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

Statistical Analysis Plan

Version 1.0

April 18, 2023

Based on Protocol Version 5.0

Version History

Version	Author	Approvers	Effective Date	Study Stage	Protocol Version
1.0	Dan Raghinaru	Craig Kollman	4/18/2021	Protocol development and study approval	5.0

Approvals

Role	Digital Signature or Handwritten Signature/Date
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1. Study Overview

The following table gives an overview of the 2IQP study.

Table 1. Study Overview

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 • To assess the efficacy of use of Control-IQ technology in adults with type 2 diabetes using basal-bolus insulin therapy • 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 *These endpoints will be tested in the following hierarchy to control for the type 1 error* • HbA1c (primary) • Time in range 70-180 mg/dL • Mean glucose • Time >180 mg/dL • Time >250 mg/dL • Prolonged hyperglycemia events (≥90 minutes >300 mg/dL within a 120-minute period) • Time <70 mg/dL • Time <54 mg/dL • CGM-measured hypoglycemia events (15 or more consecutive minutes <54 mg/dL) • Coefficient of variation *Calculation of CGM metrics for the treatment group comparison will exclude the challenges and the 24-hour period following the end of the challenge* Key Safety Endpoints: • Severe hypoglycemia

PARTICIPANT AREA	DESCRIPTION
	• 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 <u>Other Endpoints</u> • % time in closed loop • Total daily insulin delivery • Weight change • Change in lipid levels • Cardiovascular events • Patient-reported outcome (PRO) measures o Diabetes Distress Scale o Diabetes Impact and Device Satisfaction Scale o PROMIS (Sleep Related Impairment Questionnaire) o DAWN-Impact of Diabetes Profiles o HFS I and II o EQ5D o Study-specific survey o System Usability Scale (SUS) • Frequency of non-severe hypoglycemia Exploratory analyses will evaluate endpoints in subgroups based on diabetic medication use, body mass index, baseline HbA1c
Eligibility Criteria	**Inclusion Criteria** 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

PARTICIPANT AREA	DESCRIPTION
	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 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. 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

PARTICIPANT AREA	DESCRIPTION
	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 **Exclusion Criteria** 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. **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 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. 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. Approximate Study Goals - 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

PARTICIPANT AREA	DESCRIPTION
	- 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 25% 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: • Intervention group: t:slim X2 insulin pump with Control-IQ technology and Dexcom G6 CGM • 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** • Informed consent obtained and participant screened for eligibility. Testing for eligibility assessment and baseline will include: o Medical history, including total daily insulin dose, prior severe hypoglycemia, diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome (HHS), and hospitalizations for these events. o HbA1c with point-of-care device or local lab, unless available from the prior 30 days o Focused physical exam, including height and weight to compute body mass index (BMI) and blood pressure o Urine pregnancy test for participants capable of becoming pregnant o EKG unless performed within 12 months prior to screening o Subjective Numeracy Scale o Patient-reported outcome (PRO) surveys (see section 8.3), including frequency of non-severe hypoglycemia during the prior 3 months **CGM Run-in** • Eligible participants will be started on the study CGM, if applicable • Experienced current users of the study CGM with at least 85% of available readings from prior 14 days will skip the CGM Run-In • Otherwise, participants will use CGM for a minimum of 21 days o Training provided to use the CGM in conjunction with basal-bolus insulin therapy o Participants expected to use the CGM until return for post- run-in clinic visit.

PARTICIPANT AREA	DESCRIPTION
	○ At investigator discretion, contacts may occur with participant during run-in phase for further training on use of CGM ○ Participants will continue use of their personal insulin delivery method (pump or MDI) • Clinic visit after 21-28 days • 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.* • The most recent 14 days of CGM data will be used as the baseline for analyses **<u>Randomization Visit</u>** • 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. • If not on same day as Screening Visit, ○ Solicit any changes in medical conditions since screening that could affect eligibility for the RCT ○ Vital signs ○ Urine pregnancy test for participants capable of becoming pregnant • Blood draw for central lab measurement of HbA1c, lipids, creatinine, C-peptide, glucose, and GAD antibodies • Randomization to the AID group or Control group ○ 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.* ○ Control group: Training on use of study CGM and continuing pre-study basal-bolus insulin therapy **<u>13-week RCT protocol</u>** • 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. • 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) • Addition of glucose-lowering or weight reduction medications or dose changes in such medications in use at the time of randomization are

PARTICIPANT AREA	DESCRIPTION
	prohibited during the 13 weeks of the RCT, unless determined by the investigator to be necessary for safety. o 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. • Instructions will be provided for when to test for ketones and management when ketosis is present (see section 4.6.4) • Participants will not be restricted on diet or exercise. • Participants in the Control group will be expected to use CGM on daily basis. <u>RCT Visits and Contacts</u> • 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. • 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). At each scheduled visit/contact: o Review medications and doses o 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) o Site investigators may adjust insulin delivery profile settings ONLY for safety concerns and will document reasons for change in the CRF o Occurrence of adverse events will be solicited o Assessment of TDD over last week At 13-week visit, the following also will be done: o Height, weight, blood pressure/pulse o Blood draw for central lab measurement of HbA1c, lipids, creatinine o PRO surveys completed, including frequency of non-severe hypoglycemia during the prior 3 months • 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. • Additional visits and contacts may occur at investigator discretion **<u>Exercise and Meal Challenges</u>** • 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. • 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

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	exercise). All challenges will be performed unsupervised at home, with required study team contacts before and after each challenge. For each exercise challenge, an individual (care partner) capable of providing treatment for severe hypoglycemia will need to be present. • 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. <u>Study Safety Plan</u> Participants will be given a blood glucose and ketone meter to use throughout the study and will be trained on their use by qualified staff. BGM readings will be performed in accordance with the 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. 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. 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. <u>Analysis Plan</u> At the end of the RCT, it is planned that the database will be locked and analyses performed in preparation for 510K submission.

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The following table provides an overview of the schedule of study visits, phone contacts, and key procedures.

Table 2: Schedule of 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 80% 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 or a physician assistant). 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.

2. Comparison with the Protocol

The author of this document confirms that this SAP is consistent with version 5.0 of the Protocol, except the following:

- New formal analyses were added to compare the night following meal or exercise challenges with the previous 14 nights without any previous day challenge.

3. 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 $\alpha=0.05$ and the analyses specified below in Section 7 (i.e., $p < 0.05$).

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 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.

4. Sample Size

The sample size of 330 randomized participants was selected to provide sufficient exposure to the AID system for regulatory purposes. Given the 2:1 randomization, this equates with a maximum of 220 using the AID system for 13 weeks. Assuming a 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%. Under the null hypothesis - 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%.

5. Outcome Measures

5.1. Primary Efficacy Endpoint:

- Superiority in HbA1c at 13 weeks.

5.2. Secondary Efficacy Endpoints:

- Continuous CGM-measured endpoints during 13 weeks of follow-up:
  - Time in range 70-180 mg/dL
  - Time in range 70-140 mg/dL
  - Mean glucose
  - Time >180 mg/dL
  - Time >250 mg/dL
  - CGM-measured prolonged hyperglycemia events (defined in Section 5.3)
  - Time <70 mg/dL
  - Time <54 mg/dL
  - Area over the curve (70 mg/dL)
  - Low blood glucose index
  - CGM-measured hypoglycemia events (defined in Section 5.3)
  - Coefficient of variation
  - Time >300 mg/dL
  - Area under the curve (180 mg/dL)
  - High blood glucose index

- Binary CGM-measure endpoints during 13 weeks of follow-up:
  - 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%

- Binary HbA1c endpoints at 13 weeks:
  - 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

- Insulin delivered during 13 weeks of follow-up:
  - Total daily insulin (units and units/kg)
  - Total daily bolus (units and units/kg)
  - Total daily basal (units and units/kg)
  - Percentage of insulin units delivered as basal.

- Weight at 13 weeks:
  - Weight (kg)
  - Body mass index

- Other Endpoints at 13 weeks:
  - Total cholesterol
  - HDL cholesterol
  - LDL cholesterol
  - Triglycerides
  - Creatinine levels
  - Blood pressure

- Patient-reported outcome (PRO) measures:
  - Administered at Screening only:
    - Subjective Numeracy Survey – 8 items and 2 subscales (abilities and preferences) and total score
  - Administered at Baseline and 13 weeks:
    - Type 2 Diabetes Distress Assessment System (T2-DDAS Combined - Core and Source) – 29 items, and with 1 major + 7 minor subscales
    - DAWN Impact of Diabetes Profile (DIDP) - 7 items and total score
    - Diabetes Impact and Satisfaction (DIDS) Scale – 11 items and two subscale scores (device satisfaction and diabetes impact).
    - PROMIS Sleep-Related Impairment Questionnaire - 8 items and total score
    - System Usability Scale (SUS) - 10 items and total score
    - Hypoglycemia Fear Survey II – 33 items and two subscale scores (worry and behavior)
    - NICE-approved Quality of Life (EQ5D-5L) - 5 items
    - Study-specific survey that measure insulin management and dosing with meals – 2 items
    - Hypoglycemia Frequency Last 3 Months Survey – 4 items

- Safety measures:
  - 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
  - Cardiovascular events

5.3 Calculation of Overall CGM Metrics:

- Two Weeks of Baseline: The last 14 days of personal CGM data before enrollment or last 14 days of CGM run-in data before randomization will serve as baseline. If a participant has <72hr of data in the last 14 days of CGM personal or run-in and if more CGM data are available beyond the 14 days, then will go backwards 24hr at one time until the minimum of 72hr of CGM

data are reached. At least 72hr of data during baseline are required for the glycemic metrics to be calculated. These are Dexcom sensor data.

- Thirteen Weeks of Follow-up: All CGM data following the randomization will be included. Since the meal and exercise sessions are designed as challenges to the system and the data to be analyzed for possibly induced safety events, the CGM data between the start of the meal or exercise and 6:00AM next morning will be analyzed separately (see Sections 5.4 and 5.5 below) and not included here. If the 13-week visit is more than 13 weeks after the randomization visit for a participant, then the CGM data will be truncated at 13 weeks (i.e., 91 days). At least 168hr of data during these 13 weeks of follow-up are required for the glycemic metrics to be calculated and for a participant to be included in the glycemic analyses. These are either Tandem pump CGM data or Dexcom CGM data if obtained to fill any Tandem data gaps.
- All CGM metrics during baseline and follow-up periods will be calculated giving equal weight to each sensor reading for each participant.
- Calculation of CGM metrics for the treatment group comparisons will exclude the challenges and the period through 6AM on the day following the end of the challenge. CGM metrics during and following the challenges will be reported separately as described in Sections 5.4. and 5.5; while an overall analysis will be performed for all CGM data in the AID group (i.e., including the challenge data) as described in Section 17.
- 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.

5.4 Calculation of CGM Metrics for Meal Challenges

- The meal challenges will happen and the metrics will be calculated only during the 13 weeks of follow-up in the AID group, and are based on either Tandem pump CGM data or Dexcom CGM data if obtained to fill any Tandem data gaps.
- Will be calculated only if the meal challenge session was recorded on the CRF. The date-time of the challenge-related events, along with other relevant details about the challenge will be recorded on the CRF and will be tabulated.
- All data between the start of the meal challenge and 6:00AM next morning will be included.
- For each meal, two different periods will be considered, and two separate glycemic metrics will be calculated:
  - During and two hours following the end of the meal – the period between the start and 4 hours following the end of meal as recorded on CRF, and
  - Overnight following the meal – the period between 4 hours following the end of the meal and 6:00AM next morning.

- At least 2hr (or 24 CGM readings) are required for each one of the two periods associated with an individual meal session for the CGM metrics to be calculated.
- Each CGM reading during a meal session will be given equal weight.
- The unit of analysis is an individual meal challenge session and any participant with at least one meal challenge completed will be included in these analyses.
- The metrics calculated and reported here will include % time below 54, 70, 70-180, above 180, 250, 300 mg/dL and mean glucose.
- The above glycemic metrics will be calculated during the night following the meal challenge (10PM to 6AM) and will be compared with the corresponding metrics calculated during 14 nights without any challenge in the previous two days. Nights prior to the challenge will be used if available, then nights subsequent to the challenge if needed to obtain 14 total nights. The nights will be pooled together when compared with the night following the meal challenge. At least 6hr of CGM data are required for the night following the meal challenge and at least 72hr are required for the pooled 14 nights for these metrics to be calculated and formally compared.

5.5 Calculation of CGM Metrics during Scheduled Exercise Challenges

- The exercise challenges will happen and the metrics will be calculated only during the 13 weeks of follow-up in the AID group, and are based on either Tandem pump CGM data or Dexcom CGM data if obtained to fill any Tandem data gaps.
- Will be calculated only if the exercise session was recorded on the CRF. The date-times of the challenge-related events, along with other relevant details about the challenge will be recorded on the CRF and will be tabulated.
- All data between the start of the exercise challenge and 6:00AM next morning will be included.
- For each exercise, two different periods will be considered, and two separate glycemic metrics will be calculated:
  - During and two hours following the end of the exercise – the period between the start and 2 hours following the end of exercise as recorded on CRF, and
  - Overnight following the exercise – the period between 2 hours following the end of the exercise and 6:00AM next morning.
- At least 1hr (or 12 CGM readings) are required for each one of the two periods associated with an individual exercise session for the CGM metrics to be calculated.
- Each CGM reading during an exercise session will be given equal weight.
- The unit of analysis is an individual exercise session and any participant with at least one exercise challenge completed will be included in these analyses.
- The metrics calculated and reported here will include % time below 54, 70, 70-180, above 180, 250, 300 mg/dL and mean glucose.
- The above glycemic metrics will be calculated during the night following the exercise challenge (10PM to 6AM) and will be compared with the corresponding metrics calculated during 14 nights without any challenge in the previous two days as described above for meal challenges. The nights will be pooled together when compared with the night following the exercise challenge. At least 6hr of CGM data are required for the night following the exercise challenge and at least 72hr are required for the previous and pooled 14 nights for these metrics to be calculated and formally compared.

5.6 Calculation of Insulin Metrics

- Insulin details (like units and numbers of boluses and basal) over the previous 7 days will be captured on a CRF at randomization, 1, 8, 13 weeks, or at the early termination in both arms. In the AID arm, detailed insulin data will be available from the Tandem pump download.
- CRF data in the Control arm and CRF data (baseline) and Tandem pump data (follow-up) in the AID arm will be used for the calculation of these metrics.
- In the Control group, the CRF data completed at 1 week prior to randomization will serve as baseline; while the CRF data completed at 13 weeks (or at early termination) will serve as the follow-up data.
- In the AID group, Tandem pump data from the week prior to randomization and the week prior to the 13 weeks visit will be used to define and calculate baseline and follow up metrics. If the 13 weeks visit occurs after 91 days from randomization, then the data from days 84 to 90 will be used. If a participant terminates the study earlier than 13 weeks, then the last 7 days in the study will be used to define follow-up.
- For the AID group, will include only days with complete insulin data and at least 5 such days are required for the metrics to be calculated. If there are not 5 such days, the participants will not be included in the insulin analyses. Since Tandem pump automatically generates a basal record every hour, at least 20 such hourly records are required for a day to be considered complete with insulin data and to be counted towards the minimum of 5 days.
- Weight at baseline and at 13 weeks will be used to calculate insulin units/kg metrics.

5.7. Questionnaires

Participants are allowed to skip specific questionnaires or items within a questionnaire. The data might therefore include some missing items. If applicable, questionnaires will be scored according to the instructions given in the manual. If a total or a sub-scale score is calculated but no instructions exist, then at least 75% of the items should be non-missing for the total or sub-scale score to be calculated.

5.8 Analysis Windows

Analysis windows apply to the following outcomes measured at 13-week final visit:

- HbA1c
- Insulin (Control group only; see Section 5.6)
- Weight
- Questionnaires

To be included in the corresponding analyses, these data must be collected between days 61 and 121 from the randomization. The target date is 91 days from the randomization.

This does not apply to the CGM or insulin metrics (AID group only) which are calculated as described above in Section 5.6.

6. Description of Statistical Methods

6.1. General Approach:

- All analyses comparing the AID arm with Control arm will follow intention-to-treatment (ITT) approach, which means participants will be analyzed in the treatment arm assigned by randomization regardless of the actual system use. All randomized participants with any data will be included in the primary analysis and secondary analyses.
- In the unlikely event that an enrolled participant is later found to be ineligible, the participant will be excluded from all analyses.
- All covariates 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.
- All p-values will be two-sided.
- Standard residual diagnostics will be performed for all analyses. If values are highly skewed, then a nonparametric or robust regression using M-estimation will be used instead for the primary and secondary outcomes. Previous experience suggests that no transformation, nonparametric, or M-estimation analyses will be necessary for HbA1c, mean glucose, % time in range 70-180 mg/dL, or % above 180 mg/dL. Other outcomes like % below 54 mg/dL will likely be skewed with a need for a transformation, nonparametric, or M-estimation.

6.2 Analysis Cohorts

Primary and Secondary Analyses:

- All randomized participants with any data will be included in the primary and secondary analyses. Any partial data (i.e., missing baseline or follow-up) will be handled using the maximum likelihood method (see Section 7 below).
- All participants with at least one meal challenge and with the minimum amount of CGM data during these periods – as defined above in Section 5.4 - will be included in the corresponding meal analysis. Similar for participants with at least one scheduled exercise and the exercise analyses.

Per Protocol (PP) Analyses:

Per-protocol analyses will be performed for primary outcome and secondary hierarchical outcomes (see Section 8.2 below) 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, and
- 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.

Safety Analyses:

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

7. Primary Analyses

The primary endpoint for this study is HbA1c at 13 weeks adjusted for baseline HbA1c.

Summary statistics (mean ± SD or median (quartiles) – appropriate to the distribution) will be reported for the baseline, 13 weeks values, and their differences.

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 M-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. The method of direct likelihood will function similarly in the event of missing HbA1c at baseline for a participant.

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 (see Section 8.4 below).

8. Analysis of the Secondary Endpoints

8.1 Secondary CGM Metrics

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 M-estimation) will be used instead. Missing data will be handled using direct likelihood.

8.2 Secondary Efficacy CGM 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 16.

- HbA1c (primary outcome)
- 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 5.3)
- Time <70 mg/dL
- Time <54 mg/dL
- CGM-measured hypoglycemia events (defined in Section 5.3)
- Coefficient of variation

If the primary analysis for HbA1c described in Section 7 results in a statistically significant result ($p < 0.05$), then testing at the 0.05 level will proceed to the first outcome in the above list (i.e., time in range 70-180 mg/dL). 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.

8.3 Meal and Exercise Challenges Analyses

There will be a descriptive and a formal comparison for the analyses during the meal and exercise challenge. First, the descriptive analyses for the selected glycemic mentioned in Sections 5.4 and 5.5 and insulin metrics mentioned in Section 5.2 will include summary statistics (mean ± SD or median (quartiles)), scatterplots, boxplots, and/or individual meals or exercise CGM and insulin tracings. Meals will be grouped by the two periods (during plus up to 4hr after the end of meal and nighttime following the meal and until 6AM on the day following each challenge), type (lunch and dinner), amount of carbohydrates, and announcement in the pump or not.

Exercises analyses will be grouped by the two periods (during plus up to 2hr after the end of exercise and nighttime following the exercise and until 6AM on the day following each challenge); and additionally grouped by length, intensity, or type of exercise.

Insulin metrics and 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 (Section 9).

The number of each challenge per participant will be tabulated.

For the formal analyses, the glycemic metrics during the nights following the meal challenge will be tabulated and compared with the corresponding metrics during 14 non-challenge nights – calculated as mentioned above in Section 5.4. A mixed linear model that adjusts for clinical center as random effect will be used for this purpose. A similar approach will be used for the exercise challenges.

8.4. Sensitivity Analyses

Confounding

A sensitivity analysis for the primary outcome, HbA1c, 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.

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.

8.5. Secondary Binary HbA1c and CGM Metrics

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.

8.6. Insulin, Weight, Blood Pressure, and Lipids Analyses

For insulin, weight, BMI, blood pressure, lipid, and creatinine metrics, summaries and comparisons will be made using similar statistics and linear models as described above for the primary HbA1c analysis.

For insulin metrics, formal analyses will be done comparing the 13-week metrics between the two groups while adjusting for baseline. In addition to these, tabulations and plots will be done with insulin metrics at baseline, 1, 8, and 13 weeks. Additionally, the post-randomization insulin data in the AID

group will be differentiated by manual or automatic mode of delivery – in terms of events and amount of insulin.

8.7. Questionnaires/PRO

For each questionnaire, summary statistics (mean ± SD and n(%)) will be given for each item and at each time point when the questionnaire was administered. For questionnaires with a scoring guide available that are administered at both at the baseline and at 13 weeks and for all total scores and subscales thus calculated, the two arms will be compared using a linear model similar to the one described above for the primary outcome. All questionnaires' results will be tabulated, but formal tests will be done only for questionnaires with baseline and 13-week results and done in both arms.

9. Safety Analyses

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

All reportable adverse events will be tabulated by the 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.

The safety metrics will include:

- 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

All safety metrics listed above will be tabulated by the treatment group. 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.

10. Device Issues

All enrolled participants will be included, and all of their post-randomization reported device issues will be reported by the treatment group. Separately, any device issues occurring between screening and randomization will be reported.

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

- Device malfunctions requiring study team contact and other reported device issues.
- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by study month.

11. Protocol Adherence and Retention

The following measures of adherence will be tabulated overall pre-randomization and by treatment group post-randomization:

- Number of protocol and procedural deviations.
- Flow chart accounting for all enrolled participants up to end of the study.
- Flow chart of all scheduled visits and phone contacts.
- Number of and reasons for unscheduled visits and phone calls.
- Number of participants who stopped CGM or AID treatment.
- Modifications in non-insulin diabetes drugs during the study
- Amount of CGM data during the 13 weeks of the study

12. Intervention Adherence

The following tabulations will be made for the AID group:

- Number of participants who stopped AID use and reasons.
- % time in closed loop and other operational modes.
- 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.

13. Baseline Descriptive Statistics

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

- Age
- Sex
- Race/Ethnicity
- Diabetes duration
- Insulin method before enrollment (basal only or multiple daily injections)
- CGM use before enrollment
- HbA1c
- BMI
- C-Peptide
- GAD Antibody
- Total daily insulin
- Non-insulin glucose-lowering medications
- SH, DKA, and HHS episodes during the previous 12 months
- CHF hospital admissions during the last 12 months
- Non-Severe SH episodes during the previous 3 months

14. Planned Interim Analyses

No formal interim efficacy analyses are planned for this study.

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 in the Protocol.

The medical monitor will review all cases of severe hypoglycemia and diabetic ketoacidosis 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.

15. 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
- BMI
- 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
- Prior medication use (SGLY, GLP1/GIP analog, other)
- Prior CGM and pump use

16. Multiple Comparison/Multiplicity

Hierarchical Analyses

To preserve the overall type 1 error for the primary endpoint and key secondary endpoints as listed in Section 8.2, 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.

All Other Secondary Analyses

For the other secondary analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure in the following groups:

- CGM metrics (continuous and binary)
- HbA1c metrics (binary)
- Insulin, weight, lipids, creatinine, and blood pressure metrics
- PRO metrics
- Subgroup analyses

- Meal and exercise challenges
- Exploratory analyses

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

17. Exploratory analyses

Exploratory Treatment Group Comparisons

The following additional treatment group comparisons will be performed:

- Separate analyses for daytime (6AM to midnight) and nighttime (midnight to 6AM) for the secondary hierarchical CGM outcomes.
- Separate sub-analyses for participants negative for GAD antibodies (if GAD antibodies are present in ≥5% of participants) Efficacy (primary and hierarchical) and safety outcomes in participants using an SGLT2 inhibitor.
- Efficacy (primary and hierarchical) and safety outcomes in participants using a GLP-1 receptor agonist.
- Efficacy (primary and hierarchical) and safety outcomes in participants with TDI ≥100 units, ≥ 150 units, ≥ 200 units. These may include subgroup analyses – in addition to total daily insulin <100 units versus ≥100 units mentioned above in Section 15.

Analyses of Complete CGM Data Set

CGM metrics will be computed over the entire 13 weeks of the trial (i.e. while including the challenge periods) in the AID group 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.

Plots

Boxplots, scatterplots, and/or cumulative distribution plots will be generated for all primary, hierarchical, and insulin outcomes. Plots will be generated for any other outcomes or analyses where a visual display is considered helpful.