery device systems providing dynamic insulin infusion, while improving prandial glucose control compared to conventional open loop therapies, have been unable to normalize prandial glucose control in T1DM. Strategies that have been used/considered in AP systems to improve prandial control include a) hybrid system that requires the patient to announce meals by entering the carbohydrate content; b) system with meal announcement that is partially or completely independent of meal carbohydrate content, and c) fully automated system with no meal announcement. Notably, a fully automated CLC system would lower the significant patient burden linked to prandial glucose control. Postprandial glucose control is a key determinant of HbA1c, the clinical gold standard for optimal glucose control. While meal carbohydrate content is the major factor for prandial glucose excursions, precise determination of meal carbohydrate content (that is associated with better glycemic control and lower glucose variability) during free living remains a significant challenge for the patients with an average error in carbohydrate counting of ~20% with most patients underestimating their carbohydrate content hence leading to increased prevalence of prandial hyperglycemia.

Clinical trials with fully automated AP systems have mostly been in small number of patients and in the in-patient settings for short durations [1, 2]. These trials have demonstrated significant postprandial hyperglycemia with a risk for late postprandial hypoglycemia. The availability of newer antidiabetic drugs provide the opportunity to test these medications as adjuvants together with conventional or CLC algorithms, to determine the effects, if any, of combination therapy, for improvements in postprandial and overall glucose control in individuals with T1DM. The adjuvants that have been tried in very short-term inpatient trials include pramlintide (amylin analogue that delays gastric emptying and lowers postprandial glucagon concentrations) [3-5] and Glucagon-like-peptide 1 receptor analogues (delays gastric emptying and lowers postprandial glucagon concentrations) and GLP-1 receptor agonists [6]. These studies have demonstrated modest improvements in CGM parameters (time in range and glucose variability) without increasing hypoglycemia in T1DM subjects.

1.2 Empagliflozin (SGLT-2 inhibitor) in TID

Inhibitors of sodium-glucose cotransporter-2 have been approved for use in type 2 diabetes where large clinical trials have demonstrated clinically significant improvements in glucose control (viz., HbA1c) and cardiovascular events [7]. While not FDA approved for use in adults with Type 1 diabetes subjects, these drugs have also been tested in randomized controlled clinical trials in these patients to evaluate their safety and efficacy. The EASE program [8] included two

double-blind, placebo-controlled phase 3 trials in > 1700 patients with T1DM. These trials tested 2.5 mg, 10 mg and 25 mg tablets vs. placebo over 26-52 weeks. The results showed that Empagliflozin lowered HbA1c, lowered total daily dose of insulin (by 10-13%) while increasing time in range (by up to 12%) without any increase in the frequency or severity of hypoglycemia. Simultaneously, there were improvements in body weight (by up to 3.5 Kg), blood pressure and glucose variability.

However, adverse effects pertaining to genital infections, diabetic ketoacidosis, and ketosis without acidosis were between 2-3 fold higher with Empagliflozin than placebo. Due to the glycosuric effects of this class of drugs, it is noteworthy that the characteristic hyperglycemic milieu often seen during classical episodes of diabetic keto-acidosis are not observed in ketoacidosis related to SGLT2 drug use where the ambient glucose concentrations are frequently < 250 mg/dl. This observation has prompted the creation of the condition of "euglycemic diabetic keto-acidosis" associated with SGLT2 drug use. Risks for development of ketosis were deemed to be due to concomitant illnesses (viral infections, gastro-enteritis), insulin pump failure, alcohol excess, extreme/endurance sports and low carbohydrate diet (< 100 grams/day). Suggestions for prevention of ketosis in patients on SGLT2 inhibitor therapy are to avoid use of this class of drugs in those with HbA1c > 9%, temporary drug discontinuation for 24-48 prior to planned surgery, fasting, intercurrent illnesses or prolonged physical activity, early recognition of symptoms of ketosis (malaise, nausea, vomiting, abdominal pain, excess thirst), regular point of care ketone monitoring (6-12 hourly) especially if glucose > 9mmol. The putative STICH protocol has recently been recommended for management of diabetic ketoacidosis associated with use of SGLT2 inhibitor therapy [9]. This includes **ST**op drug, **I**nject bolus insulin (1.5 times the usual correction bolus), **C**onsume 30-60 grams of carbohydrate and **H**ydrate with 200-500 ml of fluids. The above sequence needs to be repeated every 1-2 hours with recheck of ketones in 2-4 hours. Medical attention should be sought if any of the steps cannot be followed, particularly if fluids cannot be maintained or if ketonemia does not resolve within 4-6 hours.

The increased risk of ketosis and DKA in SGLT2 users with T1DM may not preclude use of this class of drugs for the management of T1DM given their clinical benefits in RCTs in T1DM patients (described above) and the cardiovascular benefits in T2DM patients. As always, careful patient selection, patient education and monitoring strategies need to be developed and tested to ensure patient safety.

1.3 Artificial Pancreas with Empagliflozin (SGLT2-i) use in T1D

Adjuvant use of antidiabetic medications in combination with automated insulin delivery systems have been tested in short term clinical trials in T1DM. The drugs tested include pramlintide and GLP-1 receptor agonists [6]. To the best of our knowledge, there are no published clinical trials on the safety and efficacy of combining SGLT2 inhibitors with closed loop control. In contrast to

the above trials, where both pramlintide and GLP-1 agonists need to be infused or injected, Empagliflozin, an SGLT2 inhibitor, is taken as a once daily oral tablet making it simple, practical and not burdensome for patient adherence. Additionally, given its proven benefits on glucose control in several large RCTs involving >1700 patients with T1DM, it is necessary to test its efficacy and safety, in combination with automated insulin delivery systems, in T1DM subjects as part of a clinical trial that we propose. Additionally, albeit the increased prevalence of ketosis with empagliflozin use in the published trials, given the accumulated clinical information and experience, we will ensure that appropriate precautions including judicious selection of research participants (HbA1c of 9% as cutoff for enrollment), educating subjects on avoiding circumstances that could predispose to ketosis (intercurrent illnesses, alcohol excess, low carb diet etc) and careful monitoring, will prevent and further lower the risks of ketosis during the proposed, short term clinical trial.

1.4 Basal-IQ with Empagliflozin use in T1D

The Basal-IQ feature in the t:slim insulin pump reduce the frequency and duration of low-glucose events by predicting glucose levels 30 minutes ahead and suspending insulin if they are expected to drop below 80 mg/dL. Use of Empagliflozin during Basal-IQ phase is to explore its safety and feasibility as an adjunctive agent, compare its use vs Control-IQ phase and to gather data on its effect on postprandial glucose excursions.

1.5 Study Objective

The purpose of this study is to demonstrate the safety and efficacy of the use of Empagliflozin as an adjunctive therapy with the Tandem t:slim X2 insulin pump with Control IQ Technology vs. the Tandem t:slim X2 insulin pump with Basal-IQ Technology in T1D participants.

1.6 Study Design

The Main Study is a randomized control trial, aged 18 to 65 y.o. at time of consent, will be in the trial for up to 10 weeks. The first five participants will be enrolled in a Pilot Study to use the Basal-IQ with Empagliflozin 10 mg daily for approximately two weeks. These participants will participate in an estimated 36-48-hour hotel admission to initiate use of Closed Loop Control (CLC).

The safety data from the Pilot Study will be presented to the DSMB for review. Upon DSMB approval, approximately 40 participants will be randomized 1:1 in a crossover design:

With Empagliflozin:

CiQ x 4 weeks (CiQ-EMPA) then Basal-IQ x 2 weeks (BiQ-EMPA)

Basal-IQ x 2 weeks (BiQ-EMPA) then CiQ x 4 weeks (CiQ-EMPA)

Without Empagliflozin:

CiQ x 4 weeks (CiQ-NO EMPA) then Basal-IQ x 2 weeks (BiQ-NO EMPA)

Basal-IQ x 2 weeks (BiQ-NO EMPA) then CiQ x 4 weeks (CiQ-NO EMPA)

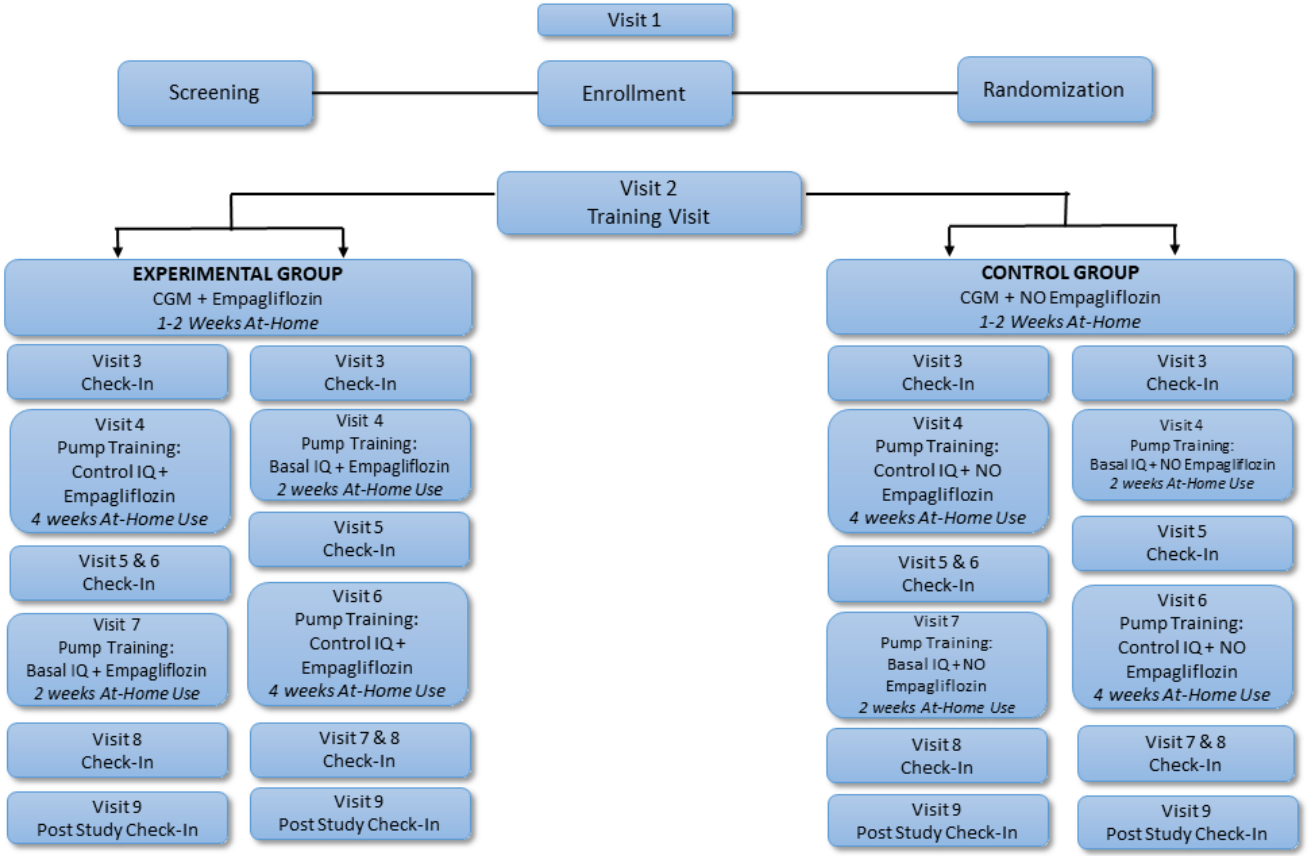

Figure 1: Study Diagram

1.7 Purpose/Objectives of Clinical Study

1.7.1 Study Participants

Enrollment for the Pilot Study will proceed with the goal of completing approximately 5 participants in the trial.

Enrollment in the Main Study will proceed with the goal of completing approximately 40 subjects, 10 subjects in each group.

Up to 60 participants may sign the consent form.

1.7.2 Clinical Sites

The study will be performed at the University of Virginia.

1.8 Primary Specific Aim

CGM-measured time in the target range 70-180mg/dl (TIR) during the day

1.9 Secondary Specific Aim

24/7 CGM time in range <70mg/dl; 24/7 CGM-measured average glucose;
CGM-measured glucose variability (coefficient of variation, CV) during the day;
Risks for hypo- and hyperglycemia.

Chapter 2 Study Devices

2.1 Insulin Pump

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

2.2 Continuous Glucose Monitor

The study CGM will include Dexcom G6 transmitter and sensors while using the Tandem t:slim insulin pumps. The CGM sensor is viable for 10 days.

2.3 Blood Glucose Meter and Strips

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

2.4 Ketone Meter and Strips

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

2.5 Study Devices Accountability Procedures

Device serial numbers will be recorded and use of equipment will be tracked.

2.6 Activity Tracker

All subjects will be asked to wear a commercial activity tracker (e.g. Fitbit).

Chapter 3 Study Medications

3.1 Insulin

Participants will use either lispro or aspart insulin prescribed by their personal physician. Participants should bring their insulin to all study appointments.

3.2 Empagliflozin – SGLT2-Inbitor

Inhibitors of sodium-glucose cotransporter-2 have been approved for use in type 2 diabetes where large clinical trials have demonstrated clinically significant improvements in glucose control (viz., HbA1c) and cardiovascular events [7, 10]. These drugs have also been tested in randomized controlled clinical trials in patients with Type 1 diabetes to evaluate their safety and efficacy.

3.3 Dosage

Experimental group participants will be advised to take Empagliflozin (trade name: Jardiance) 5 mg one time daily, with or without food. Empagliflozin is available only in 10 mg and 25 mg film coated unscored tablets. For this study, the participants will be provided 10 mg tablets and a pill splitter. They will be instructed to split only 1 tablet at a time and take each half tablet (5mg each) on subsequent days. Participants will be cautioned against spitting more than one tablet at a time. Participants will be advised to take the medication only as prescribed. If a dose is missed, it should be taken as soon as the participant remembers but will be advised not to double the next dose.

3.4 Drug Accountability and Storage

Empagliflozin will be provided by a third-party collaborator and delivered to the UVA Investigational Pharmacy. The clinical investigator will be responsible for maintaining adequate records of the disposition of the drug.

3.5 Documentation

The site will document drug receipt, subject dispensing and return, returns of used and unused supplies to a third-party collaborator (or on-site destruction), and will maintain a current accounting of all supplies in inventory—that is, a balance-on-hand log. The balance-on-hand, or dispensing, log will contain the protocol number, the investigative site(s), the drug name, and the medication units). When dispensing drug to a subject, site personnel will record the date, subject number, and amount dispensed. When a subject returns a drug, the amount used and unused will be documented, and an explanation for any inadvertent loss or destruction of supplies will also be recorded.

3.6 Storage

Participants will be instructed to store Empagliflozin at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

3.7 Compliance and Reconciliation

Site personnel will assess dosing regimen compliance and drug reconciliation in an ongoing manner. At each subject visit, subject compliance will be evaluated and documented, including calculating the expected amount of consumed drug given the regimen and amount of time between visits. This figure will be compared with the amount dispensed minus the amount the subject returned. Site personnel will question the subject regarding any discrepancies in these amounts and document the explanation.

Chapter 4 Study Screening

4.1 Participant Recruitment and Enrollment

Approximately five subjects will be enrolled into the Pilot Study. The Pilot participants will complete use the Basal-IQ Technology with Empagliflozin for 1-3 weeks. They will then participate in a 36-48 hour hotel admission where they will use the Control-IQ System with the Empagliflozin. The safety data from this admission will be presented to the DSMB for review prior to proceeding to the Main Study.

Pilot participants may enroll the Main Study. The study physician may request repeat laboratory values if values are greater than 6 weeks from Pilot screening laboratory values. A current urine/blood pregnancy test will be required prior to enrolling into the Main Study.

Enrollment in the Main Study will proceed with the goal of completing approximately 40 subjects, 10 subjects in each group. Subjects will initially be randomized to Empagliflozin use or NO Empagliflozin use during the study. They will then be randomized to which type of insulin pump will be used first.

Up to 60 participants may sign the consent form.

4.2 Informed Consent and Authorization Procedures

Before consent has been obtained, participants will be asked inclusion/exclusion criteria questions during prescreening to determine study eligibility. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. Potential eligibility may be assessed as part of a routine-care examination.

A participant is considered enrolled when the informed consent form has been signed by the participant and the study team.

Consenting procedures and documentation is defined in section 17.3.

4.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel, an ECG, and pregnancy testing (if applicable) to screen for exclusionary medical conditions.

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

4.4 Participant Inclusion Criteria

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

1. Age ≥18.0 and ≤65 years old at time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year
3. Currently using an insulin pump for at least six months
4. Currently using insulin for at least six months
5. Using insulin parameters such as carbohydrate ratio and correction factors consistently on their pump in order to dose insulin for meals or corrections
6. Access to internet and willingness to upload data during the study as needed
7. For females, not currently known to be pregnant or breastfeeding
8. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of childbearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
9. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use
10. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study
11. Total daily insulin dose (TDD) at least 10 U/day
12. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, biguanides, sulfonylureas and naturaceuticals)
13. Willingness to eat at least 100 grams of carbohydrates per day
14. An understanding and willingness to follow the protocol and signed informed consent
15. *Pilot Participants:* Agree to hotel/research house admission with other Pilot participants on a date selected by the study team.

4.5 Participant Exclusion Criteria

The participant must not have any exclusion criteria in order to be eligible to participate in the study.

1. Hemoglobin A1c >9%

2. History of diabetic ketoacidosis (DKA) in the 12 months prior to enrollment
3. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment
4. Pregnancy or intent to become pregnant during the trial
5. Currently breastfeeding or planning to breastfeed
6. Currently being treated for a seizure disorder
7. Planned surgery during study duration
8. History of cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted)
9. Clinically significant electrocardiogram (ECG) abnormality at time of Screening, as interpreted by the study medical physician
10. Use of diuretics (e.g. Lasix, Thiazides)
11. History of chronic or recurrent genital infections
12. eGFR lab value below 60 mL/min/1.73 m2
13. Treatment with any non-insulin glucose-lowering agent (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals)
14. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    a. Severe renal impairment, end-stage renal disease, or dialysis
    b. Inpatient psychiatric treatment in the past six months
    c. Presence of a known adrenal disorder
    d. Abnormal liver function test results (Transaminase>2 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function
    e. Uncontrolled thyroid disease
15. Severe renal impairment, end-stage renal disease, or dialysis
16. Use of an automated insulin delivery mechanism that is not downloadable by the subject or study team
17. Current enrollment in another clinical trial, unless approved by the investigator of both studies or if clinical trial is a non-interventional registry trial
18. Alcohol restricted to no more than 2 drinks per night in men and no more than 1 drink per night in women
19. Low carb diet (less than 100g per day)

4.6 Eligibility Screening Procedures

The participant will be evaluated for study inclusion and exclusion eligibility after the informed consent form has been signed by the participant and the study team.

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

1. Demographics
    a. Date of birth
    b. Gender
    c. Race
    d. Ethnicity
2. Medical History
    a. Duration of disease (number of years)
    b. Current insulin pump model
    c. History of CGM use
    d. Current treatment
        i. Basal rates
        ii. Carbohydrate ratios
        iii. Insulin sensitivity factors
        iv. Target glucose
        v. Average daily insulin
    e. History of diabetic ketoacidosis
    f. History of severe hypoglycemia
    g. History of seizures
    h. Loss of consciousness
3. Surgical history
4. Allergies
5. Concomitant medications
6. Physical Examination – A historical history and physical report within 52 weeks of the screening appointment may be used
    a. Weight
    b. Height
    c. Blood pressure
    d. Pulse
    e. Temperature

7. Screening Labs – A historical laboratory results within 2 weeks of the screening appointment may be used
    a. Hemoglobin A1c
    b. Comprehensive Metabolic Panel
    c. Thyroid functioning test
    d. Urine or serum pregnancy test for all women of childbearing potential

Screening procedures will last approximately 2 hours. Once all results of the screening evaluations are available, a decision will be made to determine the participant's eligibility for the study or if one or more part of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the participant will be excluded from participation with follow up and referred to their primary care physician as needed. The study physician may elect to rescreen participants and collect additional laboratory values if their clinical situation changes. The study physician has the discretion to exclude a study participant if concerned about their safety in this trial.

Chapter 5 Randomization Visit

Once eligibility is met, the participant may continue with randomization at the conclusion of the screening appointment. Screening failures and study dropout participants may be replaced.

5.1 Pilot Participants

Participants will not be randomized in the Pilot Study.

5.2 Main Study Participants

Approximately 40 participants will be randomized to using Empagliflozin 5 mg per day or not using the medication. Participants will then be randomized to the order of the insulin pump.

With Empagliflozin:
Group 1: CiQ x 4 weeks (CiQ-EMPA) then Basal-IQ x 2 weeks (BiQ-EMPA)
Group 2: Basal-IQ x 2 weeks (BiQ-EMPA) then CiQ x 4 weeks (CiQ-EMPA)

Without Empagliflozin:
Group 3: CiQ x 4 weeks (CiQ-NO EMPA) then Basal-IQ x 2 weeks (BiQ-NO EMPA)
Group 4: Basal-IQ x 2 weeks (BiQ-NO EMPA) then CiQ x 4 weeks (CiQ-NO EMPA)

Equipment training will be initiated after randomization.

Chapter 6 Study Equipment Training

Equipment training in the Main Study may begin immediately after screening eligibility has been met or may be deferred for a maximum of 30 days. Equipment training in the Pilot Study is intended to begin immediately after screening eligibility has been met. The study physician may elect to delay a participant's equipment training session if needed. The purpose of this training is to introduce the study insulin pump and study CGM to the participant.

The participant's insulin parameters will be programmed into their study insulin pump by two research staff. Subjects will then switch to the study insulin pump. The participant's personal pump and infusion site will be removed.

The participant will have the insulin pump and sensor on them at all times. Study supplied phones will be available upon request.

Participants will download the study equipment approximately one time per week or as frequently as needed.

6.1 CGM Training

A study CGM will be provided to all participants at the training session. The participants will be provided with CGM equipment and instructed to use the study CGM on a daily basis. If the participant has prior use of the CGM, re-training will be specific to the individual. The study team may elect to have less frequent CGM users watch the Dexcom online training videos (https://www.dexcom.com/training-videos) to assist in the training session. Study staff training may include review of study CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Study staff will specifically identify how alarms are set using the app and the frequency that these alarms will repeat when

The participants personal CGM will be discontinued. The participants will be observed placing the sensor and will learn/review how to access the CGM trace via the t:slim X2 insulin pump user interface. The participants will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the study CGM device.

An electronic copy of the CGM user's guide will be provided for the participants to take home. The study team will be sure that the participants will leave the clinic knowing how to use proper use the CGM. The study team will be available for any questions.

Participants will have the option of using their personal smartphone or receive a study smartphone to use in order to collect the data from the devices. If the participant elects to use a

personal device, the Dexcom app will be downloaded to their phone in order to monitor the participant's CGM values and alerts in real-time may be used.

6.2 Blood Glucose Training

Participants will be provided with a study blood glucose meter and test strips to be used at home per manufacturer guidelines.

All study blood glucose meters will be QC tested by study staff with at least two different concentrations of control solution, if available. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.

6.3 Blood Ketone Training

Participants will be provided with a study blood ketone meter and test strips to be used at home per manufacturer guidelines.

All study blood ketone meters will be QC tested by study staff with at least two different concentrations of control solution, if available. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

Participants will be instructed to perform blood ketone testing at <u>any</u> symptoms, change of conditions, and as described in Glycemic Treatment Guidelines (section 10.2). A home glucagon emergency kit will be required. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

6.4 Activity Tracker

All subjects will be asked to wear an activity tracker (e.g. Fitbit). Information about movement and heart rate will be recorded though not an endpoint in this study.

6.5 Insulin Pump Training

6.5.1 Insulin Pump Topics

The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.

The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed. Infusion sets manufactured by Tandem will be provided to the study subject and a sample list is below and may be provided in different cannula lengths (e.g. 6mm or 9mm) and tubing lengths (e.g. 23 or 43 inch):

- Tandem Autosoft Line (e.g. Autosoft 30, Autosoft 90, Autosoft XC)
- Tandem Varisoft
- Tandem TruSteel

Insulin pump training specific to the Basal-IQ Technology & Control-IQ Technology functions will include:

How to turn on and off the equipment
How to understand when the insulin pump is increasing or decreasing basal rates
How to administer a meal or correction bolus
How to enable the sleep function and set the sleep schedule
The participant will be assessed for understanding of the system interface and how to react to safety/alert messages
The participant will be given electronic versions of the user guides as a reference

6.5.2 Basal-IQ Training

Participants will be instructed how the t:slim X2 insulin pump with Basal-IQ technology differs from their personal insulin pump. Specifically, participants will be instructed how the technology is able to predict glucose levels 30 minutes ahead and will suspend insulin delivery in the event of a low glucose event. They will also be advised that the system can turn on and turn off every 5 minutes and can suspend insulin up to 2 hours when identifying a hypoglycemic trend. While the Basal-IQ technology can be on (active) or off when in normal use, participants will be instructed to have the Basal-IQ feature "ON" when assigned to the Basal-IQ treatment arm.

6.5.3 Control-IQ Training

The participant will be instructed to how to use the system 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, the participant will be instructed to turn off Control-IQ for approximately four hours.

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

The participant will also be asked to call the study clinical staff for technical issues with t:slim X2 with Control IQ. The participant should use the study pump without Control-IQ activated and study CGM (open loop mode) during periods of component disconnections or technical difficulties. Study staff contact information will be provided to the participant.

Upon completion of each insulin pump training, study staff will document, using a checklist, that the participant is familiar with the function/feature and/or capable of performing each of the tasks specified.

The participant will be provided Glycemic Treatment Guidelines (Chapter 10:) to use at home.

6.5.4 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings can occur any time during the study, particularly if the participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Chapter 7 Pilot Study

The Pilot Study will be performed at a local hotel/research house. The duration of the hotel admission will be approximately 36-48 hours with the intent of collecting appropriate safety data that will be presented to the DSMB for review.

7.1 Run-In Phase

After participant's eligibility is confirmed, the participant will undergo Study Equipment & Medication Training (Chapter 6) and receive education regarding the use of Empagliflozin (section 3.2).

The participant will be on the study equipment and study medication for about 7-14 days prior to the hotel admission. The study physician may elect to have the study participant take the medication for a shorter or longer period of time, depending on side effects. Participants of the study will stay at the hotel/research house with study staff and other study participants.

7.2 Qualifications and Role of the Staff

There will be at least two study staff present at all times at the study site, at least one of whom will be clinical staff (e.g. nurse, physician, nurse practitioner). There will be a physician available either on-site or nearby off-site at all times. In addition, one of the study medical physicians and one senior engineer will be on call during the entire admission. Glucagon for the emergency treatment of hypoglycemia will be available on-site.

7.3 Pre-Admission Check-In Visit

Pilot participants will be contacted by the study team approximately 48 hours prior to the hotel admission to verify the following information:

Inquire about any changes to the participant's medical history
Study equipment (e.g. insulin pump, CGM, and activity tracker) has occurred
Determine pump profile(s) the participant uses on certain days
New CGM sensor has been placed approximately 48-72 hours prior to admission for proper warm-up
Verify with the subject that the goal CGM reading at time of arrival is less than 250 mg/dL
Should any concerns regarding medical history, pump information, or unforeseen issues arise, the admission will be cancelled for that participant at the discretion of the investigator.

7.4 Admission Check-In

Participants will arrive at the hotel on the first day of the admission. The study team will perform vital signs and inquire about any changes to the participant's medical history. Any changes to

medical history will be communicated to the medical physician to ensure continued eligibility and participation.

In the event that the participant's CGM reading is not between 80-250 mg/dL or ketone concentration is ≥0.6 mmol/L prior to the Control-IQ initiation, the study physician may recommended corrective action as outlined in Chapter 10:. Study physician may elect to cancel participant's participation in the hotel admission if concerned about their medical safety. This participant will not be replaced.

The participant's Basal-IQ insulin pump will be discontinued and the Control-IQ insulin pump will be initiated. The study team will ensure the proper function of the CGM, insulin pump, and activity tracker. The goal will be to initiate Closed Loop Control by approximately 11 a.m.

The CGM used in the study is FDA-approved for the non-adjunctive measurement of blood glucose (i.e. the CGM reading can be used for insulin dosing decisions). The CGM readings will be the primary source of blood glucose values. There are no protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Glycemic Treatment Guidelines to be used during the hotel admission are defined in Chapter 10:.

7.5 Hotel Admission Glycemic Treatment Guidelines

Upon arrival, the subject will be asked to check the CGM reading and ketone concentration using the study ketone meter. If CGM is <70 mg/dL or >250 mg/dL, or ketone test is >0.6 mmol/L, the study physician will suggest appropriate treatment. The study team may request fingersticks as needed. The study subject may continue participation in the trial once CGM is between 70-250 mg /dL and ketone concentration is ≤0.6 mmol/L.

If CGM is ≥200mg/dL for more than 2 hours or ≥300 mg/dL at any time for experimental group participants, study physician will be notified to suggest appropriate treatment and ketones will be checked. If CGM is ≥300mg/dL for more than 2 hours or ≥400 mg/dL at any time for control group participants, study physician will be notified to suggest appropriate treatment and ketones will be checked. If ketone concentration is ≥0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin and will consider the proper remedy based on the study physician judgement via the subject's insulin pump. The study team will monitor CGM changes and ketones will be checked every 60 minutes until ketone concentration is <0.6 mmol/L.

If ketone concentration is ≥3.0 mmol/L, the study physician will recommend the appropriate medical treatment.

If CGM ≤60 mg/dL at any time, subjects will be given approximately 16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM <80 mg/dL after approximately 20 minutes. Hypoglycemic treatments can occur at any time per study physician request.

7.6 Study Meals

Participants may eat freely during the admission, eating a minimum of 100g of carbs per day. The estimated time of meals will be 8 a.m., 1 p.m., and 7 p.m.

7.7 Admission Activities

Participants will be free to engage in low-intensity activity (walking, shopping) during the morning and afternoon hours in a group setting. Participants will enjoy quiet activities in the evening.

7.8 Admission Discharge

Discharge will be at approximately7p.m. if the CGM and ketone values are within parameters outlined in Chapter 10. A snack will be provided for the participant at the time of discharge.

Participants will be asked to continue monitoring ketone levels for 24-48 hours after discharge from the hotel.

7.9 Post Admission Check-In Visit

Approximately 48 hours after the hotel admission, the study team will contact the participant via phone/email/text to assess:

adverse events, adverse device effects, and device issues

Review download of activity tracker, glucometer and ketone meter to assess occurrence of glucose values <60 mg/dL and >300 mg/dL

Chapter 8 DSMB Review

8.1 DSMB Pilot Study Safety Data Review

The Data Safety Monitoring Board (DSMB) will be provided all adverse event data from the onset of the Pilot Study through the hotel admission for review. While approximately 5 participants will be scheduled for the hotel admission, the goal is to provide at least 75% of the data to the DSMB for review. Replacing dropped study participants will not be required in the Pilot Study. The DSMB will review data related to individual stopping criteria as detailed in the study protocol.

8.2 DSMB Decisions

After their review, the DSMB can recommend that the current study continue without modification, continue with specified modifications, discontinue one or more arms of the study, or halt or modify the study until more information is available.

The DSMB may recommend modifications to individual stopping rules if additional safety concerns arise during from their continuing reviews of the study data.

The hotel admission will not be repeated unless required by the Data Safety Monitoring Board (DSMB).

8.3 DSMB Main Study Safety Data Review

A Data and Safety Monitoring Board (DSMB) will review compiled safety data after the completion of 10 Main Study participants. As a safety measure, the Board will review if the rate of mild ketosis greater than 40% (B-OH-B level > 0.6 mmol), 20% significant ketosis (B-OH-B > 1.5 mmol) and more than 5% DKA (B-OH-B > 3 mmol) to be considered significant to stop the study.

A Data and Safety Monitoring Board (DSMB) will review compiled safety data after 10 participants complete 4 weeks of the Main Study. Absence of serious adverse events related to Empaglifozin, the participants will continue with study participation pending DSMB review. The DSMB will review compiled safety data after 10 participants complete the trial. In addition, the DSMB will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, study drug, and all serious events (including UADEs) related to study device use at the time of occurrence. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Study PI requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available.

Chapter 9 Main Study

After DSMB review and approval of the hotel admission safety data, Main Study participants will be screened, randomized and trained on the study equipment. Pilot participants may be enrolled in the Main Study. Screening and consenting of the Main Study participants may be concurrent to the DSMB review. Virtual study visits may take the place of in-person study visits.

9.1 Empagliflozin Treatment Group

9.1.1 Run-In Phase

Participants will be asked to record two days of baseline ketone values before initiating the use of the study drug. Participant will then be directed to use the study CGM with Empagliflozin for 1-2 weeks. Proceeding to the pump treatment is dependent upon the participant's tolerance to the medication. The study physician may elect to provide the participant additional time in the event of medication side effects.

Participants will be instructed on the Glycemic Treatment Guidelines with special focus upon CGM readings (section 10.3) and Hyperglycemic Management (section 10.5).

Participant will meet the following criteria to continue study participation:

- Adherence to study protocol
- Ketone testing at least 2 times daily, preferably 4 times, with monitored values not greater than 0.6/mmol on at least two successive occasions (first measurement should be obtained upon waking in a fasting state)
- No adverse events relating to perineal infections, symptomatic postural hypotension, no evidence of significant hypoglycemia (< 54 mg/dl) or any other listed adverse effects of medication.

9.2 Insulin Pump Training Visit

Participants will receive pump training dependent upon the randomization group (i.e. Control-IQ pump for 4 weeks then Basal-IQ pump for 2 weeks.) Training provided is described in Section 6.5.

9.3 Optimization of Insulin Pump Settings

Data driven optimization of pump settings can occur any time during the study, particularly if the study participant contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

While initiating and maintaining Empagliflozin therapy, the study physician will carefully monitor insulin dose reductions, especially basal insulin decreases.

9.4 Check-In Visits

All participants will be contacted by the study team in the week following the Run-In Phase and the Basal-IQ Pump Training Visits to address issues relating to the study equipment and side effect of the Empagliflozin if randomized to the treatment group. Two check-in visits will occur after the Control-IQ Training Visit. Extra contact with subjects will occur as needed.

9.5 Study Device Download

Participants will be instructed to download the study devices (i.e. insulin pumps, CGM, activity tracker, etc…) each week, or as needed, to secure data collection. Study participants will log daily ketone values in an online resource for ongoing assessment purposes. The study team will download the ketone meter whenever the study subject attends an in clinic visit. If the subject owns a personal laptop device, he/she will be asked to bring it to the visit for the study team to download specific software to be used during data collection. If the subject does not own a laptop device but owns a desktop computer, he/she will be provided with a memory drive storing the appropriate resources to be used at home.

9.6 Study System Issues

The Basal-IQ Technology will continue working for the first 15 minutes after CGM readings become unavailable. The Basal-IQ Technology requires three of the last four data points to make a prediction. If connectivity with the CGM is lost during a suspension, the Basal-IQ Technology will continue the suspension for 15 minutes. If connectivity is not resolved within 20 minutes, Basal-IQ Technology will resume insulin automatically.

The Control-IQ Technology will continue to operate for the first 15 minutes after CGM readings become unavailable. If connectivity is not restored after 20 minutes, the Control-IQ Technology will stop operation until CGM readings are available. While the Control-IQ Technology is not operating, the participant's pump will continue to deliver insulin according to the participant's personal profile settings. Once CGM readings are available, the automated insulin delivery feature will automatically resume.

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

If the Control-IQ Technology detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the participant will be instructed to contact Tandem Technical Support via the study team.

9.7 Repeating Visits & 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.

9.8 Equipment Training/Initiation

All participants will complete both the Basal-IQ and Control-IQ insulin pump training at a virtual clinic visit prior to using the equipment.

9.9 Study Conclusion Visit

The following procedures will be performed in both groups at the study conclusion visit:

All study devices and all remaining Empagliflozin supplies, including empty medication bottles
Study team will download the study equipment
Blood will be drawn for creatinine, HbA1c, and pregnancy assessment

Study participants will be instructed on how to transition back to the home insulins and the doses to be used. Subjects will be informed that there may be a risk of severe hypoglycemia and/or severe hyperglycemia during the transition back to the subject's usual home basal insulin. The study physician will be available for consultation during this transition period.

9.10 Post-Study Check-In Visit

Approximately 48 hours after the home use of the equipment, the study team will contact the participant via phone/email/text to assess:

Adverse events, adverse device effects, and device issues

Chapter 10 Glycemic Treatment Guidelines

10.1 Hypoglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app but will be instructed to choose a value no less than 60 mg/dL.

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

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

CGM values are updated every 5 minutes and will be able to see it on the pump and Dexcom App.

CGM alarms on the study team controlled Dexcom App will be set at 70 mg/dl for 30 minutes and 300 mg/dl for 60 minutes.

If CGM < 80 mg/dL during the day, the patient will be treated until CGM reads ≥80 mg/dL. If CGM < 70 mg/dL during the night. Hypoglycemia treatment will be provided until CGM reads ≥ 80 mg/dL.

10.2 Hyperglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app but will be instructed to choose a value no greater than 250 mg/dL

The t:slim X2 with Control-IQ system will issue a predictive hyperglycemia alert (Control-IQ High Alert) when the system has increased insulin delivery, but detects a CGM value above 200 mg/dL and does not predict the value will decrease in the next 30 minutes.

If the participant receives a Control-IQ High Alert, a message appears on the UI that is accompanied by vibration followed by vibrations and/or sound if not acknowledged by the user in 5 minutes. This alert remains on the screen until acknowledged by the user. The user is prompted to check the site for occlusion and test blood glucose.

10.3 Empagliflozin Randomized Participants

If a participant's CGM readings ≥200 mg/dL for over 2 hours or ≥300 mg/dL at any point,

If the CGM is ≥200 mg/dL, check for blood ketones with the study ketone meter
If the ketone level is ≥0.6 mmol/L, consider correction insulin and/or consider infusion site change. Contact study staff.
If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours

10.4 No Empagliflozin Randomized Participants

If a participant's CGM reading is ≥300 mg/dL for over 2 hours or ≥400 mg/dL at any point, the participant will be instructed to take the following steps:

If CGM is ≥300 mg/dL, check for blood ketones with the study ketone meter.
If the ketone level is ≥0.6 mmol/L, consider correction insulin and/or consider infusion site change. Contact study staff.
If a participant administers correction insulin via insulin syringe, participants will be instructed to turn Control-IQ off for approximately four hours.

10.5 Ketoacidosis Management

Due to the higher risk of ketoacidosis while using Empagliflozin, experimental participants will be instructed to measure ketone levels at a minimum of 2 times daily but preferable 4 times daily. Required measurement upon waking (fasting state) and prior to bedtime. If ketones ≥ 0.6 mmol/L, participants will be advised to stop the drug and then recheck ketones in 3-4 hours. Participants may restart the use of Empagliflozin after the ketone measurement is <0.6 mmol/L. All ketosis events should be recorded and evaluated in participants who are taking the study drug.

Experimental participants will be advised to check ketones if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated.

Experimental participants will be instructed on the proper use of the STICH Protocol:

STop drug,
Inject bolus insulin (1.5 times the usual correction bolus)
Consume 30 grams of carbohydrate
Hydrate with up to 500 ml of water

Blood Ketone (BHB) Level	Remedial Actions
<0.6 mmol/L (normal)	No action needed
0.6-1.5 mmol/L (ketonemia)	Treat as follows or per clinician instructions: • Ingest 30-60g rapidly absorbed carbohydrates and maintain fluid consumption (200-500 mL) every 1-2 hours • Administer rapid-acting insulin based on carbohydrate intake every 1-2 hours • Check blood ketones (every 2-4 h) until resolution • Check blood glucose frequently to avoid hyperglycemia and hypoglycemia Seek medical attention if levels persist and symptoms present
1.6-3.0 mmol/L (impending DKA)	Follow treatment recommendations listed above Consider seeking immediate medical attention
>3.0 mmol/L (probable DKA)	Seek immediate medical attention

BHB=β-hydroxybutyrate

*Danne, et al….Diabetes Care v42, June 2019 [11]

Experimental group participants will be advised to measure ketones in the event of the following symptoms/events:

- Malaise
- Fatigue
- Nausea, or vomiting.
- Infection
- Injury
- Occlusion of infusion cannula
- Pump malfunction
- Stress
- Changes in diet
- Changes in physical activity

Control participants will be advised to measure and document ketone levels each morning. Experimental Participants will also be instructed on the importance of prompt treatment of symptoms as recommended in the **STICH** Protocol.

Chapter 11 Testing Procedures

11.1 Laboratory / Point of Care Testing

11.1.1 HbA1c

A blood sample will be obtained at screening to obtain a baseline hemoglobin A1c level. Blood test may be obtained within 2 weeks prior to enrollment may be used for eligibility purposes.
HbA1c level may be measured by study team using the DCA2000, a comparable point of care device, at time of screening
Labs may be obtained at a local laboratory convenient to the participant.

11.1.2 Comprehensive Metabolic Panel

A blood sample will be obtained at screening to assess kidney and liver functioning.
Specifically, creatinine will be evaluated at the screening visit, at end of study, and if subject has nausea, vomiting, diarrhea or intercurrent illnesses during study.
Labs may be obtained at a local laboratory convenient to the participant.

11.1.3 Thyroid Stimulating Hormone (TSH)

A blood sample will be obtained at screening to assess thyroid functioning. Blood test may be obtained within 2 weeks prior to enrollment may be used for eligibility purposes.

11.1.4 Pregnancy Test

Pilot Study Participants: A serum or urine pregnancy test will be required for women of childbearing potential at the screening visit, prior to the study equipment training session, prior to the start of the hotel admission, and at the end of the study. Test must be negative to participate in the study.
Main Study Participants: A serum or urine pregnancy test will be required for women of childbearing potential at the screening visit, prior to each study equipment training sessions, and at the end of the study. Test must be negative to participate in the study.

11.2 Questionnaires

Questionnaires are completed as noted below during the Main Study for all participants.

11.2.1 Questionnaire Schedule

Screening:

Diabetes Distress Scale (DDS)
Fear of Hypoglycemia Survey (HFS-II) – Adult

Administration time is approximately 10 minutes.

Post Control-IQ Insulin Pump Use:

Diabetes Distress Scale (DDS)
Fear of Hypoglycemia Survey (HFS-II) – Adult
Control-IQ Questionnaire Survey Technology Acceptance

Post Basal-IQ Insulin Pump Use:

Diabetes Distress Scale (DDS)
Fear of Hypoglycemia Survey (HFS-II) – Adult
Basal-IQ Questionnaire Survey Technology Acceptance

11.2.2 Diabetes Distress Scale – Adult

The Diabetes Distress Scale [12] is a measure of diabetes-related emotional distress and consists of a scale of 28 items. These include 7 items from each of four domains central to diabetes-related emotional distress. Patients rate the degree to which each item is currently problematic for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem).

Administration time is approximately 5 minutes.

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

The Hypoglycemia Fear Survey-II [13] was developed to measure behaviors and worries related to fear of hypoglycemia in adults with type 1 diabetes. It is composed of 2 subscales, the Behavior (HFS-B) and Worry (HFS-W). HFS-B items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood glucose levels higher, making sure other people are around, and limiting exercise or physical activity). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident). Items are rated on a 5-point Likert scale (0=never, 4=always), with higher scores indicating higher fear of hypoglycemia.

Administration time is approximately 10 minutes (both versions).

11.2.4 Control-IQ / Basal-IQ Survey Technology Acceptance

The Technology Acceptance Surveys [14] were developed for a Bionic Pancreas camp study. The 38 items in the Questionnaire were based on interviews conducted with individuals who had participated in previous Bionic Pancreas trials about their experience regarding the Bionic Pancreas. It was subsequently adapted to assess these same measures for the inControl closed-loop system. It assesses both positive and negative experiences with inControl, including blood glucose management, device burden, and overall satisfaction. Items were rated on a 5-point scale.

910 Administration time is approximately 10 minutes.

Chapter 12 Risks Associated with Clinical Trial

12.1 Potential Risks and Benefits of the Investigational Device

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

12.1.1 Venipuncture Risks

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

12.1.2 Fingerstick Risks

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

12.1.3 Subcutaneous Catheter Risks (CGM)

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

Study staff should verbally alert the participant that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling, or pain at the insertion site. The participant should be further instructed to notify the study coordinator immediately if this occurs.

12.1.4 Risks of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures

(convulsions) and that for a few days the participant may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery.

12.1.5 Risks 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.

12.1.6 Risks of Device Reuse

Participant will be informed that FDA or relevant national authorities have approved the insulin pump, CGM, glucometer and ketone meter for single use and that by using them among multiple patients, bloodborne pathogens (e.g. Hepatitis B) may be spread through the use of multiple users.

The study CGM system is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is attached to the sensor but does not enter the skin and the receiver, if used, is a hand held device.

The study insulin pumps are labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.)

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, these devices may be reused after cleaning adhering to a hospital-approved cleaning procedure.

12.1.7 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 PLATINUM (Professional) Cleaning and Disinfection manual (current edition). The transmitter should be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. Transmitter is then rinsed under flowing tap water

for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

Per the pump manufacturer, the insulin pump will be cleaned with a damp lint-free cloth. Use of household or industrial cleaners, solvents, bleach, scouring pads, chemicals, or sharp instruments are prohibited. The pump should never be submerged in water. If needed, use only a very mild detergent, such as a bit of liquid soap with warm water. A soft towel will be used to dry the pump.

The Bayer Contour Next glucometer is cleaned and disinfected with two separate Super Sani-Cloths (EPA number 9480-4). The entire surface will be cleaned, making sure the surface stays wet for 2 minutes. This step is repeated with a clean cloth for disinfecting the device.

The Precision Xtra User's Guide suggests that healthcare professionals use 10% bleach, 70% alcohol or 10% ammonia to clean the device.

Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. Cavicide, EPA number 46781) or household bleach. The contact time on the surface depends on the method used to clean the equipment. Cavicide requires three minutes on the surface of the equipment. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid.

In the event a manufacturer updates cleaning procedures for their device, the study team will adhere to the most current recommendations.

There is the risk of blood sampling collection and contamination from sampling techniques. Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study subject. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the subject's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed and hands washed or sanitized prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.

12.1.8 Hb1Ac Risk

An NGSP Point of Care analyzer (i.e. DCA Vantage Analyzer) will be utilized at the research site to obtain the subject's HbA1c level.

12.1.9 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion.

If these reactions occur, different adhesives or “under-taping” (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

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

Data downloaded from the CGM, pump, and glucose and ketone meter, if accessible, will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

12.1.10 Known Potential Benefits

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

12.1.11 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

12.2 Potential Risks and Benefits of the Medication

12.2.1 Empagliflozin Adverse Reactions

The most recognized adverse reactions associated with the use of Empagliflozin are urinary tract infections and mycotic genital infections occurring in both men and women.

Nausea, vomiting, abdominal pain, generalized malaise, acute febrile illness, reduced caloric intake due to illness or surgery, alcohol abuse, and shortness of breath may result in adverse reactions. The study physician may consider temporarily discontinuing Empagliflozin in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure).

After initiating therapy, participants will be monitored for increased urination and dehydration. Participants will be informed that dehydration may increase the risk of hypotension and, therefore, will be encouraged to increase their fluid intake while taking the medication. Participates will also be advised that a majority of infections can be prevented by maintaining attention to basic hygiene include regular washing after urination.

Ketoacidosis is a common adverse reaction with the use of Empagliflozin. Ketone measurement instructions are detailed in section 10.5.

While very rare, participants treated with Empagliflozin may present with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, and should be assessed for necrotizing fasciitis. If suspected, the study team will assess and refer the participant for appropriate care. Empagliflozin will be discontinued and blood glucose levels will be closely monitored, and provide appropriate alternative therapy for glycemic control. The study physician will contact the participant's personal physician.

12.3 General Considerations

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

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

The protocol is considered a significant risk device study, due to the fact that the closed loop system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

Chapter 13 Adverse Events, Device Issues, and Stopping Rules

13.1 Definitions

13.1.1 Adverse Events (AE)

Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event, the study drug, and the device(s) under investigation (section 13.2) for reportable adverse events for this protocol). Pregnancy will not be considered an adverse event.

13.1.2 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 (life 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).

13.1.3 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)).

13.1.4 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.

13.1.5 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).

13.2 Reportable Events

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

A serious adverse event as defined in section 13.1.2
An Adverse Device Effect as defined in section 13.1.4, unless excluded from reporting in section 13.7
An Adverse Event as defined in section 13.1.4 occurring in association with a study procedure
An AE as defined in section 13.1.1 which leads to discontinuation of a study device for 2 or more hours
Hypoglycemia meeting the definition of severe hypoglycemia as defined in section 13.2.1
Diabetic ketoacidosis (DKA) as defined in section 13.2.2 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.

13.2.1 Hypoglycemia Event

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;
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.

13.2.2 Hyperglycemia Events/Diabetes Ketoacidosis

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

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

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

Symptoms such as polyuria, polydipsia, nausea, or vomiting
Serum ketones ≥1.5 mmol/L or large/moderate urine ketones
Ketosis as defined by symptoms and ketones regardless of 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 a Study Physician to verify the coding and the reporting that is required.

13.3 Relationship of Adverse Event to Study Device

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

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

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.
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.

13.4 Intensity of Adverse Event

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

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

13.5 Coding of Adverse Events

Adverse events will be coded per the UVA IRB website instructions (i.e. mild, moderate, severe). The DSMB will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and DSMB's assessments will be recorded. The DSMB will have the final say in determining the causality.

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

13.6 Outcome of Adverse Events

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

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

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

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.

13.7 Reportable Device Issues

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

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

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

13.8 Timing of Event Reporting

UADEs must be reported within 10 working days to the FDA after the sponsor first receives notice of the adverse effect.
Other reportable adverse events, device malfunctions (with or without an adverse event) and device complaints should be reported promptly, but there is no formal required reporting period.

The IDE Sponsor will investigate the UADE and if indicated, report the results of the investigation to the IRBs, FDA, and DSMB within 10 working days of the study team becoming aware of the UADE per 21CFR 812.46(b) (2).
The DSMB will determine if the UADE presents an unreasonable risk to participants. If so, the DSMB 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 DSMB 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 manufacturer by the study personnel.

13.9 Stopping Criteria

13.9.1 Participant Discontinuation

Rules for discontinuing study device use are described below.

The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
The participant requests that the treatment be stopped
Two distinct episodes of DKA that are not attributable to the study drug
One distinct episode of DKA directly attributable to the study drug
Two distinct severe hypoglycemia events as defined in section 13.2.1.

13.9.2 Suspending/Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 13.2), use of the study device system will be suspended while the problem is diagnosed.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. The study Medical Monitor will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). The DSMB may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

In the event that two subjects experience urosepsis, AKI, fournier's gangrene, severe genital mycotic infections and hypotension requiring hospitalization, the study will be paused to discuss events with the DSMB.

13.10 Independent Safety Oversight

A DSMB will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB document.

Chapter 14 Miscellaneous Considerations

14.1 Prohibited Medications, Treatments, and Procedures

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

The study devices (study insulin pump, study CGM) 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.

14.2 Participant Withdrawal

Participation in the study is voluntary. Participant may withdraw at any time. For participants who do withdraw from the study, the study team will determine if their data will be used in analysis.

14.3 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study may be shared with the third party collaborators. De-identified subject information may also be provided to collaborators involved in the study after the appropriate research agreement has been executed.

Chapter 15 Statistical Consideration

15.1 Design and Randomization

As presented in Figure 1, this study uses a randomized controlled design, with participants randomly assigned to four groups as follows:

a. Groups 1 and 2 are assigned to Experimental condition – use of SGLT2 inhibitor (Empagliflozin) plus technology (CGM, Basal IQ or Control IQ)

b. Groups 3 and 4 are assigned to Control condition – no use of SGLT2 inhibitors; use of technology only (CGM, Basal IQ or Control IQ)

All four groups participate in a 1-2 week baseline CGM sessions, after which Groups 1 and 3 begin use of Control IQ, while Groups 2 and 4 begin use of Basal IQ. After using Control IQ or Basal IQ for 4 or 2 weeks, respectively, all groups switch to use of the alternative technology (Figure 1).

The primary purpose of this pilot study is to evaluate the safety and efficacy of combining SGLT2 inhibitors with closed loop control, and to gauge the effect size of the outcomes listed below. Nevertheless, the projected sample size of N=40 (N= 60 recruited) participants is expected to results in statistically significant differences on some outcomes:

Primary Outcome: CGM-measured time in the target range 70-180mg/dl (TIR) during the day;

Hierarchical secondary outcomes: 24/7 CGM time in range <70mg/dl; 24/7 CGM-measured average glucose; CGM-measured glucose variability (coefficient of variation, CV) during the day; risks for hypo- and hyperglycemia.

Analysis Overview: The overall analysis will follow Intention-to-treat (ITT) approach, with each participant analyzed according to the treatment assigned by initial randomization. The study design includes repeated measures on all outcomes; thus, we will use a linear mixed-effect model that corresponds well to this structure. The mixed model will use “Subject” as a random factor and “Group” as a fixed factor, e.g. using the Linear Mixed Models procedure in SPSS. We should note that similar results may be generated by repeated measures ANOVA, but mixed models handle missing data better (e.g. ANOVA only uses listwise deletion, which could reduce power and introduce bias towards study completers). A mixed model is also more flexible and will allow us to address additional questions, such as clustering of subjects or introducing time between assessments as a continuous variable.

Data Sources: Continuous glucose monitoring (CGM) data acquired every 5 minutes during the baseline and throughout the study. CGM data will be used to compute established metrics of glycemic control (e.g. time in ranges), risks for hypo- and hyperglycemia, e.g. the Low and High BG Indices (LBGI/HBGI), and CV, as recommended by the Consensus on Use of CGM, to which our team contributed substantially.

Handling of Missing Data: All randomized participants who have at least 50% of their CGM readings during the study period will be included in the analysis. Occasional missing CGM data do occur during normal CGM use and these values will be ignored when summary CGM metrics (e.g. percent times in range, LBGI, HBGI) are computed. Typically, CGM data are voluminous and the percent of missing values is low; thus no imputation would be required. For example, in the recently completed multi-center Protocol 3 of the International Diabetes Closed Loop Trial, N=168 subjects (of N=168 recruited) completed the entire 6-month protocol, and CGM data were available 96% of the time [15] (Table 1).

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

Data Analysis: The objectives of this study are addressed by different sub-analyses of our general analytical scheme, as follows:

Objective 1: Effect of adding Empagliflozin to predictive low glucose suspend (Basal IQ – 2 weeks) and closed-loop control (Control IQ – 4 weeks) will be assessed by the study randomized design (Figure 1). In this design we will have N=20 participants on Empagliflozin and N=20 participants off Empagliflozin, beginning with Control IQ and then switching to Basal IQ, or beginning with Basal IQ and then switching to Control IQ. This analysis will be done using the baseline data as covariates in a general linear model.

Objective 2: CGM-measured effect of Empagliflozin will be assessed using the baseline CGM data, (between Visits 2 and 3) via direct contrast between the two Experimental and two Control groups (N=20 participants in Groups 1-2 vs 20 participants in Groups 3-4);

Objective 3: CGM-measured effects of Empagliflozin added to Basal IQ will be assessed by direct comparison of the Experimental vs Control groups during the Basal IQ sessions (N=20 participants per arm will be available to this analysis);

Objective 4: CGM-measured effects of Empagliflozin added to Control IQ will be assessed by direct comparison of the Experimental vs Control groups during the Control IQ sessions (N=20 participants per arm will be available to this analysis);

To preserve the overall type 1 error, a hierarchical testing procedure will be used: if the primary analysis for CGM-measured TIR 70-180mg/dL during the day is statistically significant ($p < 0.05$), then testing will proceed to the next outcome metric in the following order: CGM-measured 24/7 percent time <70mg/dL; CGM-measured average glucose; CGM-measured CV during the day; LBGI and HBGI. This process will continue iteratively moving to the next variable down on the list until a non-significant result ($p \geq 0.05$) is observed, or all variables have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any variables remaining on the list become exploratory.

15.2 Sample Size

Sample Size Determination is based on data from our Protocol 3 of the recently completed iDCL Trial (Table 1) conducted with the same algorithm in the same population. The Pre-Post changes in TIR in **Table 1**indicate effect size of >0.7 of Control IQ compared to SAP. Knowing the action of Basal IQ and Control IQ, and the action of Empagliflozin, we can assume that Empagliflozin will double the effect of Basal IQ and Control IQ during the day and will preserve their benefits overnight. This, a 1:1 randomization into two Experimental vs. two Control groups and N=20 participants per study arm, yields a sample size on N=40 subjects to complete the study. This sample size was computed using the G*Power 3 software under the assumptions of power=90% and type 1 error α=0.01, further reinforcing the feasibility of the hierarchical analyses described above. In our experience with long-term AP studies, we observe attrition rate of 20%, with most dropouts occurring during the baseline prior to randomization. Thus, the recruitment sample size was increased to N=60 to accommodate up to 20% attrition rate without sacrificing statistical power. We should also note that technology improvement appears to increase the retention rate in recent large-scale trials. For example, it the iDCL protocol 3, only 2 out of 170 recruited participants dropped out and all 168 randomized participants completed the 6-month study.

Table 1: Glycemic control results from Protocol 3: N=168 patients who used Control IQ for 6 months	**Baseline** (2 weeks)		**Post-Randomization** (26 weeks)			
	CLC	**SAP**	**CLC**	**SAP**	**Difference**	**p value**
CGM use during the study			97%	96%		
Percent below 70 mg/dL	3.59 ± 3.39%	2.82 ± 2.53%	1.59 ± 1.15%	2.25 ± 1.46%	-0.88%	<0.0001
Percent 70-180 mg/dL (study primary outcome)	**60 ± 17%**	**59 ± 14%**	**71 ± 12%**	**59 ± 15%**	**+11%**	**<0.0001**
Percent above 180 mg/dL	36 ± 19%	38 ± 15%	27 ± 12%	39 ± 15%	-10%	<0.0001

Percent above 250 mg/dL	12.4 ± 12.8%	11.9 ± 9.9%	7.0 ± 6.7%	12.4 ± 10.3%	-5.5%	<0.0001
HbA_{1c}	7.4%	7.4%	7.06%	7.4%	-0.33%	=0.0014
Mean glucose [mg/dL]	166 ± 32	169 ± 25	156 ± 19	170 ± 25	-13	<0.0001
Coefficient of Variation	37 ± 6%	36 ± 5%	34 ± 5%	36 ± 5%	-3%	<0.0001

*Overall, the studies using the AP algorithm originally developed at the University of Virginia, have logged >65,000 days of use to date, in 31 clinical trials enrolling over 600 children and adults with type 1 diabetes at 15 clinical centers in the U.S. and Europe (*Table 1*). Control IQ is the third commercial-grade generation of this algorithm, which will be used in this study.*

15.3 Outcome Measures

15.3.1 Primary Efficacy Endpoint

To demonstrate the efficacy of Empagliflozin as adjuvant therapy added to a closed loop artificial pancreas system (AP-EMPA) in patients with T1DM. The primary efficacy outcome variable will be time in range (70-180 mg/dl). Secondary efficacy outcomes will be: time below 70 mg/dl, time above 180 mg/dl, time between 70-140 mg/dl 5 hours postprandial, glucose variability indices (HBGI, LBGI, ADRR). The corresponding variables obtained from the NO-AP-EMPA arm will be the comparator.

15.3.2 Secondary Outcome

To evaluate the safety of Empagliflozin as adjuvant therapy added to a closed loop artificial pancreas system (AP-EMPA) in subjects with T1DM by monitoring:

Episodes of diabetic ketoacidosis (DKA)
Episodes of severe hypoglycemia (glucose <50 mg/dl)
Genital infections (balanitis, urethritis, vulvar infections, Fournier's gangrene)
Urinary tract infections
Other AE CGM based LBGI & HBGI

Furthermore, we will compute

Total amount of insulin used
Number of hyperglycemic episodes as defined by contiguous CGM above 300mg/dL

15.4 Safety Analyses

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

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

15.5 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by treatment group.

Will include:

Age
HbA1c
Gender
Race/ethnicity
CGM use before enrollment
Diabetes duration
BMI

15.6 Device Issues

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

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

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

Performance metrics, describing the CLC system and its components like:

a. % time CGM data were available to the CLC system – overall and by month
b. % time in different operational modes per week - overall and by month
c. Rate of different failure events and alarms per 48 hours recorded by the CLC system – overall and by month

Rationale for sample size determination: Use of Empagliflozin could potentially 'double the effect' of Basal-IQ and Control IQ during the day by lowering postprandial glucose concentrations based on the following rationale.

a. Studies have demonstrated reduced hepatic glycogen synthesis resulting in reduced net hepatic glycogen content in poorly controlled T1D compared to nondiabetic controls [16]. In contrast, in well controlled T1DM subjects, initial splanchnic glucose uptake was not reduced when compared to matched nondiabetic controls [17]. Taken together, assuming usual daily carbohydrate intake of ~ 180 grams (i.e., 60 grams per main meal) in an adult with T1DM, and a net splanchnic extraction of ingested carbohydrates of ~ 25% [17], ~ 75% of ingested carbohydrates (~ 135 grams) would appear daily into the circulation. Given a relatively conservative estimate that ~ half the ingested carbohydrates are taken up by the peripheral tissues, that leaves ~ 70 grams of ingested carbohydrates/day to contribute to postprandial glucose excursions.

b. Based on data obtained from the prescribing information of Empagliflozin that 10 mg of Empagliflozin results in net urinary loss of 64 grams of glucose per day [18], it is reasonable to assume that adjuvant use of this medication with Control-IQ or Basal-IQ would at least "double the effects" of lowering postprandial glucose concentrations in this clinical trial.

Chapter 16 Data Collection and Monitoring

16.1 Case Report Forms and Device Data

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

When data are directly collected in electronic case report forms, this will be considered the source data. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

16.2 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.

16.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices (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 may be developed by the site and implemented as appropriate. Major deviations will be reported to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.

Chapter 17 Ethics/Protection of Human Participants

17.1 Ethics 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.

17.2 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.

17.3 Informed Consent Process

17.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual's agreement 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. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator or their delegate 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. Participant will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document will be given to the participant 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.

17.3.2 Participant and Data Confidentiality

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Virginia Center for Diabetes Technology. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the University of Virginia Center for Diabetes Technology.

Chapter 18 References

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