# Signature Page

# A Randomized Trial Evaluating the Efficacy and Safety of Control-IQ Technology in Adults with Type 2 Diabetes Using Basal-Bolus Insulin Therapy (2IQP)

**Protocol Identifying Number: TP-0013437**

**IND/IDE Sponsor: Tandem Diabetes Care, Inc.**

**Version Number: v. 8.0**

**October 31, 2023**

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|---|---|
| **JCHR Protocol Director** | |
| **Name, degree** | John Lum, MS / Jaeb Center for Health Research |
| **Signature/Date** | John Lum<br>I am digitally signing this document<br>2023-11-13 09:17-05:00 |
| | |
| **Sponsor** | Tandem Diabetes Care, Inc. |
| **Name, degree** | Jordan Pinsker, M.D. |
| **Signature/Date** | Jordan Pinsker<br>Digitally signed by Jordan Pinsker<br>Date: 2023.11.13 13:58:42 -08'00' |
| | |
| **Protocol Chair** | |
| **Name, degree** | Yogish Kudva, M.D. / Mayo Clinic |
| **Signature/Date** | DocuSigned by:<br>Yogish C. Kudva, M.B.B.S.<br>A70BC8A99A014E1...<br>November 14, 2023 |
| | |
| **Medical Monitor** | |
| **Name, degree** | Roy Beck, MD, Ph.D. / Jaeb Center for Health Research |
| **Signature/Date** | Roy Beck<br>I am digitally signing this document<br>2023-11-13 16:07-05:00 |

# A Randomized Trial Evaluating the Efficacy and Safety of Control-IQ Technology in Adults with Type 2 Diabetes Using Basal-Bolus Insulin Therapy (2IQP)

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**October 31, 2023**

# VERSION HISTORY

| VERSION NUMBER | AUTHOR | APPROVER | EFFECTIVE DATE | REVISION DESCRIPTION |
|---|---|---|---|---|
| 1.0 | J. Lum, R. Beck., N. Mba-Oduwusi, J. Pinsker, R. Sasson-Katchalski | J. Pinsker | December 7, 2022 | Original version |
| 2.0 | J. Lum, R. Beck., N. Mba-Oduwusi, J. Pinsker, R. Sasson-Katchalski | J. Pinsker | January 6, 2023 | Incorporates FDA feedback on version 1.0: *(content-related changes are listed below by protocol section and are also reflected in the Protocol Summary and the Schedule of Visits and Procedures table)* |
| | Section 1.5.1.2: Added potential risks of CGM<br><br>Section 2.1:<br>• The maximum number that can be randomized by any site is 66 (20% of 330).<br>• Added maximum of 30 participants randomized from Canada<br>• Increased minimum recruitment goal to 30% of a minority race or ethnicity; 20% using an SGLT2 inhibitor, 20% using a GLP-1 receptor agonist, and 10% using both; 15% with TDI>100 units/day and attempt to enrich cohort with participants with TDI >200 units; 25% using a form of fixed dosing to calculate meal boluses (e.g., fixed dose at meal or fixed dose for small/medium/large meal [i.e., dose not determined by carbohydrate counting]). Changed HbA1c goal to be maximum of 25% with HbA1c <8% (based on screening HbA1c or HbA1c available within the last 30 days) and maximum of 10% with screening HbA1c <7%<br><br>Section 2.2.1:The following changes were made in the inclusion criteria<br>• Added requirement that type 2 diabetes was diagnosed at least 6 months prior to screening<br>• Modified insulin use requirement to be: Using basal-bolus insulin therapy with at least one injection containing rapid-acting insulin per day or an insulin pump for at least 3 months prior to enrollment, with no major modification to insulin regime in the last 3 months<br>• Dropped requirement of TDI $\leq$ 250 units<br>• Added: If using noninsulin glucose-lowering medications (such as GLP-1 receptor agonist, SGLT2 inhibitor, or other) or weight-reduction medications, dose has been stable for the 3 months prior to screening; and participant is willing to not change the dose unless required for safety purposes<br>• Added: Participant willing to not initiate use of any new glucose-lowering medications during the trial<br>• Dropped requirement for HbA1c 7.0% to 11.9%<br><br>Section 2.2.3: The eligibility for the exercise challenges was changed to be the following: All participants will have a screening EKG or review of an EKG completed in the 12 months prior to screening. To participate in the exercise challenges, a participant must have either no history of a cardiovascular event in the year prior to screening and no EKG abnormalities associated with increased risk during exercise.<br><br>Section 2.3.1: The following changes were made in the screening data collection and testing:<br>• HHS and hospitalization for SH, DKA, HHS added to medical history information<br>• Blood draw for central lab HbA1c deleted<br>• Added EKG for all participants unless performed in the prior 12 months<br><br>Section 4.4: information added about IRB-approved handouts for training<br><br>Section 4.6: need for AID group to have care partner trained in treatment of hypoglycemia present | | | |

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| | during exercise challenges<br><br>Section 4.6.2: Added that sleep activity will be enabled during normal sleep time for all users unless a safety concern arises as judged by the investigator<br><br>Section 5.2. Changed the training/check-in contact with the AID group participants to be 3 ±1 days to conform current practices<br><br>Section 5.2.1:<br>• Added that site investigators may adjust insulin delivery profile settings only for safety concerns and the reasons will be documented on CRF<br>• Deleted recording of non-severe hypoglycemia treatments at each visit (correction of protocol)<br><br>Section 5.3: Added that at final visit when transitioning back to pre-study insulin delivery method, participants must have two CGM or fingerstick blood glucose values, separated by at least 15 minutes, that are above 80 mg/dL prior to discharge from the clinic.<br><br>Section 5.4: Regarding glucose-lowering or weight reduction medications, add the following: The only changes of glucose-lowering or weight-reduction medications permitted will be a reduction in dose for safety reasons, or an adjustment to an equivalent dose of a different formulation if participant's insurance coverage changes. No increased doses or initiation of a new glucose-lowering or weight-reduction medication will be permitted.<br><br>Section 6.1: Challenges<br>• Plan for exercise and meal challenges modified to require the 3 challenges of each type to be on consecutive days and to have about 25% of each type of challenge within the following 4 periods timed from randomization: 1-2 weeks, 3-4 weeks, 5-6 weeks, 7-8 weeks.<br>• Added need for trained care partner to be present during exercise challenges<br><br>Section 6.2 Meal Challenges:<br>• Added that CGM trend error must not be rapidly rising at the start of the challenge<br>• Added information about the need to reschedule a challenge<br><br>Section 6.3 Exercise Challenges:<br>• Added that exercise mode will be active during exercise challenges, with the timing of activation determined by investigator and participant<br>• Added if CGM glucose is <120 mg/dL at start of session, carbohydrate can be taken and exercise should not begin until glucose is ≥120 mg/dL<br>• Added that the participant will be asked to record whether the prior insulin meal bolus was intentionally reduced in preparation for exercise<br>• Added information about the need to reschedule a challenge<br><br>Section 9.5: Added that cases of HHS will have expedited reporting to DSMB in addition to SH and DKA<br><br>Section 9.6.2: Added that the DSMB will be immediately notified of all adverse events related to SH, DKA, or HHS, as well as any recurrence of these events across participants or study sites.<br><br>Section 10.1: added that only insulin approved for the study pump can be used by the AID group<br><br>Section 10.3: added that dose increases in glucose-lowering or weight-reduction medications in use at the time of randomization are not permitted<br><br>Section 11.1: Added reference to section 11.15 regarding single-arm analyses to be performed for the AID group.<br><br>Section 11.2: Statistical hypotheses added for the secondary endpoints<br><br>Section 11.4.2: Clarification added that statistical testing is for superiority<br><br>Section 11.5.1: Clarified the criteria for inclusion in the per-protocol analysis and added 'no major |

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| | protocol deviation'.<br><br>Section 11.7.1: Added that CGM metrics during and following the challenges will be reported separately as described in section 11.15.3 and an overall analysis within the AID group will be performed for all CGM data including the challenge data as described in section 11.15.2.<br><br>Section 11.7.1: Definitions and statistical methods added for CGM-measured prolonged hyperglycemia events and CGM-measured hypoglycemia events.<br><br>Section 11.12: Added the following subgroup analyses<br>• Total daily insulin (<100 units versus ≥100 units)<br>• C-peptide level<br>• Baseline scores on the Subjective Numeracy Scale<br><br>Section 11.14. Added the following exploratory treatment group comparisons<br>• Separate sub-analyses for participants negative for GAD antibodies (if GAD antibodies are present in ≥5% of participants)<br>• Efficacy and safety outcomes in participants with TDI ≥100 units<br><br>Section 11.15.1. Added the following tabulations for the AID group<br>• Frequency of use of sleep mode and exploratory outcomes for times with versus without sleep mode<br>• Frequency of use of exercise mode<br><br>Section 11.15.2. Added an additional analysis in which CGM metrics will be computed over the entire 13 weeks of the trial (including the challenge periods) and statistically compared with baseline metrics | | | |
| 3.0 | J. Lum, J. Pinsker, D. Raghinaru | J. Pinsker | January 16, 2023 | Insulin will now be provided to study participants using the study device (changes to Protocol Summary, Table 1, Potential Risks, Eligibility Criteria, study pump training, Chapter 7, Chapter 10);<br>clarification of capture of hypoglycemia in last 3 months via participant survey (changes to Protocol Summary, Table 1, Screening and Visit procedures, Questionnaires section);<br>Added sub-analysis of > 150, > 200 units TDI (changes to Chapter 11, Statistical Considerations) |
| 4.0 | N Mba-Oduwusi, | J. Lum | February 16, 2023 | IRB edits and criteria of no plan to become pregnant adjusted from 2 months to study period.<br>Inserted AE, SAR, SUSAR in section 9.2 per Novo Nordisk request. |
| 5.0 | N. Mba-Oduwusi | J. Pinsker | March 09, 2023 | Corrected line 371 to indicate use of HbA1c within a 30-day timeframe (not 91 days).<br>Clarified Schedule of Study Visits and Procedures to indicate that the central HbA1c is required at randomization, irrespective of whether this visit occurs at the same time as screening.<br>Clarified Schedule of Study Visits and Procedures to indicate that height and weight will be done at randomization, 4 week visit, 8 week visit (if done in person), and 13 week visit, while physical examination is only required at screening. |

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| 6.0 | J. Lum | J. Pinsker | August 03, 2023 | Removed erroneous reference to "semi-structured interviews." Resolved conflicting statement about allowable meals for challenges. Clarified study insulin is branded as NovoRapid in Canada. Clarified definition of individuals permitted to perform physical exams. Resolved other minor conflicting statements. |
| 7.0 | J. Lum | J. Pinsker | October 02, 2023 | Changed study goal to maximum percent of participants with A1c ≤8.0 to 60%. This version was approved by FDA but never submitted to IRB or used clinically. |
| 8.0 | J. Lum | J. Pinsker | October 31, 2023 | Revised section 10.6 to indicate that glucagon will be offered to exercise challenge participants by study staff. |

# KEY ROLES

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| **Protocol Chair** | |
| **Name, degree** | Yogish Kudva, M.D. |
| **Institution Name** | Mayo Clinic |
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| **JCHR Coordinating Center Director** | |
| **Name, degree** | John Lum, MS |
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| **Sponsor** | |
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| **Institution Name** | Tandem Diabetes Care, Inc.<br>12400 High Bluff Drive<br>San Diego, CA 92130 |

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| ADE | Adverse Device Event |
| AE | Adverse Event |
| AID | Automated Insulin Dosing |
| AUC | (Glucose) Area under the curve |
| BMI | Body Mass Index |
| CFR | Code of Federal Regulations |
| CGM | Continuous Glucose Monitoring |
| CRF | Case Report Form |
| Control-IQ System | t:slim X2 insulin pump with Control-IQ technology |
| CSII | Continuous Subcutaneous Insulin Infusion |
| DCA2000 | Siemens/Bayer DCA 2000+ Hematology Analyzer |
| DKA | Diabetic Ketoacidosis |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EKG | Electrocardiogram |
| FDA | United States Food and Drug Administration |
| GAD | Glutamic Acid Decarboxylase |
| GCP | Good Clinical Practice |
| HbA1c | Hemoglobin A1c |
| HCL | Hybrid Closed-loop |
| HHS | Hyperosmolar Hyperglycemic Syndrome |
| HRPP | Human Research Protection Program |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| IQR | Interquartile Range |
| IRB | Institutional Review Board |
| MDI | Multiple Daily Injections of insulin |
| POC | Point-Of-Care |

| ABBREVIATION | DEFINITION |
|---|---|
| PRO | Patient-reported Outcomes |
| RBM | Risk-based Monitoring |
| SAE | Serious Adverse Event |
| TDD | Total Daily Dose |
| QA | Quality Assurance |
| QC | Quality Control |
| QoL | Quality of Life |
| RCT | Randomized Control Trial |
| SAR | Serious Adverse Reaction |
| SC | Standard of Care |
| SD | Standard Deviation |
| SUS | System Usability Scale |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T2D | Type 2 diabetes |
| TDD | Total Daily Dose of insulin |
| TIR | Time in range |
| UADE | Unexpected Adverse Device Event |

# SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

**Protocol Title**: A Randomized Trial Evaluating the Efficacy and Safety of Control-IQ Technology in Adults with Type 2 Diabetes Using Basal-Bolus Insulin Therapy (2IQP)

**Protocol Version/Date**: 8.0/October 31, 2023

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

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

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

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

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

Investigator's Name: _____

Site Name/Number: _____

## PROTOCOL SUMMARY

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| **Title** | A Randomized Trial Evaluating the Efficacy and Safety of Control-IQ Technology in Adults with Type 2 Diabetes Using Basal-Bolus Insulin Therapy |
| **Précis** | A randomized controlled trial (RCT) will evaluate 13 weeks of home use of the t:slim X2 insulin pump with Control-IQ technology in adults with type 2 diabetes age 18 and older using basal-bolus insulin therapy compared with continuation of pre-study insulin delivery plus continuous glucose monitoring (CGM). Exercise and meal-related challenges will be performed by all participants in the Control-IQ group unless there is a cardiac contraindication or other safety concern. |
| **Investigational Device** | t:slim X2 insulin pump with Control-IQ technology v1.5 (Control-IQ System) |
| **Objectives** | • To assess the safety of use of Control-IQ technology in adults with type 2 diabetes using basal-bolus insulin therapy<br>• To assess the efficacy of use of Control-IQ technology in adults with type 2 diabetes using basal-bolus insulin therapy<br>• To assess user satisfaction and quality of life with use of Control-IQ technology in adults with type 2 diabetes using basal-bolus insulin therapy |
| **Study Design** | RCT |
| **Number of Sites** | ~20-25 clinical centers in the U.S. and Canada |
| **Key RCT Endpoints** | Key Effectiveness Endpoints<br>*These endpoints will be tested in the following hierarchy to control for the type 1 error*<br>• HbA1c (primary)<br>• Time in range 70-180 mg/dL<br>• Mean glucose<br>• Time >180 mg/dL<br>• Time >250 mg/dL<br>• Prolonged hyperglycemia events (≥90 minutes >300 mg/dL within a 120-minute period)<br>• Time <70 mg/dL<br>• Time <54 mg/dL<br>• CGM-measured hypoglycemia events (15 or more consecutive minutes <54 mg/dL)<br>• Coefficient of variation<br>*Calculation of CGM metrics for the treatment group comparison will exclude the challenges and the 24-hour period following the end of the challenge*<br>Key Safety Endpoints:<br>• Severe hypoglycemia<br>• Diabetic ketoacidosis<br>• Hyperosmolar hyperglycemic syndrome<br>• Other serious adverse events |

| PARTICIPANT AREA | DESCRIPTION |
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| | • Unanticipated adverse device effects<br>• Hypoglycemia and prolonged hyperglycemia endpoints listed as effectiveness endpoints<br>• Infusion set failures<br>• Other device malfunctions/device issues<br><u>Other Endpoints</u><br>• % time in closed loop<br>• Total daily insulin delivery<br>• Weight change<br>• Change in lipid levels<br>• Cardiovascular events<br>• Patient-reported outcome (PRO) measures<br>  ○ Diabetes Distress Scale<br>  ○ Diabetes Impact and Device Satisfaction Scale<br>  ○ PROMIS (Sleep Related Impairment Questionnaire)<br>  ○ DAWN-Impact of Diabetes Profiles<br>  ○ HFS I and II<br>  ○ EQ5D<br>  ○ Study-specific survey<br>  ○ System Usability Scale (SUS)<br>• Frequency of non-severe hypoglycemia<br>Exploratory analyses will evaluate endpoints in subgroups based on diabetic medication use, body mass index, baseline HbA1c |
| **Eligibility Criteria** | **Inclusion Criteria**<br>1. Age ≥18 years old at time of screening<br>2. Currently resides in the U.S. or Canada with the ability to complete in-person study visits at one of the participating clinical sites<br>3. Clinical diagnosis, based on investigator assessment, of type 2 diabetes of at least 6 months duration at time of screening.<br>4. Using basal-bolus insulin therapy with at least one injection containing rapid-acting insulin per day or an insulin pump for at least 3 months prior to enrollment, with no major modification to insulin regime in the last 3 months<br>  • *Mixed insulin with a rapid component is acceptable*<br>5. If using noninsulin glucose-lowering medications (such as GLP-1 receptor agonist, SGLT2 inhibitor, or other) or weight-reduction medications, dose has been stable for the 3 months prior to screening; and participant is willing to not change the dose unless required for safety purposes<br>6. Participant willing to not initiate use of any new glucose-lowering medications during the trial<br>7. Willing to use an approved insulin while using the study pump if assigned to the AID group<br>8. Willing to not use concentrated insulin above U-100 or inhaled insulin while using the study pump |

| PARTICIPANT AREA | DESCRIPTION |
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| | 9. Willing to participate in the study meal and exercise challenges if assigned to the AID group, and have a care partner, trained in hypoglycemia treatment guidelines, to include glucagon use, present during and immediately after the exercise challenges.<br>10. Has the ability to read and understand written English<br>11. Investigator believes that the participant has the cognitive capacity to provide informed consent<br>12. Investigator believes that the participant can successfully and safely operate all study devices and is capable of adhering to the protocol and completing the study<br>13. No medical, psychiatric, or other conditions, or medications being taken that in the investigator's judgement would be a safety concern for participation in the study<br>• This includes considering the potential impact of medical conditions known to be present including cardiovascular, liver, kidney disease, thyroid disease, adrenal disease, malignancies, vision difficulties, active proliferative retinopathy, and other medical conditions; psychiatric conditions including eating disorders; drug or alcohol abuse.<br>14. Participants capable of becoming pregnant must meet one of the following criteria:<br>a. has a negative urine pregnancy test and agrees to use one of the accepted contraceptive regimens throughout the entire duration of the trial from screening until last follow-up visit. The following contraceptive measures are considered adequate:<br>i. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)<br>ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)<br>iii. Placement of an intrauterine device or intrauterine hormone-releasing system<br>iv. Bilateral tubal occlusion<br>v. Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository).<br>vi. Has a vasectomized or sterile partner (where partner is sole partner of subject) and where vasectomy has been confirmed by medical assessment<br>vii. Exercises true sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.<br>or<br>b. Participant is of non-childbearing potential due to menopause with at least one year since last menses or a medical |

| PARTICIPANT AREA | DESCRIPTION |
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| | condition confirmed by the investigator<br><br>**Exclusion Criteria**<br>1. Current use of hybrid closed-loop system<br>2. Current use of systemic glucocorticoids or anticipated use of glucocorticoids during the RCT (*topical or inhaled -ie, non-systemic is acceptable)*.<br>3. Current use of sulfonylurea or meglitinide medications<br>4. Current use of hydroxyurea<br>5. Tape allergy or skin condition that will preclude use of the study pump or CGM<br>6. Presence of a hemoglobinopathy or other condition that is expected to affect the measurement of HbA1c<br>7. Pregnant (positive urine hCG), breast feeding, plan to become pregnant during the study period, or sexually active without use of accepted contraceptive measures<br>8. Current participation in another diabetes-related interventional clinical trial<br>9. Anticipated change of residency or travel for more than 7 days at a time during the study that may, per investigator judgment, interfere with the completion of study visits, contacts, or procedures<br>10. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is an investigative site personnel directly affiliated with this study or who is an employee of Tandem Diabetes Care, Inc.<br>**Eligibility for Exercise Challenges**<br>All participants will have a screening EKG or review of an EKG completed in the 12 months prior to screening.<br>To participate in the exercise challenge, a participant must not have a history of a cardiovascular event in the year prior to screening and/or EKG abnormalities associated with increased risk during exercise. |
| **Sample Size** | A maximum of 450 individuals may be enrolled (consented for screening) in order to achieve the goal of 330 randomized participants.<br>This equates with a maximum of 220 using the AID system for 13 weeks and 110 using pre-study basal-bolus insulin delivery method plus the study CGM. Assuming 10% drop out rate in each group, there will be 200 using the system for 13 weeks.<br>Approximate Study Goals<br>- Minimum 25% MDI users<br>- Minimum 30% of a minority race or ethnicity<br>- Minimum 10% older than 50 years old<br>- Minimum 20% using an SGLT2 inhibitor,20% using a GLP-1 receptor agonist, and a minimum of 10% using both<br>- Minimum of 15% with TDI> 100 units/day and attempt to enrich cohort with participants with TDI >200 units |

| PARTICIPANT AREA | DESCRIPTION |
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| | - Minimum of 25% using a form of fixed dosing to calculate meal boluses (e.g., fixed dose at meal or fixed dose for small/medium/large meal [i.e., dose not determined by carbohydrate counting])<br>- Maximum of 60% with HbA1c <8% (based on screening HbA1c or HbA1c available within the last 30 days) and maximum of 10% with screening HbA1c <7% |
| **Treatment Groups** | Random assignment 2:1 to an intervention group or control group:<br>• Intervention group: t:slim X2 insulin pump with Control-IQ technology and Dexcom G6 CGM<br>• Control group: Continuation of pre-study basal-bolus insulin delivery method, plus use of study CGM (Dexcom G6) |
| **Participant Duration** | ~13-17 weeks, depending on duration of run-in phase |
| **Study Duration (planned)** | ~9 months from first enrollment until last participant visit (assuming 4-month recruitment period; study duration will be extended as needed to complete recruitment) |
| **Protocol Overview/Synopsis** | **Screening Visit**<br>• Informed consent obtained and participant screened for eligibility. Testing for eligibility assessment and baseline will include:<br>o Medical history, including total daily insulin dose, prior severe hypoglycemia, diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome (HHS), and hospitalizations for these events.<br>o HbA1c with point-of-care device or local lab, unless available from the prior 30 days<br>o Focused physical exam, including height and weight to compute body mass index (BMI) and blood pressure<br>o Urine pregnancy test for participants capable of becoming pregnant<br>o EKG unless performed within 12 months prior to screening<br>o Subjective Numeracy Scale<br>o Patient-reported outcome (PRO) surveys (see section 8.3), including frequency of non-severe hypoglycemia during the prior 3 months<br>**CGM Run-in**<br>• Eligible participants will be started on the study CGM, if applicable<br>• Experienced current users of the study CGM with at least 85% of available readings from prior 14 days will skip the CGM Run-In<br>• Otherwise, participants will use CGM for a minimum of 21 days<br>o Training provided to use the CGM in conjunction with basal-bolus insulin therapy<br>o Participants expected to use the CGM until return for post- run-in clinic visit.<br>o At investigator discretion, contacts may occur with participant during run-in phase for further training on use of CGM |

| PARTICIPANT AREA | DESCRIPTION |
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| | ○ Participants will continue use of their personal insulin delivery method (pump or MDI)<br>• Clinic visit after 21-28 days<br>• Participant must have used CGM for at least 85% of the time during the most recent 14 days. *If this requirement is not met, the run-in phase can be extended for an additional 14-21 days at the investigator's discretion.*<br>• The most recent 14 days of CGM data will be used as the baseline for analyses<br>**Randomization Visit**<br>• For participants completing the CGM Run-in, Randomization Visit typically occurs on same day as End of Run-in Visit; if participant is not ready to start the AID system if randomly assigned to the intervention group, it must occur within 14 days after completion of the run-in phase. For participants skipping the CGM Run-in, Randomization Visit may occur on same day as Screening Visit (so long as all eligibility criteria have been verified) or within 14 days following the Screening Visit.<br>• If not on same day as Screening Visit,<br>○ Solicit any changes in medical conditions since screening that could affect eligibility for the RCT<br>○ Vital signs<br>○ Urine pregnancy test for participants capable of becoming pregnant<br>• Blood draw for central lab measurement of HbA1c, lipids, creatinine, C-peptide, glucose, and GAD antibodies<br>• Randomization to the AID group or Control group<br>○ AID group: Initiation of AID system and training on its use *(initial training typically will be completed and AID system use initiated on day of randomization but if investigator does not believe that participant is ready to start the study pump, initiation of the study pump can be deferred for further training, but initiation of the AID system must occur within 7 days of randomization). Insulin aspart will be provided for participants who prefer to use the study insulin.*<br>○ Control group: Training on use of study CGM and continuing pre-study basal-bolus insulin therapy<br>**13-week RCT protocol**<br>• Participants in AID group will have a contact 3 ±1 days after initiation of closed loop (may coincide with 7-day visit) for further review of training materials and to answer questions. Participants will be specifically instructed to contact the site for any issues that arise during the first infusion set change.<br>• Participants in AID group will be expected to use the system continuously until the 13-week visit (unless a condition occurs, such as illness, in which the participant is instructed by the site to temporarily switch to open-loop)<br>• Addition of glucose-lowering or weight reduction medications or dose changes in such medications in use at the time of randomization are prohibited during the 13 weeks of the RCT, unless determined by the investigator to be necessary for safety. |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | ○ If a participant in the AID group has a change in dose or addition of a new glucose-lowering or weight-reduction medication, an unscheduled visit will occur after 1-2 days and ~7 days to assess safety.<br>• Instructions will be provided for when to test for ketones and management when ketosis is present (see section 4.6.4).<br>• Participants will not be restricted on diet or exercise.<br>• Participants in the Control group will be expected to use CGM on daily basis.<br><br><u>RCT Visits and Contacts</u><br>• As noted earlier, the AID group will have a contact 3 ±1 days after initiating the AID system to address any questions after initial use of the AID system and further training as needed.<br>• For both groups, in-clinic visits will occur 4 weeks ± 4 days and 13 weeks ± 4 days; and a remote (phone or video) visit will occur after 7±2 days for a safety check. An additional clinic visit or contact will occur after 8 weeks ± 4 days (depending on whether participant is able to upload device data at home and whether investigator believes clinic visit is needed).<br>At each scheduled visit/contact:<br>○ Review medications and doses<br>○ AID system and CGM data will be reviewed (participants without the ability to upload the device data from home will be provided with a laptop to use during the study)<br>○ Site investigators may adjust insulin delivery profile settings ONLY for safety concerns and will document reasons for change in the CRF<br>○ Occurrence of adverse events will be solicited<br>○ Assessment of TDD over last week<br>At 13-week visit, the following also will be done:<br>○ Height, weight, blood pressure/pulse<br>○ Blood draw for central lab measurement of HbA1c, lipids, creatinine<br>○ PRO surveys completed, including frequency of non-severe hypoglycemia during the prior 3 months<br>• At the completion of the RCT, participants will be transitioned back to their pre-study insulin regimen and have a safety contact after 3 ± 1 days.<br>• Additional visits and contacts may occur at investigator discretion<br>**<u>Exercise and Meal Challenges</u>**<br>• All participants in the AID group will perform the meal challenges and all participants in the AID group will perform the exercise challenges unless ineligible due to cardiac or other safety concerns.<br>• Each participant will perform 3 meal and 3 exercise challenges during the RCT. This will include a full bolus, half bolus, and no bolus meal, as well as three one-hour exercise periods (with at least 30 minutes moderate exercise). All challenges will be performed unsupervised at home, with required study team contacts before and after each challenge. For each |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | exercise challenge, an individual (care partner) capable of providing treatment for severe hypoglycemia will need to be present.<br>• Approximately 25% of each type of challenge (meal or exercise) will be performed on 3 consecutive days within each of the following 4 periods time from randomization: 1-2 weeks, 3-4 weeks, 5-6 weeks, 7-8 weeks. Challenges that cannot be scheduled during these time periods or challenges that need to be rescheduled may be performed, if necessary between weeks 9 and 13.<br>• Participants will be instructed to communicate with study staff within one day prior to each challenge to review procedures and to have a contact with study staff after the completion of each challenge within one day.<br><br><u>Study Safety Plan</u><br>Participants will be given a blood glucose and ketone meter to use throughout the study and will be trained on their use by qualified staff. BGM readings will be performed in accordance with the study safety plan and per CGM manufacturer instructions. Ketone readings will be performed per the study safety plan, based largely on the development of symptoms suggestive of ketosis.<br>Site investigators may adjust insulin delivery profile settings ONLY for safety concerns as needed throughout the study in accordance with their clinical practice. Reasons for the change will be documented in the CRF.<br>A Data and Safety Monitoring Board will provide study oversight. All severe hypoglycemia, DKA, and HHS events will be reported expeditiously to the DSMB as described in section 9.5.<br><br><u>Analysis Plan</u><br>At the end of the RCT, it is planned that the database will be locked and analyses performed in preparation for 510K submission. |

**Figure 1: Schematic of Study Design**

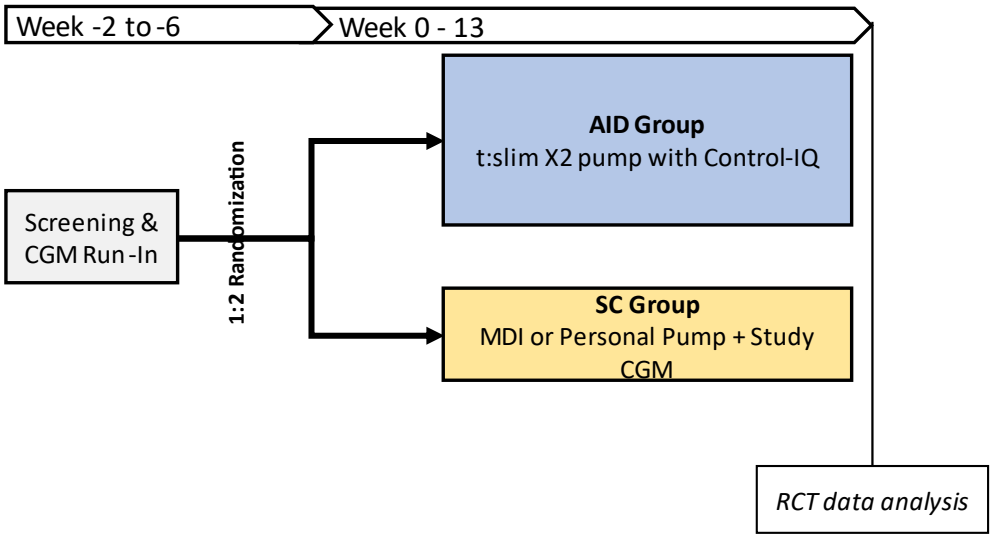

**Table 1: Schedule of Study Visits and Procedures**

| **Visit Designation** | **Screening** | **End of Run-in** | **Randomization (Day 0)** | **3d** | **1w** | **4w** | **8w** | **13w** |
|---|---|---|---|---|---|---|---|---|
| **Visit Window** | | * | ** | **± 1da** | **±2d[a]** | **±4d** | **±4d** | **±4d** |
| **Visit (V) or Contact (C)** | **V** | **V** | **V** | **C** | **C** | **V** | **V or C[b]** | **V** |
| Informed Consent/Assent | **X** | | | | | | | |
| Eligibility Assessment | **X** | | | | | | | |
| Medical history/ focused physical[c] | **X** | | | | | | | |
| Review medications and doses | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Blood pressure, pulse, height & weight[d] | **X** | | **X[e]** | | | **X** | **X[b]** | **X** |
| HbAlc (POC or local lab) | **X[f]** | | | | | | | |
| Pregnancy test (for participants capable of becoming pregnant) | **X** | | **X[e]** | | | | | |
| HbA1c (central lab) | | | **X** | | | | | **X** |
| Lipids, creatinine (central lab) | | | **X** | | | | | **X** |
| C-peptide, glucose, GAD antibodies (central lab) | | | X | | | | | |
| Subjective Numeracy Scale | **X** | | | | | | | |
| Questionnaires/Surveys (PRO Assessments)[g] | **X** | | | | | | | **X** |
| Initiation of Study CGM[h] | **X** | | | | | | | |
| Assessment of CGM Use | | **X** | | | | | | |
| Study system training; dispense study insulin | | | **X[i]** | **X** | | | | |
| Upload device data from home or at clinic visit | **X** | **X** | | **X** | **X** | **X** | **X** | **X** |
| AE Assessment | | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| EKG and assessment of eligibility for exercise challenges[j] | **X** | | | | | | | |
| Exercise and Meal challenges[k] | | | | ***See below*** | | | | |

*Clinic visit after 21-28 days for participants required to complete CGM run-in.

- To proceed to randomization, participant must have used CGM for at least 85% of the time during the most recent 14 days. *If this requirement is not met, the run-in phase can be extended for an additional 14-21 days at investigator discretion.*

- The most recent 14 days of CGM data will be used as the baseline for analyses

** Randomization Visit should be on the same day as the End of Run-in visit, following which closed-loop participants have up to 14 days to begin study pump use. Pump training can occur over more than 1 session if necessary.

[a] Target and windows for 3-day visit, and 7-day visit are calculated from study pump initiation date for AID group.

[b] At 8 weeks, clinic visit or contact depending on whether participant is able to upload device data at home and whether investigator believes clinic visit is needed.

[c] A focused physical exam will be performed by the study investigator or designee (a physician, fellow, nurse practitioner, physician assistant, or equivalent licensed provider). This will include parts of the exam relevant to device use, such as skin changes from device or insulin use. At screening, it may include physical exam techniques related to assessment of cardiovascular disease if participation in the exercise and meal challenges is being considered.

[d] Vital signs (including blood pressure and pulse) and height and weight measurements may be obtained by non-study support staff according to the clinic's usual processes.

[e] Not performed if Randomization Visit is same day as Screening Visit. May be performed at other visits at the discretion of the investigator.

[f] Can be skipped if result is available from within prior 30 days

[g] See section 8.3 for list of questionnaires to be completed; includes frequency of non-severe hypoglycemia during the prior 3 months

[h] Study CGM training provided and CGM use initiated for all participants except those who are experienced current users of the study CGM with at least 85% of readings available from the prior 14 days

[I] Only for participants assigned to AID group; initial training typically will be completed and AID system use initiated on day of randomization but if investigator does not believe that participant is ready to start the study pump, initiation of the study pump can be deferred for further training but initiation of the AID system must occur within 7 days of randomization. Insulin aspart will be provided for participants who prefer to use the study insulin.

[j] EKG not required if performed within prior 12 months

[k] Exercise and meal challenges:

- All participants in the AID group will perform the meal challenges and all without a safety contraindication will perform the exercise challenges.
- Each participant will perform 3 meal and 3 exercise challenges during the RCT. This will include a full bolus, half bolus, and no bolus meal, as well as three one-hour exercise periods (with at least 30 minutes moderate exercise). All challenges will be performed unsupervised at home, with required study team contacts before and after each challenge.
- Approximately 25% of each type of challenge (meal or exercise) will be performed on 3 consecutive days within each of the following 4 periods time from randomization: 1-2 weeks, 3-4 weeks, 5-6 weeks, 7-8 weeks. Challenges that cannot be scheduled during these time periods or challenges that need to be rescheduled may be performed, if necessary between weeks 9 and 13.

# Chapter 1: Background Information

## 1.1 Disease Background

More than 34 million people in the United States have diabetes, with type 2 diabetes accounting for approximately 90% to 95% of cases. In the last 20 years, the number of adults diagnosed with diabetes has more than doubled as the American population has aged and become more overweight or obese. Diabetes is the 7th leading cause of death in the United States (and may be underreported) (1).

## 1.2 Device Background

The t:slim X2 insulin pump with Control-IQ technology (Control-IQ) is an advanced hybrid closed-loop (HCL) system, developed and manufactured by Tandem Diabetes Care, Inc. and cleared in the U.S. by the FDA for individuals with type 1 diabetes. Control-IQ is integrated with the Dexcom G6 continuous glucose monitor (CGM) and uses CGM values to predict glucose values 30 minutes in the future. Based on the predicted glucose, Control-IQ modulates basal insulin delivery, and delivers automated correction boluses to mitigate impending hyperglycemia. The current Control-IQ system is FDA approved down to age 6 years old for individuals with type 1 diabetes, and has been found to improve time in range (70-180 mg/dL) and decrease both time <70 mg/dL and time >180 mg/dL (2,3). There are over 150,000 users of the system since it became commercially available in 2020. A recent evaluation of real-world use of the system in 9,451 users age ≧6 years with at least 12 months of system use found results comparable to those found in the randomized trials (4).


**Figure 2. t:slim X2 with Control-IQ and Dexcom G6 system**

Since the initial approval of the system, modifications have been made in the software, which is referred to as version 1.5. These modifications include modest usability improvements and other enhancements intended to further reduce risk. The Control-IQ 1.5 algorithm also removes the 3 units/hr basal clipping, allowing the pump to deliver programmed user profile basal rates above 3 units/hr. This has the potential to further improve outcomes in individuals with type 2 diabetes who are often using basal rates at or above this threshold.

## 1.3 Control-IQ Use in Type 2 Diabetes

Insulin pump use in individuals with type 2 diabetes is relatively low. However, there is an increasing uptake of pump use in this population. The benefits of insulin pump use with Automated Insulin Dosing (AID) technology in individuals with type 2 diabetes has not been well established in clinical trials, although real-world data have shown that use of Control-IQ can produce significant glycemic benefits in this population, whether transitioning from multiple daily injections (MDI) or prior pump use. Retrospective analysis of 134 prior pump users with type 2 diabetes who purchased a new Tandem insulin pump with Control-IQ technology showed time in range was 76% (IQR 69-82%) and time below range was 0.5% (IQR 0.2-1.0%) after 180 days of use. For 173 participants transitioning from MDI, use of Control-IQ technology resulted in time of range 70-180 mg/dL of 74% (IQR 63-83%) and time below 70 mg/dL 0.3% (IQR 0.1-0.6%) at 180 days of use (5). Additionally, retrospective analysis of real-world use out to one year in 378 individuals with type 2 diabetes who software updated from Basal-IQ technology to Control-IQ technology showed significant improvements in time in range 70-180 mg/dL (69% at baseline versus 78% at one year) (4). In an analysis of Medicare and Medicaid Control-IQ users, 500 individuals with type 2 diabetes improved from 64% TIR at baseline to 72% after using Control-IQ for at least 30 days (6).

A prospective single-arm 6-week trial, conducted to provide preliminary data on the safety and glycemic outcomes with use of Control-IQ in adults with T2D, showed that use of Control-IQ was safe, with no increase in CGM-measured hypoglycemia and a substantial improvement in time in range and mean glucose related to a reduction in hyperglycemia (7). Thirty adults with T2D (mean age 54±12 years, mean HbA1c 8.6±1.2, median BMI 31) using either MDI (N=15), pump (N=2) or basal without bolus insulin (N=13) collected unblinded CGM data (baseline) followed by an open-loop period prior to initiating use of CIQ for 6 weeks. Primary outcomes were superiority for CGM time >180 mg/dL and non-inferiority for time <54 mg/dL. Mean time >180 mg/dL decreased from 44% at baseline to 29% with CIQ, a reduction of 3.6 hours per day (P=0.004), mean time 70-180 mg/dL increased from 56% to 71% (P= 0.004), and mean glucose decreased from 184 to 163 mg/dL (P=0.01). Median time >250 mg/dL decreased by more than one hour per day. Median time <54 mg/dL was 0.00% at baseline and during CIQ use (IQR -0.02% - +0.02%). Median time in closed loop was 96% (interquartile range 93% to 96%). There were no severe hypoglycemia or DKA events. On the Diabetes Impact and Device Satisfaction Scale, participants indicated a high level of satisfaction with CIQ (mean item score 8.8±1.9 on scale of 1-10). Both prior MDI or pump and prior basal insulin only participants showed similar levels of improvement in all outcomes.

### 1.4 Rationale and Objectives

There are many patients with T2D who are unable to achieve optimal glucose control despite the use of intensive insulin therapy often with the concomitant use of other glucose-lowering drugs. An AID system such as Control-IQ offers the potential for lower HbA1c levels and increased time in range without increasing hypoglycemia and for improved quality of life. In view of the promising results from the preliminary study evaluating Control-IQ in T2D, a larger trial with a randomized trial design is needed to more broadly and rigorously evaluate the efficacy and safety of Control-IQ in adults with T2D using basal-bolus insulin therapy with or without additional glucose-lowering medications. Thus, the main objectives of this trial are:

- To assess the safety of use of Control-IQ in adults with type 2 diabetes using basal-bolus insulin therapy
- To assess the efficacy of use of Control-IQ in adults with type 2 diabetes using basal-bolus insulin therapy
- To assess user satisfaction and quality of life with use of Control-IQ in adults with type 2 diabetes using basal-bolus insulin therapy

## 1.5 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 securely to minimize this risk. Hypoglycemia and hyperglycemia and ketone formation are always a risk in participants with type 2 diabetes and insulin treatment, and participants will be monitored for this.

### 1.5.1 Known Potential Risks

#### 1.5.1.1 Potential Risks of the AID System

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

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

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

#### 1.5.1.1 Potential Risks of Using Insulin Aspart

Potential adverse reactions with study-provided insulin aspart are similar to other insulins: hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, localized cutaneous amyloidosis, pruritus, rash, weight gain, and peripheral edema.

#### 1.5.1.2 Potential Risks of CGM

CGM will be used by the control group without automation of insulin delivery. There is risk of CGM inaccuracy that could lead to an under dosing of insulin producing hyperglycemia or overdosing of insulin producing hypoglycemia.

#### 1.5.1.3 Risk of Hypoglycemia

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

#### 1.5.1.4 Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. Although less common in individuals with type 2 diabetes than in those with type 1 diabetes, DKA can still occur. Extreme levels of hyperglycemia and dehydration can lead to hyperosmolar hyperglycemic syndrome (HHS). A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery. All subjects will be issued a glucose meter and glucose test strips, as well as a ketone meter and ketone test strips, to use to carefully monitor for hyperglycemia and ketones and be given instructions on how to mitigate hyperglycemia and ketosis should it occur.

#### 1.5.1.5 Fingerstick Risks

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

#### 1.5.1.6 Venipuncture Risks

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

#### 1.5.1.7 Subcutaneous Catheter Risks

Whenever the skin is broken there is the possibility of bleeding and bruising. The CGM sensor and pump infusion sets are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection, which could produce swelling, redness, and pain. These occur very infrequently, but if an infection were to occur, oral and/or topical antibiotics may be prescribed. The risk of skin problems could be greater if a sensor or infusion set is used for longer than it is intended to be used. Therefore, participants will be carefully instructed about proper use of these components.

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

#### 1.5.1.8 Risk of Exercise

Exercise may lead to injury, hypoglycemia or hyperglycemia, or significant events, such as myocardial infarction or other significant cardiac events. Participants completing the exercise challenges will be evaluated for their suitability to participate in the exercise challenges, which will minimize the risk. Participants will be instructed on how to prepare for exercise by study staff and intended use of the exercise activity feature.

#### 1.5.1.9 Risk of Device Reuse

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

#### 1.5.1.10 Questionnaires

As part of the study, participants will complete questionnaires which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires and interviews to be mildly upsetting. Similar questionnaires and interviews have been used in previous research and these types of reactions have been uncommon.

#### 1.5.1.11 Other Risks

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

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

### 1.5.2 Known Potential Benefits

Participants may experience a significant improvement in glucose control. Hypoglycemia is the number one fear of many individuals taking insulin, and this fear often prevents optimal glycemic control. Hyperglycemia will likely be reduced as well.

In addition, users of insulin pumps often take less insulin than users of basal/bolus injection therapy. This may lead to weight loss, which will be tracked over the course of the study.

It is expected that this protocol will yield increased knowledge about using an AID system to control glucose levels in people with type 2 diabetes. The individual participant may or may not benefit from study participation.

### 1.5.3 Risk Assessment

It is the assessment of the investigators that this protocol is a clinical investigation involving greater than minimal risk but that it does present the prospect of direct benefit to individual subjects based on the following: (1) individuals with diabetes experience hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may reduce the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may reduce the likelihood of hyperglycemia, (3) if any, hypo and/or hyperglycemia occur, 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, In addition, it is the

belief of the investigators that this study also presents prospect of general benefit to others with diabetes.

### 1.6 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).

In accordance with 21 CFR 812.66, the protocol is considered a significant risk device study, due to the fact that the closed loop system is investigational in the population under study. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

# Chapter 2: Study Enrollment and Screening

## 2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of 330 participants being randomized in the trial and at least 300 participants completing the trial. A maximum of 450 individuals may be consented for screening in order to achieve this goal. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the completion goal has been reached.

Study participants will be recruited from ~20-25 clinical sites in the United States and Canada. The maximum number that can be randomized by any site is 66. Up to 30 participants will be randomized from Canada. All eligible participants will be included without regard to gender, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each clinical center toward the overall recruitment goal.

There will be approximate recruitment goals for the following:

- Minimum 25% MDI users
- Minimum 30% of a minority race or ethnicity
- Minimum 10% older than 50 years old
- Minimum 20% using an SGLT2 inhibitor, 20% using a GLP-1 receptor agonist and a minimum of 10% using both
- Minimum of 15% with TDI>100 units/day and attempt to enrich cohort with participants with TDI >200 units
- Minimum of 25% using a form of fixed dosing to calculate meal boluses (e.g., fixed dose at meal or fixed dose for small/medium/large meal [i.e., dose not determined by carbohydrate counting])
- Maximum of 60% with HbA1c <8% (based on screening HbA1c or HbA1c available within the last 30 days) and maximum of 10% with screening HbA1c <7%

Individuals generally will be recruited from each site's existing patient population or from a list of individuals who contact the site. Study recruitment methods may consist of one or more of the following:

- Culling of pre-existing databases at the clinical sites to identify patients who may be eligible. Those identified will be contacted via IRB-approved mailing sent through post, email, or via phone and will be provided information about the study and how to proceed if potentially interested;
- IRB-approved press release announcing study and study fact sheet;
- IRB-approved information about the study distributed through support groups, other internet groups, patient education classes, not-for-profit organizations;
- IRB-approved paper and digital advertisements;
- IRB-approved digital advertisements posted on social media sites like LinkedIn, Twitter, YouTube, Instagram, Facebook, and other public forums;
- In-person recruitment of patients seen in the clinic; and

- An IRB-approved website dedicated to clinical trial recruitment.

All recruitment methods and specific advertising materials will be approved by the Central and/or local IRB prior to their implementation. The JCHR IRB is the Central IRB for this study, and where permissible, sites shall rely on the JCHR IRB.

#### 2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, documented informed consent will be obtained. Additionally, as part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The informed consent process is described in section 13.3.

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

## 2.2 Participant Eligibility Criteria

### 2.2.1 Participant Inclusion Criteria

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

1. Age ≥18 years old at time of screening
2. Currently resides in the U.S. or Canada with the ability to complete in-person study visits at one of the participating clinical sites
3. Clinical diagnosis, based on investigator assessment, of type 2 diabetes of at least 6 months duration at time of screening.
4. Using basal-bolus insulin therapy with at least one injection containing rapid-acting insulin per day or an insulin pump for at least 3 months prior to enrollment, with no major modification to insulin regime in the last 3 months
   - *Mixed insulin with a rapid component is acceptable*
5. If using noninsulin glucose-lowering medications (such as GLP-1 receptor agonist, SGLT2 inhibitor, or other) or weight-reduction medications, dose has been stable for the 3 months prior to screening; and participant is willing to not change the dose unless required for safety purposes
6. Participant willing to not initiate use of any new glucose-lowering medications during the trial
7. Willing to use an approved insulin while using the study pump if assigned to the AID group
8. Willing to not use concentrated insulin above U-100 or inhaled insulin while using the study pump
9. Willing to participate in the study meal and exercise challenges, and have a care partner, trained in hypoglycemia treatment guidelines, to include glucagon use, present during and immediately after the exercise challenges.
10. Has the ability to read and understand written English

11. Investigator believes that the participant has the cognitive capacity to provide informed consent

12. Investigator believes that the participant can successfully and safely operate all study devices and is capable of adhering to the protocol and completing the study

13. No medical, psychiatric, or other conditions, or medications being taken that in the investigator's judgement would be a safety concern for participation in the study
    - This includes considering the potential impact of medical conditions known to be present including cardiovascular, liver, kidney disease, thyroid disease, adrenal disease, malignancies, vision difficulties, active proliferative retinopathy, and other medical conditions; psychiatric conditions including eating disorders; drug or alcohol abuse.

14. Participants capable of becoming pregnant must meet one of the following criteria:
    a. has a negative urine pregnancy test and agrees to use one of the accepted contraceptive regimens throughout the entire duration of the trial from screening until last follow-up visit. The following contraceptive measures are considered adequate:
        i. Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
        iii. Placement of an intrauterine device or intrauterine hormone-releasing system
        iv. Bilateral tubal occlusion
        v. Barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository).
        vi. Has a vasectomized or sterile partner (where partner is sole partner of subject) and where vasectomy has been confirmed by medical assessment
        vii. Exercises true sexual abstinence. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Or

    b. Participant is of non-childbearing potential due to menopause with at least one year since last menses or a medical condition confirmed by the investigator

#### 2.2.2 Participant Exclusion Criteria

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

1. Current use of hybrid closed-loop system
2. Current use of systemic glucocorticoids or anticipated use of glucocorticoids during the RCT (*topical or inhaled -ie, non-systemic is acceptable)*.
3. Current use of sulfonylurea or meglitinide medications

4. Current use of hydroxyurea
5. Tape allergy or skin condition that will preclude use of the study pump or CGM
6. Presence of a hemoglobinopathy or other condition that is expected to affect the measurement of HbA1c
7. Pregnant (positive urine hCG), breast feeding, plan to become pregnant during the study period, or sexually active without use of accepted contraceptive measures
8. Current participation in another diabetes-related interventional clinical trial
9. Anticipated change of residency or travel for more than 7 days at a time during the study that may, per investigator judgment, interfere with the completion of study visits, contacts, or procedures
10. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is an investigative site personnel directly affiliated with this study or who is an employee of Tandem Diabetes Care, Inc.

#### 2.2.3 Eligibility for Exercise Challenges

All participants will have a screening EKG or review of an EKG completed in the 12 months prior to screening.

To participate in the exercise challenges, a participant must not have a history of a cardiovascular event in the year prior to screening and/or EKG abnormalities associated with increased risk during exercise.

### 2.3 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 focused physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions.

The screening visit may be completed on one or over multiple days but must be completed within 28 days of participant enrollment.

#### 2.3.1 Data Collection and Testing

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

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race, and ethnicity)
- Contact information (retained at the site and not entered into study database)
- Medical history, including existing comorbidities deemed clinically relevant (e.g. retinopathy, nephropathy, neuropathy, history of cardiovascular events); in addition,

details specific to type 2 diabetes, including age at diagnosis, duration of disease, previous therapy, and frequency of severe hypoglycemia and diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS), and hospitalization for these glycemic events will be collected

- Concomitant medications
- Focused physical examination
  - Performed by study investigator or designee (physician, fellow, nurse practitioner, physician assistant, or equivalent licensed provider)
  - Weight, height, and vital signs (blood pressure and pulse) may be obtained by non-study support staff according to the clinic's usual processes.
- If applicable, assessment will be made with respect to eligibility for the exercise challenges (see section 2.2.3)
- Fingerstick or blood draw for point-of-care or local laboratory determination of HbA1c level (not required if HbA1c result available from prior 30 days)
- Urine pregnancy test for participants capable of becoming pregnant
- EKG unless performed within the 12 months prior to screening
- Completion of Subjective Numeracy Scale
- Completion of PRO questionnaires by participant, described in section 8.3, including recording of frequency of non-severe hypoglycemia in the prior 3 months using a validated survey *(Davis et al. Current Medical Research and Opinion, 21:9, 1477-1483, DOI: 10.1185/030079905X61929)*

Screening procedures will last approximately 1-2 hours.

### 2.4 Screen Failures

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

# Chapter 3: CGM Run-in

## 3.1 CGM Run-in Overview

This phase will generally begin on the day when screening is complete but must begin within 7 days of completion of screening. The purpose of this CGM run-in phase is 1) to initiate use of the study CGM (unblinded) in participants without current use of a Dexcom CGM and 2) to assess compliance with use of the CGM and study procedures over a period of at least 21 days.

Participants who currently use a Dexcom G6 CGM with at least 85% of possible CGM readings captured during the 14 days prior to enrollment can skip the CGM Run-in phase. Participants who do not currently use a Dexcom G6 CGM, or who do use that CGM but have <85% of possible CGM readings in the 14 days prior to the time of enrollment, will be required to participate in the CGM Run-in.

Participants will continue to use their personal insulin delivery method (pump or MDI) during the Run-in.

Participants will be provided with CGM supplies, the study blood glucose meter, study ketone meter, and test strips; and will be trained on their use.

## 3.2 Initiation of CGM

During an in-clinic visit, participants required to complete the CGM Run-in will be trained and a sensor will be inserted. Study CGM supplies will be provided and the participant will be instructed to use the study CGM on a daily basis. Participants using a personal CGM prior to the study will discontinue their personal CGM while using a study CGM.

### 3.2.1 CGM Training

CGM training will be provided by a qualified trainer to participants not currently using a personal CGM identical to the study CGM with respect to how to use it in real-time to make management decisions and how to review the data after an upload for retrospective review. CGM training will include:

- Instruction on how to insert the sensor and transmitter, including observation/supervision of placement of a sensor
- Instruction on how to calibrate the CGM, if needed, in accordance with manufacturer labelling
- Guidance on accessing the CGM trace, either through a manufacturer-provided software app or via a study-provided CGM receiver unit, or via a personal insulin pump if participants use a pump that integrates with the study CGM
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

A copy of the study CGM user's guide will be provided to the participant.

Participants may use available manufacturer-provided CGM software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose.

Upon completion of the CGM training components, study staff will document, using a checklist, that the participant is familiar with the functions/features/tasks addressed during the training.

At investigator discretion or participant request, contacts may occur with participant during run-in phase for further training on use of CGM.

Adjustments can be made in the participant's insulin dosing at investigator discretion during the CGM Run-in.

### 3.3 Assessment of Successful Completion of the CGM Run-in Phase

Participants will have a follow-up visit 21-28 days (target 21 days) after initiation of the run-in phase to assess CGM usage. Procedures will include downloading of the study CGM data and the following:

- Assessment of compliance with the use of CGM to obtain at least 85% of possible CGM values during the most recent 14 days of CGM data collection
- Assessment of skin reaction in areas where a CGM sensor was worn or other safety issues associated with CGM use

Participants who fail to meet the minimum CGM use requirement, or whom the investigator believes may benefit from an extension of the CGM run-in period, may at the investigator's discretion be allowed to continue CGM run-in for up to an additional 14 days. These participants will have another follow-up visit approximately 14 days after the prior visit for a reassessment using the same procedures as described above.

Participants who do not meet CGM use requirements after the second CGM wear period or otherwise fail to meet study eligibility requirements will be withdrawn from the study.

For participants entering the RCT, the most recent 14 days of CGM data will be used as the baseline for analyses.

# Chapter 4: Randomization Visit

## 4.1 Overview

For participants completing the CGM Run-in, the randomization visit generally will occur on the same day immediately following the CGM Run-in Visit. If the participant is not ready to start the AID system if assigned to the intervention group, the Randomization Visit must occur within 14 days after completion of the run-in phase. For participants skipping the CGM Run-in, the Randomization Visit could occur on same day as Screening Visit (once all eligibility has been verified) or within 14 days following the Screening Visit.

At this visit, eligibility will be reaffirmed and participants will be randomly assigned to the AID group or Control group.

## 4.2 Testing and Procedures

The following will be done at the Randomization Visit:

- Review medical history since Screening Visit to verify that there have been no changes or events that affect participant eligibility, any adverse events that may have occurred since their last study visit, and any changes in medications or doses (if not on the same day as the Screening Visit)
- Verify that participant understands the protocol and is willing to accept assignment to either treatment group
- Measure height, weight, blood pressure and pulse (if Randomization Visit is not on same day as Screening Visit)
- Urine pregnancy test for participants capable of becoming pregnant (if Randomization Visit is not on the same day as the Screening Visit)
- Blood draw for central lab measurements of HbA1c, lipids, creatinine, C-peptide, glucose, GAD antibodies
- Randomization
- Training and instructions for each treatment group
- Distribution of study devices and supplies to participants according to the assigned treatment group
    - Both groups will be provided with Dexcom G6 sensors and transmitters, the study blood glucose meter, study ketone meter, and test strips; and will be trained on their use

## 4.3 Randomization

Participants will be randomly assigned in a 2:1 ratio to the AID group or the Control group.

The participant's randomization group assignment is determined by entering the Randomization Visit data on the study website. JCHR will construct a Master Randomization List using a block design separately for each center.

*Note: To minimize an imbalance in the number of participants assigned to each group, randomization will not be stratified by age, HbA1c or other factors because of the small number per site that is possible and considering the 2:1 randomization.*

### 4.4 Instructions for Both Groups

Study staff will review the use of the study CGM, blood glucose meter, and ketone meter. The following instructions will be given to both groups:

- Participants will be advised not to use alcohol or other drugs in sufficient quantity to reduce sensitivity to symptoms of hypoglycemia or hinder appropriate decision-making.
- Any medical advice needed by the participants during their participation that is not directly related to the study protocol should be obtained in the usual manner with their own physician.
- There are no restrictions of any kind on diet, exercise, or other activities
- Hypoglycemia low threshold alerts will be set to no lower than 70 mg/dL. If a low alarm occurs, the participant will be trained to verify the glucose level with a fingerstick glucose using the study blood glucose meter. If the blood glucose meter confirms hypoglycemia, participants will be instructed to treat with ~15 grams of carbohydrate and to continue to monitor their glucose levels until hypoglycemia has resolved.
- Additional material that is IRB approved, to include Tandem infusion set insertion videos, may be used to supplement training. The IRB approved handouts related to fixed dosing, small/medium/large meals, carb counting, and pump therapy basics may be used by the training staff as judged necessary for a given participant's needs, whether in the Control or AID group.

### 4.5 Instructions for the Control Group

Participants in the Control group will be instructed to follow their usual diabetes management with respect to insulin delivery. They will be asked to use CGM daily throughout the RCT in accordance with manufacturer labelling. Participants will receive training on hyperglycemia and ketosis management, similar to that described for the AID Group in section 4.6.4, that is customized for the participant based on the type of insulin delivery being used.

### 4.6 Instructions for the AID Group

The approach to training will depend on whether the participant is already a pump user. The training on use of the AID system may occur completely at this visit or may be spread out over a few days in multiple visits or contacts. Initiation of the study pump and closed-loop control generally will occur on the day of the Randomization Visit but can be deferred if the investigator believes additional training is needed prior to initiating the study pump. In such cases, initiation of the study pump and Control IQ should occur no more than 7 days following randomization.

Participants will be informed of the need to have a care partner trained and capable of treating severe hypoglycemia, including use of glucagon as indicated in section 6.3.

#### 4.6.1 Study Pump Training

Participants will receive study pump training on use of the pump in open-loop mode by a qualified trainer:

- Participants will be fully instructed on the study insulin pump. The trainer will discuss differences from the participant's personal pump, if applicable, in important aspects such as calculation of insulin on board and correction boluses and optional additional topics such as: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- Participants will be instructed to change the study insulin pump infusion set at least once every 3 days or per manufacturer guidelines, whichever is shorter.
- Participants will be trained to use the pump's bolus calculator.
- 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, if applicable. The participant's personal pump, if used, 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 written information provided with the pump and infusion sets after the training is completed.
- The participant will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon.
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- To prevent insulin stacking from long-acting basal insulin that is on board, participants using long-acting insulin injections at baseline will be instructed, and supervised by study staff, to set a temp basal rate to 0% that will end 24 hours after last injection of long-acting insulin, at which time the pre-programmed basal rate will be turned on. Study investigators may adjust this procedure per their usual clinical practice, and may customize this plan based on the type of basal insulin used (for example, insulin degludec with a longer half-life may require a basal rate of 50% for a second day).

A copy of the study pump user's guide will be provided to the participant.

Study-provided insulin aspart will be offered to the participant, who will be instructed on the proper storage and use of the insulin during the course of the study.

##### 4.6.1.1 Initiation of Pump by MDI Participants

For MDI participants being started on the study pump, an initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures' manual.

Site investigators may make further adjustment to insulin delivery profile settings ONLY for safety concerns and will document reasons for change in the CRF.

### 4.6.2 Training on Using the Pump with Control-IQ Technology

Participants will receive instruction from a qualified trainer on use of the study pump in closed-loop mode, to include the following:

- How to turn on and off Control-IQ technology
- How to understand when Control-IQ is increasing or decreasing basal rates
- How to administer a meal or correction boluses during closed-loop system use
- What to do when exercising while using the system in closed-loop mode
- How to enable the sleep function and set the sleep schedule
    - Sleep activity will be enabled during normal sleep time for all users unless a safety concern arises as judged by the investigator.
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.

Upon completion of the study pump training components, study staff will document, using a checklist, that the participant is familiar with the functions/features/tasks addressed during the training.

### 4.6.3 System Use Guidelines

The participant will be instructed to use the system in closed-loop mode except 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 four hours.

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with the system. They will be instructed to contact study staff in case of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), other 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.

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

### 4.6.4 Hyperglycemia and Ketosis Detection and Management

Unlike in type 1 diabetes, for participants with type 2 diabetes, hyperglycemia by itself, without any other symptoms, is not a medical emergency indicating the need for ketone checking. Participants may have had significant amount of hyperglycemia prior to the study and may periodically have hyperglycemia for missed boluses. Participants who are on SGLT inhibitors,

GLP-1 receptor agonists, or DPP-IV inhibitors could also develop ketones at lower glucose values (<250 mg/dl), where euglycemic DKA could occur. Therefore, participants will be instructed to check ketones based on signs or symptoms of ketonemia or general illness, to include abdominal pain/nausea/emesis/increased polyuria or feeling unwell, as well as during times of intercurrent illness (i.e., fever). Participants will be instructed to contact the study site for any ketone values ≥ 0.6 mmol/L or for additional guidance on sick day management. If the ketone value is <0.6 mmol/L but symptoms persist, the participant will be instructed to recheck ketones after one hour.

If ketone level is ≥ 0.6 mmol/L and study staff cannot be immediately contacted, the participant will be instructed to:

- Perform a blood glucose meter check.
- Take correction insulin calculated to achieve a target glucose of 150 mg/dL with an insulin syringe and change insulin pump infusion site.
- Continue to monitor their glucose and blood ketone levels until ketones are < 0.6 mmol/L.
- If correction insulin is administered via insulin syringe, turn Control-IQ off for four hours.
- If vomiting, go to the Emergency Room.

Participants will be permitted to change the hyperglycemia alarm setting, but will be instructed to choose a value no greater than 300 mg/dL.

# Chapter 5: RCT

## 5.1 Overview

The RCT will last for 13 weeks. Procedures to be followed by the Control Group are described in section 4.5 and procedures to be followed by the AID group in section 4.6.

## 5.2 Follow-up Visits and Contacts

The AID group will have a training/check-in contact 3 ±1 days after initiating the AID system for further review of training materials and to answer questions. Participants will be specifically instructed to contact the site for any issues that arise during the first infusion set change.

Otherwise the visit and contact schedule will be the same for both groups.

- Contact (phone or video) will occur after 7±2 days for a safety check.
- Clinic visits will occur at 4 weeks ± 4 days and 13 weeks ± 4 days.
- Visit or contact at 8 weeks ± 4 days (depending on whether participant is able to upload device data at home and whether investigator believes clinic visit is needed).

Additional office visits may occur as needed at investigator discretion.

If necessary, visits should be completed out-of-window rather than missed. A visit is not considered missed until the next visit/phone window opens. In the event that in-person visits cannot be conducted due to institutional restrictions or the participant's unwillingness to attend an in-person clinic visit, visits may be conducted virtually via a HIPAA-compliant Zoom or similar video conference mechanism to collect whatever data is possible to collect remotely.

Participants will be instructed to download the study CGM and pump prior to each scheduled contact.

### 5.2.1 Contact and Visit Procedures

At each scheduled contact and visit for both groups, the following will be done:

- AID system and CGM data will be reviewed (participants without the ability to upload the device data from home will be provided with a laptop to use during the study)
- Site investigators may adjust insulin delivery profile settings ONLY for safety concerns and will document reasons for changes in the CRF.
- Occurrence of adverse events will be solicited
- Assessment of TDD over last week

At the 4-week clinic visit and 8-week clinic visit (if it occurs in clinic), the following also will be done:

- Height, weight, blood pressure/pulse measured

At 13-week visit, the following also will be done:

- Height, weight, blood pressure/pulse measured

- Blood draw for central lab measurement of HbA1c, lipids, creatinine
- PRO surveys completed

## 5.3 Transition to Pre-study Insulin Therapy

At the end of the RCT, study staff will supervise the participant's transition back to their prior therapy.

- Study staff will re-evaluate the subject's baseline therapy doses, noting changes in basal rates, carbohydrate ratios, and correction factors in use at the end of the trial.
- Participants must have two CGM or fingerstick blood glucose values, separated by at least 15 minutes, that are above 80 mg/dL prior to discharge from the clinic.
- Study staff will confirm subjects have carbohydrates on hand for their drive back home, and instruct subjects to check their glucose levels when they arrive at home, prior to bedtime, and at least one time overnight on the first night to monitor for hypoglycemia, reminding subjects that insulin on board can be active for the next few hours even after stopping the study pump.

### 5.3.1 3-Day Post-Study or Discontinuation of AID System Contact

Participants will have a post-study contact 3 (±1) days after permanently discontinuing the study AID system and transitioning back to their prior insulin therapy (which for most participants will be at the end of the RCT), during which the following will occur:

- Check on transition back to usual home diabetes care
- Assessment of adverse events

## 5.4 Safety Visits Following Changes in Glucose-Lowering or Weight-Reduction Medications

The only changes of glucose-lowering or weight-reduction medications permitted will be a reduction in dose for safety reasons, or an adjustment to an equivalent dose of a different formulation if participant's insurance coverage changes. No increased doses or initiation of a new glucose-lowering or weight-reduction medication will be permitted.

If a participant in the AID group has a reduction in dose or requires a change of glucose-lowering or weight-reduction medication due to insurance coverage, an unscheduled visit will occur after 1-2 days and 7 days to assess safety.

## 5.5 Early Termination Visit

Participants in the AID group who discontinue use of the AID system will be asked to continue using the study CGM and remain in the study through the 13-week visit.

In the event of participant withdrawal or early termination in both groups, participants will be asked to come to clinic for an end of study visit. If the visit occurs 4 or more weeks after randomization, the procedures listed for the 13-week visit will be completed (may be combined with the 4-week visit if in window for the 4-week visit).

Participants in the AID group who discontinue use of the AID system prior to the end of the RCT and have not already resumed their pre-study insulin regimen will be transitioned back to their pre-study insulin regimen as described in section 5.3 and will have a 3-day post-study call.

# Chapter 6: Exercise and Meal Challenges

## 6.1 Overview

All participants in the AID group will be asked to perform 3 meal challenges and 3 exercise challenges unless ineligible due to cardiac or other safety concerns, with the expectation that the majority of participants in the AID group will complete all challenges.

Participants will be advised that for the exercise challenges, they must have a care partner capable of providing treatment for severe hypoglycemia, including glucagon use, who will be present during and for one hour following each study exercise challenge. Training will be provided by study staff to the care partner as needed.

Approximately 25% of each type of challenge (meal or exercise) will be performed on 3 consecutive days within each of the following 4 periods time from randomization: 1-2 weeks, 3-4 weeks, 5-6 weeks, 7-8 weeks. Challenges that cannot be scheduled during these time periods or challenges that need to be rescheduled may be performed, if necessary, between weeks 9 and 13.

Participants will be instructed to communicate with study staff within one day prior to each challenge to review procedures and to have a contact with study staff after the completion of each challenge within one day.

## 6.2 Meal Challenges

The 3 meal challenges will be performed on 3 consecutive days while the study AID system is being used. The same meal should be used for each of the 3 meal challenges—either lunch or dinner (participant choice).

The three meal challenges will consist of:

- No bolus for the meal
- 50% bolus – calculate the bolus dose using the bolus calculator and deliver half the recommended dose of insulin.
- Full bolus for the meal based on calculated bolus dose using the bolus calculator.

For each meal challenge, participants will:

1. Be in a fasting state for two hours prior to consuming the meal and the last manual insulin bolus more than two hours prior to the meal.
2. Only begin the meal challenge if CGM glucose is between 70 mg/dL and 200 mg/dL and CGM trend arrow is not rapidly rising (straight up arrow). *Subjects with hyperglycemia > 200mg/dL will reschedule their challenge for another time. If < 70 mg/dL, carbohydrate treatment can be given, after which the meal challenge can continue.*
3. Consume at least 50 grams carbohydrate for the meal. *Each participant will use the same meal for all of their meal challenges in the study. Participants will be encouraged to use the same frozen entrée of their choice for consistency.*

4. Write down the start and end time of eating the meal, as well as the meal content (to include amount of carbohydrate, protein and fat) on the study provided logbook.
5. Not give an additional bolus for up to 3 hours after the meal challenge, unless BG is above 300 mg/dL for more than 1 hour, or symptoms of hyperglycemia develop.
6. Not take additional carbohydrates for up to 3 hours after the meal challenge, unless BG is < 70 mg/dL, or symptoms of hypoglycemia develop.
7. Not exercise for 3 hours after the meal challenge.
8. Notify the site within 24 hours after completion of each meal challenge.
9. The meal challenge will end 3 hours after the meal is completed.

If a meal challenge needs to be rescheduled due to out-of-range glucose value or an unforeseen circumstance, it should be completed on a separate day (same meal, lunch or dinner) as soon as possible.

### 6.3 Exercise Challenges

The 3 exercise challenges will be performed on 3 consecutive days while the study AID system is being used.

The 3 exercise challenges will include one-hour exercise periods, which include at least 30 minutes of moderate exercise. All challenges will be performed unsupervised at home, with required study team contacts before and after each challenge. As indicated below, a care partner will need to be present during and for one hour after the exercise session.

For each exercise challenge, participants will:

1. Have a care partner, capable of providing treatment for severe hypoglycemia, to include glucagon use, who is present during and for 1 hour after the exercise challenges. *The care partner will receive training as needed.*
2. Have carbohydrate containing snacks and glucagon on hand during and after exercise.
3. Activate “exercise activity” (required) on the pump up to 45 to 60 minutes ahead of actual exercise, to allow for less insulin on board when starting exercise. The timing of exercise activity activation may be adjusted per their usual routine and investigator guidance. Consider reducing the last meal bolus prior to exercise as a way to reduce insulin on board and limit hypoglycemia.
4. Perform one hour of exercise, including at least half an hour of moderate activity. Exercise does not need to be the same activity each time.
5. Only begin exercise if CGM glucose is ≥ 120 mg/dL and CGM glucose is not trending downward. *If glucose is <120 mg/dL, carbohydrate can be taken and exercise may begin once the glucose level is ≥120 mg/dL.*
6. Write down the start time of last meal and amount and time of last insulin dose, whether the prior meal insulin bolus was intentionally reduced in preparation for exercise, type of exercise performed, as well as the start and stop time of each exercise session in the study logbook *(as this may not correlate exactly with exercise activity use on the pump)*. Participants may take breaks if needed, as long as the full hour of activity is completed.

7. Stop the exercise challenges at any point for injury or development of new symptoms; development of chest pain/pressure, feeling unwell, development of hypoglycemic symptoms, undue shortness of breath, signs of poor perfusion (leg pain/claudication), or for any other reason.
8. Immediately contact the study team for acute symptoms (such as chest pain, leg pain, persistent shortness of breath), or seek immediate medical assistance for acute symptoms if the study team is not reachable.
9. Notify the site within 24 hours after completion of each exercise challenge. Participants will be asked if they developed new symptoms and review guidance on the need to stop future exercise challenges if any adverse events or new symptoms occurred per clinician judgement based on the severity of symptoms.
10. The exercise challenge will end after 1 hour of the required activity is completed.

If an exercise challenge needs to be rescheduled due to out-of-range glucose value or an unforeseen circumstance, it should be completed on a separate day as soon as possible.

### 6.4 Meal and Exercise Challenge Follow-Up

Participants will be instructed to contact study staff within 24 hours of completing each exercise challenge. The follow up call will review:

- The start and stop time, as well as the type of exercise performed.
- Assessment of adverse events
- Documentation of any safety concerns if future exercise challenges are cancelled.

# Chapter 7: Study Devices and Study Insulin

## 7.1 Description of the Investigational Device

### 7.1.1 Insulin Pump

The study system will include the Tandem t:slim X2 insulin pump (K201214, Tandem Diabetes Care, San Diego, CA) using the Control-IQ version 1.5 algorithm. The study insulin pump is designed to revert to open-loop delivery of preprogrammed basal insulin levels in the event that CGM data are not available. The pump also includes various alarms and alerts to notify the user when there is a problem with insulin delivery.

### 7.1.2 Continuous Glucose Monitoring

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

### 7.1.3 Blood Glucose Meter and Strips

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

### 7.1.4 Ketone Meter

The study blood ketone meter is the Precision Xtra Blood Glucose and Ketone Monitoring System for U.S. sites and the FreeStyle Precision Neo for Canadian sites (Abbott Diabetes Care).

Blood ketone levels will be measured when indicated as described in section 4.6.4. The blood glucose meter component of the device will not be used.

## 7.2 Description of Study-Provided Insulin

The study drug offered to AID group participants only is NovoLog (insulin aspart injection) 100 U/mL, branded as NovoRapid for Canadian sites. The insulin is provided by Novo Nordisk. This is a non-investigational insulin that is functionally identical to commercially-available NovoLog.

- **Acquisition**

  The study insulin will be shipped by the manufacturer, in coordination with the study Coordinating Center, directly to each clinical site for storage and dispensation to study participants.

- **Formulation, Appearance, Packaging, and Labeling**

  The study insulin is a sterile, aqueous, clear, and colorless solution for subcutaneous or intravenous administration. Each mL contains 100 units of insulin aspart. Package labelling will be functionally identical to commercial drug.

- **Product Storage and Stability**

  Dispense in the original sealed carton with the enclosed Instructions for Use.

Refrigerate unopened study insulin vials between 36°F to 46°F (2°C to 8°C) until time of use and keep in the original carton to protect from light. Do not freeze or use study insulin if it has been frozen. Do not expose to direct heat. Discard opened or unopened study insulin vials stored at room temperature below 86°F (30°C) after 28 days.

- **Post-Study Disposal**

  At the conclusion of study activities, remaining unopened vials of study insulin will be disposed/destroyed by each clinical site in accordance with local disposal policies.

### 7.3 Study Device Accountability Procedures

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

### 7.4 Participant Access to Study Device at Study Closure

Participants will be returned to their pre-study insulin therapy at the conclusion of the study and must return study-assigned devices and unopened insulin to the clinical site as instructed by study staff.

# Chapter 8: Testing Procedures and Questionnaires

## 8.1 Laboratory Testing

1. HbA1c:
    - HbA1c level measured using the DCA2000 or comparable point of care device or local lab at the Screening visit, if no comparable measurement is available within 30 days prior to enrollment *(since this measurement is not used for analysis, there will be no centralized quality control measures implemented)*
    - HbA1c level measured at a Central Lab from blood draw performed at Randomization Visit and 13-week Visit.
2. C-peptide/Glucose:
    - C-peptide with concurrent glucose level measured at a Central Lab from blood draw performed at Randomization Visit
3. Urine Pregnancy:
    - Performed locally for participants capable of becoming pregnant at Screening Visit and Randomization Visit. Pregnancy testing will also be done anytime pregnancy is suspected.
4. GAD Antibodies:
    - GAD antibodies measured by Central Lab at Randomization Visit
5. Lipid Levels and Creatinine
    - Measured by Central Lab at Randomization Visit and 13-week Visit.

*Local laboratory testing will be performed if needed to screen for medical conditions that might preclude study participation.*

## 8.2 Physical Examination

A focused physical exam will be performed by the study investigator or designee (a physician, fellow, nurse practitioner, physician assistant, or equivalent licensed provider). This will include parts of the exam relevant to device use, such as skin changes from device or insulin use. At screening, it may include physical exam techniques related to assessment of cardiovascular disease if participation in the exercise and meal challenges is being considered.

Vital signs and height and weight measurements may be obtained by non-study support staff according to the clinic's usual processes.

## 8.3 Questionnaires

### 8.3.1 Baseline Surveys

The following surveys will be completed at the Screening Visit to characterize the cohort:

| MEASURE | DESCRIPTION |
|---|---|
| **Subjective Numeracy Survey** | A validated tool that subjectively measures (i.e., self-assessment) a person's quantitative ability that distinguishes low- and high-numerate individuals. Four items measure people's beliefs about their skill in performing various mathematical operations, and 4 items measure people's preferences regarding the presentation of numerical information. (2 min) |

### 8.3.2 Patient-reported Outcome Surveys

The PRO questionnaires are completed by all participants at the study visits indicated in the table below. Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

**Table 2.** Study Patient-reported Outcome Questionnaires

| MEASURE | CONSTRUCT MEASURED/RELEVANT POINTS | ADMINISTRATION POINTS |
|---|---|---|
| **Type 2 Diabetes Distress Assessment System (T2-DDAS Combined - Core and Source)** | A 29-item questionnaire includes a Core Tool (8 items) and a Sources Tool (assessing 7 separate Sources of diabetes distress, each with 3 items). The new T2-DDAS allows for an enhanced level of assessment precision: it makes it possible to differentiate between the level or intensity of diabetes distress experienced and the primary sources of diabetes distress. (3 min). | Baseline, 13 weeks |
| **DAWN Impact of Diabetes Profile (DIDP)** | A 7-item questionnaire providing a valid and reliable measure of the perceived impact of diabetes on quality of life, suitable for adults with Type 1 or Type 2 diabetes mellitus. (2 min) | Baseline, 13 weeks |
| **Diabetes Impact and Satisfaction (DIDS) Scale** | An 11-item questionnaire focused on satisfaction related to insulin delivery devices (e.g., trust and ease of use) and diabetes-related impact on daily life, such as worry around hypoglycemia and sleep interruptions. (3 min) | Baseline, 13 weeks |
| **PROMIS Sleep-Related Impairment Questionnaire** | An 8-item questionnaire that measures sleep disturbance and sleep-related impairment. (2 min) | Baseline, 13 weeks |
| **System Usability Scale (SUS)** | A 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. (2 min) | Baseline, 13 weeks |
| **Hypoglycemia Fear Survey II** | A 33-item survey that measures several dimensions of fear of hypoglycemia among individuals with diabetes. It measures worry (18 items) and behavior (15 items) (5-10 min) | Baseline, 13 weeks |
| **EQ5D-5L** | A 5-item NICE approved Quality of Life (QOL) measure that translates into economics (2 min) | Baseline, 13 weeks |
| **Study-specific survey** | A 2-item questionnaire that explores time spent on insulin management and insulin dosing with meals (2 min) | Baseline, 13 weeks |
| **Hypoglycemia Frequency Last 3 Months Survey** | A 4-item questionnaire that captures occurrence and frequency of mild, moderate, severe, and nocturnal hypoglycemia over the past 3 months (3 min) | Baseline, 13 weeks |

# Chapter 9: Unanticipated Problem, Adverse Event, and Device Issue Reporting

## 9.1 Unanticipated Problems

Site investigators will promptly report all unanticipated problems meeting the criteria below on an eCRF. Sites relying on the Central IRB must report potential Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

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

The Sponsor (or CRO on behalf of the Sponsor) also will report to the Central IRB all potential unanticipated problems not directly involving a specific site such as unanticipated problems that occur study-wide or at another participating entity such as a pharmacy or laboratory. These instances must be reported to the Central IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting to fulfill the reporting obligations of the HRPP.

## 9.2 Adverse Events

### 9.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures or occurring during the course of a study in which a device, biologic, or drug is used in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

For this protocol an adverse event is considered any untoward medical occurrence, unintended disease or injury, or untoward clinically significant clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. As used here, a participant is considered enrolled once consent has been executed.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting. Suspicion of transmission of infectious agents must always be considered an SAE.

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

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device. (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in section 9.3).

Adverse Reaction (AR): An AR is an AE for which the causal relationship between a drug and the AE is suspected.

Serious Adverse Reaction (SAR): An Adverse event which fulfill both the criteria for a Serious Adverse Event and the criteria for an Adverse Reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An SAR which is unexpected and regarded as possibly or probably related to the trial/study drug product. This event requires a submission of an IND Safety Report. See 21 CFR 312 for more information.

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

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

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

### 9.2.2 Reportable Adverse Events

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

1. An SAE as defined in section 9.2.1
2. An ADE as defined in section 9.2.1, unless excluded from reporting in section 9.3
3. An AE as defined in 9.2.1 occurring in association with a study procedure
4. An AE as defined in 9.2.1not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. An AE as defined in 9.2.1that affects the participant's ability to complete any study procedures
6. An AE as defined in 9.2.1for which a visit is made to a hospital emergency department
7. Hypoglycemia meeting the definition of reportable hypoglycemia in section 9.2.3
8. Hyperglycemia or ketosis event meeting the criteria defined in section 9.2.4.
9. An AE as defined in section 9.2.1 considered to be related to either ineffective insulin (e.g., insulin exposed to high temperature that loses potency), signs or symptoms related to insulin infusion, or changing of type of insulin related to an AE.

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

All reportable AEs—whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means—

will be reported on an AE form online. Each AE form is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

### 9.2.3 Hypoglycemic Events

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

- A hypoglycemic event occurred meeting the following definition of severe hypoglycemia: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself independently, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia
- Participant contacted the site because of the occurrence of hypoglycemia
- Hypoglycemia occurred that was associated with an ADE as defined in section 9.2.1
- Study device discontinued due to hypoglycemia

When a severe hypoglycemia event occurs (as defined above), a Hypoglycemia Form should be completed in addition to the Adverse Event Form. Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 9.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

### 9.2.4 Hyperglycemic/Ketotic Events

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

- Evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis
- The event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
    - Symptoms such as polyuria, polydipsia, nausea, or vomiting;
    - Serum ketones >1.5 mmol/L or large/moderate urine ketones;
    - Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or $CO_2$) <15; and

- Treatment provided in a health care facility

- The event involved hyperosmolar hyperglycemic syndrome (HHS), as defined by the American Diabetes Association and described below
  - Symptoms such as polyuria, polydipsia, nausea, or vomiting;
  - Plasma glucose levels are very elevated (typically > 600 mg/dL);
  - Plasma effective osmolarity is >320 mOsm/L;
  - Absence of significant ketones; and
  - Treatment provided in a health care facility
- Hyperglycemia occurred that was associated with an ADE as defined in section 9.2.1
- Study device discontinued due to hyperglycemia

When a hyperglycemia/ketotic event qualifies as an AE, or as an SAE as defined in section 9.2.1, a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA or HHS criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA or HHS generally will not be considered as serious adverse events unless one of the SAE criteria in section 9.2.1 is met.

When a hyperglycemia/DKA event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 9.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

#### 9.2.5 Relationship of Adverse Event to Study Investigational Device or Study Procedure

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 or study procedure. The Medical Monitor also will make this assessment, which may or may not agree with that of the site investigator. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect. Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative, with both the site investigator's and the Medical Monitor's assessment reported.

Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative.

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

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

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

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

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

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

Where these relatedness categories are used, events determined to be Possibly Related, Probably Related, or Definitely Related will be considered to meet the *reasonable possibility* causality standard for relatedness and necessitate reporting as required (see 21 CFR 312.32 for more information about this standard).

#### 9.2.6 Severity (Intensity) of Adverse Events

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

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

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

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

#### 9.2.7 Expectedness

For a serious adverse event that is considered possibly related to the study, a study procedure, or the study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the approved labelling of the study system (most recent summary of product characteristics in the labelling).

#### 9.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting).

### 9.2.9 Outcome of Adverse Events

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

- RECOVERED/RESOLVED (COMPLETE RECOVERY) – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. 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.
- ONGOING (NOT RECOVERED/NOT RESOLVED) – An ongoing AE/SAE is defined as an ongoing event 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.
- ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

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

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

## 9.3 Reportable Device Issues

All UADEs and ADEs as defined in section 9.2.1will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

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

- CGM sensor needing replacement prior to labelled maximum use duration
- Infusion set needing replacement prior to labelled maximum use duration
- CGM tape adherence issues

- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

User error (as defined in section 9.2.1) will only be reported on a Device Issue form if an AE as defined in section 9.2.1 results from the error. In these cases, both a Device Issue form and an Adverse Event form will be completed.

### 9.4 Timing of Event Reporting

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

The Sponsor (or CRO) will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within ten (10) working days after the Sponsor becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements of his/her local Institutional Review Board or Ethics Committee and the Central IRB (as applicable). Sites relying on the Central IRB must report all serious, related adverse events within seven (7) calendar days (in addition to meeting any local IRB reporting requirements).

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE is confirmed, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within ten (10) working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b)(2). The Sponsor in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than five (5 )working days after the Sponsor makes this determination and no later than fifteen (15) working days after first receipt notice of the UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification and must submit to their local IRB as required.

The investigators are also required to report, without unjustified delay, all reportable device deficiencies, irrespective of whether an adverse event occurred.

Device malfunctions will be handled by the Sponsor or designee as described below. In the case of a CGM transmitter or sensor device malfunction, information will be forwarded to Dexcom by the site personnel, to be handled by their complaint management system.

Where an adverse event is suspected to be related only to the study provided insulin from Novo Nordisk, and does not result from a possible interaction with the investigational medical device, the investigator or the sponsor are encouraged to report the case to the FDA or competent authority. Where made aware of such case, the competent authority should apply the guidance provided in the Good Pharmacovigilance Practices Module VI with regard to the management of this type of safety report. While reporting the suspected adverse reaction, the relevant information regarding the CT (i.e. clinical trial number) or Study ID number must be included in the report.

## 9.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within twenty-four (24) hours of reporting. Other AEs typically will be reviewed on a weekly basis.

The Sponsor and Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA or HSS and the Medical Monitor's assessment of relationship to the study device; and informed of all reported device issues. A Data and Safety Monitoring Board (DSMB) will provide safety oversight. The DSMB will be informed of all cases of severe hypoglycemia, DKA, and HHS irrespective of device relationship, all device-related SAEs, and all UADEs at the time that they occur during the study and will review compiled safety data at periodic intervals. The DSMB also will be informed of any ADEs not meeting criteria for a UADE if the Medical Monitor requests the DSMB review. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding the DSMB's role will be documented in a separate DSMB charter.

## 9.6 Stopping Criteria

### 9.6.1 Participant Discontinuation of Study Device

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

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

- The investigator believes it is unsafe for the participant to continue on the intervention. *This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety.*
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA, HHS, or severe hypoglycemia as defined in sections 9.2.3 and 9.2.4, respectively.

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

An additional requirement for continued study participation following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor concurs. If the Medical Monitor determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the study system, the participant will be discontinued from the study.

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

### 9.6.2 Criteria for Suspending or Stopping Overall Study

The DSMB will be immediately notified of all adverse events related to SH, DKA, or HHS, as well as any recurrence of these events across participants or study sites. In addition to the suspension of closed-loop mode use due to a UADE as described above, closed-loop system use 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.

Additionally, the Medical Monitor or the DSMB may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available. The Central IRB also has the authority to suspend or terminate study activities, and local IRBs have the authority to suspend or terminate activities at the sites that they oversee.

# Chapter 10: Miscellaneous Considerations

## 10.1 Drugs Used as Part of the Protocol

Participants using the study pump will use only insulin approved by the FDA for use in the study pump.

## 10.2 Collection of Medical Conditions and Medications

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

*Medical Conditions during the study:* In addition to conditions meeting the reporting requirements for an adverse event as described in section 9.2.2, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

*Medications:* All medication for the treatment of chronic pre-existing conditions, medical conditions (including medical conditions that do not require recording), and/or adverse events that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. Medications only taken as needed either be captured with a frequency of "PRN", or can be recorded when used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

## 10.3 Prohibited Medications, Devices, Treatments, and Procedures

Only insulins approved for the study pump can be used in the study pump. Afrezza (inhaled insulin) or concurrent use of basal insulin will not be permitted during use of Control-IQ in the trial.

Sulfonylurea use and meglitinide use will not be allowed during the trial.

Addition of glucose-lowering or weight-reduction medications not in use at the time of randomization are prohibited during the 13 weeks of the RCT.

Dose increases in glucose-lowering or weight-reduction medications in use at the time of randomization are not permitted.

Hydroxyurea use is not allowed during the trial, as it may interfere with the study CGM sensor.

Additional medications may be excluded per judgement of the investigator.

The body-worn study devices (study insulin pump, study CGM system) 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.

## 10.4 Precautionary Medications, Treatments, and Procedures

Not applicable.

### 10.5 Prophylactic Medications, Treatments, and Procedures

Not applicable.

### 10.6 Rescue Medications, Treatments, and Procedures

Participants in the AID group who perform exercise challenges will be expected to have a commercially available glucagon (or glucagon analog) preparation for treatment as needed for severe hypoglycemia. Glucagon will be offered to these participants by the study team.

### 10.7 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported to the Sponsor/CRO within seven (7) calendar days and to the Central IRB on the Unanticipated Problem form within seven (7) calendar days.

### 10.8 Participant Compensation

Participant compensation will be specified in the informed consent form.

### 10.9 Participant Withdrawal

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

### 10.10 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

# Chapter 11: Statistical Considerations

## 11.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below. A detailed Statistical Analysis Plan will be written and finalized prior to the completion of the study.

The primary statistical analyses will involve comparisons of the randomized treatment groups. Additionally, certain single-arm analyses will be conducted on the data collected for the AID group as described in section 11.15.

## 11.2 Statistical Hypotheses

The primary endpoint for this study is HbA1c at 13-weeks adjusted for baseline HbA1c. The intervention will be considered effective if the AID group is superior to the Control group using a statistical significance of $\alpha$=0.05.

The null/alternative hypotheses for the primary endpoint are:

- *Null Hypothesis*: There is no difference in mean HbA1c at 13 weeks between AID and Control
- *Alternative Hypothesis*: Mean HbA1c at 13 weeks is different for AID and Control.

Similarly, the null and alternative hypotheses for all of the secondary efficacy endpoints in the hierarchy are:

- *Null Hypothesis*: There is no difference in the endpoint at 13 weeks between AID and Control
- *Alternative Hypothesis*: Endpoint at 13 weeks is different for AID and Control.

## 11.3 Sample Size

The sample size of 330 randomized participants was selected to provide sufficient exposure to the AID system for regulatory purposes. This equates with a maximum of 220 using the AID system for 13 weeks. Assuming 10% drop out rate in each group, there will be 200 using the system for 13 weeks.

HbA1c data from N=30 participants in the 2IQ pilot study were used to estimate the SD for the power calculation. The SD for baseline values was 1.0%. Assuming a similar SD at follow-up, correlation of 0.3 with baseline, and a two-sided test with type 1 error at 5%, a sample size of N=300 completers will be able to detect an HbA1c difference as small as 0.38% with 90% power. There will be 85% power to detect a difference of 0.35% and 80% power for a difference of 0.33%.

## 11.4 Efficacy Outcome Measures

### 11.4.1 Primary Efficacy Endpoint

- HbA1c at 13 weeks (superiority)

### 11.4.2 Secondary Efficacy Endpoints Included in Hierarchical Analysis

The following secondary endpoints will be tested for superiority, with a hierarchical testing approach to protect the type 1 error rate as described in section 11.13.

- Time in range 70-180 mg/dL
- Mean glucose
- Time >180 mg/dL
- Time >250 mg/dL
- CGM-measured prolonged hyperglycemia events (defined in section 11.7.1)
- Time <70 mg/dL
- Time <54 mg/dL
- CGM-measured hypoglycemia events (defined in section 11.7.1)
- Coefficient of variation

### 11.4.3 Other Secondary Efficacy Endpoints

The following efficacy endpoints are considered exploratory as they are not included in the overall type 1 error rate. All statistical tests are for superiority.

*Binary HbA1c Endpoints:*

HbA1c <7.0% at 13 weeks

HbA1c <7.0% at 13 weeks in participants with baseline HbA1c >7.5%

HbA1c <7.5% at 13 weeks

HbA1c improvement from baseline to 13 weeks >0.5%

HbA1c improvement from baseline to 13 weeks >1.0%

HbA1c relative improvement from baseline to 13 weeks >10%

HbA1c improvement from baseline to 13 weeks >1.0% or HbA1c <7.0% at 13 weeks

*Continuous CGM-Measured Endpoints:*

Time in range 70-140 mg/dL

Area over the curve (70 mg/dL)

Low blood glucose index

Time >300 mg/dL

Area under the curve (180 mg/dL)

High blood glucose index

*Binary CGM-Measure Endpoints*

Time in range 70-180 mg/dL >70%

Time in range 70-180 mg/dL improvement from baseline to 13 weeks ≥5%

Time in range 70-180 mg/dL improvement from baseline to 13 weeks ≥10%

Time <70 mg/dL <4%

Time <54 mg/dL <1%

Time in range 70-180 mg/dL >70% and time <54 mg/dL <1%

*Other Endpoints (analyzed for superiority as continuous variables):*

- Insulin
  - Total daily insulin delivery
  - Percentage of insulin delivered as basal
- Weight change
- Change in lipid levels
- Cardiovascular events
- Patient-reported outcome (PRO) measures (see section 8.3)

#### 11.4.4 Safety Endpoints

- Severe hypoglycemia
- Diabetic ketoacidosis
- Hyperosmolar hyperglycemic syndrome
- Other serious adverse events
- Unanticipated adverse device effects
- Hypoglycemia and prolonged hyperglycemia endpoints listed as effectiveness endpoints
- Infusion set failures
- Other device malfunctions/device issues

### 11.5 Analysis Datasets and Sensitivity Analyses

All analyses comparing the AID arm with Control arm will follow intention-to-treatment approach, which means participants will be analyzed in the treatment arm assigned by randomization regardless of actual system use. All randomized participants will be included in the primary analysis and secondary analyses of CGM metrics.

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

#### 11.5.1 Per Protocol Analyses

Per-protocol analyses will be performed for primary outcome and secondary hierarchical outcomes only if >5% of participants will be excluded. All of the following criteria must be met for a participant to be included in the per-protocol analyses. The criteria are as follows:

- 13-week visit completed
- No major protocol deviations

- Device use: AID group - closed loop mode active for at least 80% of the time over the 13-week period; control group - CGM use for at least 80% of the time over the13-week visit period

### 11.5.2 Other Sensitivity Analyses

*Confounding*

A sensitivity analysis will also be conducted if potential confounding factors collected at baseline are detected.

The imbalance will be assessed based on clinical judgment reviewing the distributions in the two treatment arms, not on a p-value. The person making this judgement will be unaware of whether there is an association between baseline variables and study outcome. All variables obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the outcome. In such a case, categorization and/or transformation will be explored.

*Missing Data*

Missing data will be handled using direct likelihood method for the primary analysis. It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

To that end, sensitivity analyses will be performed to explore whether results are similar for primary analysis when using different methods. The following methods will be applied:

- Rubin's multiple imputation with treatment group in the imputation model
- Available cases only
- Multiple imputation with pattern mixture model assuming the dropout trajectory of the AID group was that of the Control group (Mallinckrodt and Clark, 2003)
- Tipping point analysis to determine the magnitude of selective dropout bias necessary to alter conclusions of the study.

## 11.6 Analysis of the Primary Efficacy Endpoint: HbA1c

HbA1c at 13 weeks will be compared between the AID and Control Groups using a linear mixed effects regression model adjusting for baseline HbA1c and clinical center (random factor). A separate variance will be modelled for each treatment group. HbA1c is expected to be normally distributed, but regression diagnostics will be performed to check the residuals and an appropriate alternative transformation or robust statistical method (e.g., non-parametric or MM estimation) will be performed if the residuals have a skewed distribution. In the event that some HbA1c values are not available at 13 weeks, then the linear mixed effect regression model will use the method of direct likelihood to incorporate information from baseline measurements to calculate the maximum likelihood at 13 weeks. Only central lab HbA1c measurements will be used in the analyses. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the sensitivity analyses by including factors potentially associated with the outcome for which there is an imbalance between groups (11.5.2).

## 11.7 Analysis of Secondary Endpoints

### 11.7.1 CGM Metrics

Baseline values for each CGM metric will be computed from 14 days of CGM data prior to randomization. A minimum of 72 hours of CGM data will be required to calculate baseline metrics.

CGM data starting from randomization visit through the 13-week visit will be included in the calculation of each CGM metric for each participant, giving equal weight to each CGM point.

Calculation of CGM metrics for the treatment group comparisons will exclude the challenges and the period through 6 AM on the day following the end of the challenge. CGM metrics during and following the challenges will be reported separately as described in section 11.15.3 and an overall analysis within the AID group will be performed for all CGM data including the challenge data as described in section 11.15.2.

CGM-measured prolonged hyperglycemia events are defined as ≥90 cumulative minutes with CGM glucose >300 mg/dL within a 120-minute period (the participant becomes eligible for another prolonged hyperglycemia event after the CGM glucose is <180 mg/dL for ≥15 consecutive minutes). CGM-measured hypoglycemia events are defined as ≥15 consecutive minutes with CGM glucose <54 mg/dL (the participant becomes eligible for another hypoglycemia event after the CGM glucose is ≥70 mg/dL for ≥15 consecutive minutes). For each of these metrics, the number of events per week is calculated for each participant and each metric is then analyzed as a continuous variable as described below.

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured metrics at baseline and during follow up as well as for differences from baseline by treatment group. CGM metric differences between AID and Control Groups will be compared using a linear mixed effects regression model adjusting for the baseline value of the metric and clinical center (random effect). A separate variance will be modelled for each group. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. Missing data will be handled using direct likelihood.

### 11.7.2 Binary Outcomes

For the binary HbA1c outcomes, risk-adjusted percentages by treatment group will be computed at 13 weeks from a logistic regression model. The logistic regression will adjust for baseline HbA1c (as a continuous factor) and clinical site using generalized estimating equations (GEE). Similar analyses will be done for the binary CGM outcomes.

## 11.8 Questionnaires and Other Outcomes Analyses

For questionnaires administered to both randomization groups, comparisons will be made using similar linear models as described above for the primary and key secondary outcomes. If questionnaires include a total score, separate models will be run for the total score and selected subscales.

Similarly, for insulin, weight and BMI metrics comparisons will be made using similar linear models as described above for the primary HbA1c analysis.

### 11.9 Safety Analyses

All randomized participants will be included in the safety analyses and all of their post-randomization safety events will be reported. Separately, any adverse events occurring between screening and randomization will be reported.

All reportable adverse events will be tabulated by treatment group. Details will be provided in a listing of each event, including Medical Dictionary for Regulatory Activities (MedDRA) term and MedDRA System Organ Class. Safety analyses for the RCT will include events occurring on or after randomization until and including the 13-week visit or Day 98 from randomization, whichever occurs first.

Formal statistical testing only will be performed for selected safety endpoints. For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group and formal statistical comparisons will be performed if there are enough events (at least 5 events combined between the two treatment groups):

- Number of SH events and SH event rate per 100 person-years
- Number of DKA events and DKA event rate per 100 person-years
- Number of hyperosmolar hyperglycemic syndrome events and rate per 100 person-years
- Other serious adverse events

If enough events occur for the severe hypoglycemia and DKA outcomes and other serious adverse events, the numbers of events will be compared between the two treatment groups during the RCT using a robust Poisson regression as detailed in the SAP.

#### 11.9.1 Safety Tabulations Specific to the AID Group

For the AID Group, all of the following will be tabulated:

- Adverse device effects (ADE)
- Serious adverse device events (SADE)
- Unanticipated adverse device effects (UADE)

### 11.10 Additional Tabulations and Analyses

The following tabulations will be performed according to treatment group:

- Baseline demographics and clinical characteristics
- A flow chart accounting for all participants for all visits
- Visit completion rates for each follow-up visit
- Protocol deviations
- Modifications in non-insulin diabetes drugs during the study
- Number and reasons for unscheduled visits and phone calls
- Amount of CGM data during the 13 weeks of the study

### 11.11 Planned Interim Analyses

No formal interim efficacy analyses are planned. The DSMB will review safety data at intervals, with no formal stopping rules other than the guidelines provided in the participant-level and study-level stopping criteria (as defined in Section 9.6.2).

### 11.12 Subgroup Analyses

In exploratory analyses, the primary outcome (HbA1c) and time in range 70-180 mg/dL will be compared in baseline subgroups. Treatment group by subgroup factor interaction terms will be added to the linear models described above.

Formal tests will be done only if the overall result is statistically significant. Results will be tabulated by subgroups regardless of statistical significance. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous. If there is insufficient sample size in a given subgroup, the cutpoints for continuous measures may be adjusted per the observed distribution of values. Cutpoint selection for display purposes will be made masked to the outcome data.

Subgroups will be analyzed according to the following baseline factors:

- Baseline HbA1c
- Baseline time in range 70-180 mg/dL
- Diabetic medication use
- Body mass index
- Total daily insulin (<100 units versus ≥100 units)
- Sex
- Age (>50 years old versus ≤50 years old—assuming sufficient numbers in each category)
- Race/Ethnicity
- Scores on the Subjective Numeracy Survey
- C-peptide level
- Additional subgroups to be defined in the SAP

### 11.13 Multiple Comparison/Multiplicity

*Hierarchical Analyses*

To preserve the overall type 1 error for the primary endpoint and key secondary endpoints as listed in section 11.4.2, a hierarchical testing procedure will be used. If the primary analysis for HbA1c results in a statistically significant result ($p < 0.05$), then testing at the 0.05 level will proceed to the next outcome metric. This process continues iteratively moving to the next variable down on the list until a non-significant result is observed, or all 10 variables have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any variables lower on the list will not be formally tested.

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment group for each hierarchical outcome. A 95% confidence interval for the treatment group difference also will be calculated for all hierarchical outcomes listed above. However, a confidence interval that excludes zero will not be considered a statistically significant result if an outcome variable higher on the hierarchical list failed to reach statistical significance.

*All Other Secondary Analyses*

For the other secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

P-values from safety analyses, sensitivity analyses, and per-protocol analyses will not be adjusted for multiple comparisons.

## 11.14 Exploratory Treatment Group Comparisons

The following additional treatment group comparisons will be performed:

- Separate CGM analyses for daytime and nighttime
- Separate sub-analyses for participants negative for GAD antibodies (if GAD antibodies are present in ≥5% of participants) Efficacy and safety outcomes in participants using an SGLT2 inhibitor
- Efficacy and safety outcomes in participants using a GLP-1 receptor agonist
- Efficacy and safety outcomes in participants with TDI ≥100 units, ≥ 150 units, ≥ 200 units. These may include subgroup analyses.

## 11.15 Additional Analyses and Tabulations for the Single-Arm AID Group

### 11.15.1 Tabulations Specific to the AID Group

The following tabulations will be made for the AID group

- Number of participants who stopped AID use and reasons
- % time in closed loop
- Occlusion events that occur while using the AID system
- Reportable device malfunctions and other reported device issues
- Frequency of use of sleep mode and exploratory outcomes for times with versus without sleep mode
- Frequency of use of exercise mode

### 11.15.2 Analyses of Complete CGM Data Set

CGM metrics will computed over the entire 13 weeks of the trial (including the challenge periods) and compared with the baseline CGM metrics using paired t-tests or nonparametric approaches depending on the distribution of the data. Binary outcomes will be assessed using McNemar's test.

### 11.15.3 Analysis of Data from Meal and Exercise Challenges

The number of each challenge per participant will be tabulated. Any adverse events occurring during these challenges will be reported by type of challenge in addition to their being included in the overall safety analyses. Selected CGM metrics for hypoglycemia and hyperglycemia will be computed for each challenge and reported as summary statistics for the time period during and until 6 AM on the day following each challenge.

# Chapter 12: Data Collection and Monitoring

## 12.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.)

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

## 12.2 Study Records Retention

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

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.

## 12.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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

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

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

### 12.4 Protocol Deviations

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

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

# Chapter 13: Ethics/Protection of Human Participants

## 13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 13.2 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.

## 13.3 Informed Consent Process

### 13.3.1 Consent Procedures and Documentation

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

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

This process shall be document in the study records at each site (e.g., consent process note).

### 13.3.2 Participant and Data Confidentiality

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

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

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

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

# Chapter 14: References


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