The International Diabetes Closed Loop Protocol 3 (DCLP3) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology

Statistical Analyses Plan

Version 1.0

October 12, 2018

Based on Protocol Version 9.0

Note: The table shells are included in a separate document

Version History

Version	Author	Approvers	Effective Date	Revision Description	Study Stage
1.0	Dan Raghinaru	Craig Kollman John Lum Boris Kovatchev Sue Brown	10/12/2018	Original Version	The trial started the enrollment on 6/28/2018. Interim safety analyses for November 2, 2018 DSMB meeting in progress. SAP draft finalized before any data reviewed by DSMB.

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1. Study Overview

This document outlines the statistical analyses to be performed for the Original DCLP3 Trial and to be included in the primary manuscript data packet.

The following table excerpted from the protocol gives an overview of the study.

Table 1. Study Overview

PARTICIPANT AREA	DESCRIPTION
Title	The International Diabetes Closed Loop (iDCL) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology
Précis	A randomized controlled trial of 6 month at home closed loop system vs. sensor-augmented pump.
Investigational Device	t:slim X2 with Control-IQ and Dexcom G6 system
Objectives	The objective of the study is to assess efficacy and safety of a closed loop system (t:slim X2 with Control-IQ Technology) in a large randomized controlled trial.
Study Design	Randomized Clinical Trial with 2:1 randomization to intervention with the closed loop system vs. sensor-augmented pump for 6 months.
Number of Sites	Seven US clinical sites
Endpoint	The primary outcome is time in target range 70-180 mg/dL measured by CGM in CLC group vs. SAP group at 6 months
Population	**Key Inclusion Criteria** • Type 1 Diabetes • Ages 14 and older **Key Exclusion Criteria** • Use of any non-insulin glucose-lowering agents except metformin
Sample Size	Up to seven clinical sites in the United States may enroll up to 225 total participants with the goal of randomizing 168 participants such that at least 150 participants complete the 6-month randomized trial.
Treatment Groups	Randomized Trial • Intervention Group: t:slim X2 with Control-IQ Technology and Study CGM. • Control Group: Sensor-augmented pump (SAP) with no automated insulin delivery, and study CGM
Participant Duration	6-8 months
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants not currently using an insulin pump and Dexcom G4, G5, or G6 CGM with minimum data requirements will initiate a run-in phase of 2 to 8 weeks that will be customized based on whether the participant is already a pump or CGM user. Participants who skip or successfully complete the run-in will be randomly assigned 2:1 to the use of closed-loop control (CLC group) using t:slim X2 with Control-IQ Technology vs SAP for 6 months.

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

Table 2. Study Procedures over Time

	Pre	Pre	0	1w	2w	4w	6w	9w	13w	17w	21w	26w
Visit (V) or Phone (P)	V	V	V	P	V	P	V	P	V	P	P	V
Comment	Screen/ Enroll	Run-in	Rand									
Eligibility Assessment	X	X	X									
HbA1c (DCA Vantage or similar point of care device, or local lab)	X		X						X			X
HbA1c (Central lab)			X						X			X
C-peptide (Central lab) and blood glucose assessment			X									
Pregnancy test (females of child-bearing potential)	X		X						X			X
Device Data download(s)	X	X	X	X	X	X	X	X	X	X	X	X
Review diabetes management and AEs		X	X	X	X	X	X	X	X	X	X	X
Questionnaires			X						X			X

2. Statistical Hypotheses

The primary outcome for this study is CGM-measured % in range 70-180 mg/dL over a 26-weeks period. The intervention will be considered effective if the Closed-Loop Control [CLC] treatment arm is superior to the Sensor Augmented Pump [SAP] control arm using a statistical significance of $\alpha=0.05$ and the model specified below in Section 6 (i.e. $p < 0.05$).

The null/alternative hypotheses are:

1. *Null Hypothesis*: There is no difference in mean CGM-measured % in range 70-180 mg/dL over 26 weeks between SAP and CLC
2. *Alternative Hypothesis*: The mean CGM-measured % in range 70-180 mg/dL over 26 weeks is different for SAP and CLC.

3. Sample Size

Sample size has been computed for the primary outcome (CGM-measured % in range 70-180 mg/dL). Data from the CGM arm of the JDRF CGM RCT from participants meeting the eligibility criteria for the current trial were used to project the distribution of % in range 70-180 mg/dL as measured by CGM for the SAP group in the proposed study.

The total minimum sample size was computed to be 123 for the following assumptions: (1) 2:1 [CLC:SAP] randomization, (2) 90% power, (3) a 7.5% absolute increase in % in range 70-180 mg/dL, (4) an effective SD of 12%, (5) and 2-sided type 1 error of 5%.

The total sample size has been increased to 168 to account for dropouts and to increase the number of participants who will be exposed to the CLC system for an enhanced safety and feasibility assessment.

4. Outcome Measures

4.1. Primary Efficacy Endpoint:

- CGM-measured % in range 70-180 over 26 weeks

4.2. Secondary Efficacy Endpoints

4.2.1. Hierarchical Endpoints

The following secondary endpoints will be tested in a hierarchical fashion as described in section 7.1 below.

- CGM-measured % above 180 mg/dL over 26 weeks
- CGM-measured mean glucose over 26 weeks
- HbA1c at 26 weeks
- CGM-measured % below 70 mg/dL over 26 weeks
- CGM-measured % below 54 mg/dL over 26 weeks

4.2.2. Other Secondary Endpoints

The following endpoints are considered exploratory.

- CGM metrics related to overall control over 26 weeks
  - % in range 70-140 mg/dL
  - glucose variability measured with the coefficient of variation
  - glucose variability measured with the standard deviation
- CGM metrics related to hypoglycemia over 26 weeks
  - % <60 mg/dL
  - low blood glucose index
  - hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- CGM metrics related to hyperglycemia over 26 weeks
  - % >250 mg/dL
  - % >300 mg/dL
  - high blood glucose index
- CGM metrics by time of day
  - Calculate all CGM metrics listed above (including the primary outcome) for:
  - All 24 hours of the day (primary analysis for time in range)
  - Daytime only (06:00AM to 00:00AM)
  - Nighttime only (00:00AM to 06:00AM)
- CGM metrics for the first three months post-randomization
- HbA1c at 26 weeks
  - HbA1c <7.0%
  - HbA1c <7.5%
  - HbA1c improvement from baseline >0.5%
  - HbA1c improvement from baseline >1.0%
  - HbA1c relative improvement from >10%
  - HbA1c improvement from baseline >1.0% or HbA1c <7.0%
- Insulin at 26 weeks
  - Total daily insulin (units/kg)
  - Basal: bolus insulin ratio
- Weight and body mass index at 26 weeks
- Fear of Hypoglycemia Survey (HFS-II) at 26 weeks – total score and 3 subscales:
  - Behavior (avoid)
  - Behavior (maintain high BG)
  - Worry
- Hyperglycemia Avoidance Scale at 26 weeks – total score and 4 subscales:
  - Immediate action
  - Worry
  - Low BG preference
  - Avoid extremes
- Diabetes Distress Scale at 26 weeks – total score and 4 subscales:
  - Emotional burden
  - Physician-related distress

- Regimen-related distress
- Interpersonal distress

- Hypoglycemia Confidence Scale at 26 weeks – total score
- Clarke Hypoglycemia Awareness Scores at 26 weeks
- INSPIRE survey scores at 26 weeks
- System Usability Scale (SUS) at 26 weeks
- Technology Expectance/Acceptance Survey at 26 weeks (CLC arm only)

4.3 Calculation of CGM Metrics (primary and secondary):

- Baseline: CGM data to calculate baseline metrics will either come from the run-in period, or from the subject's personal CGM device if the run-in is not necessary:
  - If an enrolled subject can show CGM use at least 11 out of the 14 days prior to enrollment, then he/she can proceed directly to randomization.
  - Otherwise, the subject will need go through 2-8 weeks of run-in that includes CGM use, prior to randomization.
  - In either case, the last 2 weeks of CGM data prior to randomization will be used in the calculation of baseline CGM metrics. If <24hr of CGM data are available for any reason (e.g., lost data or device failure), then the baseline metrics will not be calculated and will be set to missing.
- Follow-up:
  - 6 Months: All data starting from randomization (based on both date and time of randomization) and up through midnight on the earlier of Day 189 from randomization or the 26 week visit date, will be included.
  - First 3 Months: Another version of the CGM metrics will be calculated limiting to the first 3 months following randomization. Data will be included from the date and time of randomization through midnight on the earlier of Day 98 from randomization or the 13 week visit date.
- All CGM metrics at baseline and follow-up will be calculated giving equal weight to each sensor reading for each subject.

4.4. Questionnaires

All questionnaires will be administered online and subjects can skip specific questionnaires or items within a questionnaire. All questionnaires will be scored according to the instructions given in the manual. In case no manual exists for a given questionnaire or the manual does not provide guidance on how to handle missing, then the following criteria will be applied.

At least 75% of the questions must be completed to be included in the analysis. This 75% rule will be applied separately for the total score and each subscale so it is possible the sample size will be different for some subscales. The score used for analysis will be based on the average among the questions that were answered and then scaled accordingly.

4.5 Analysis Windows

Analysis windows apply to the following outcomes measured at the follow-up visits:

- HbA1c

- Insulin metrics
- Height/Weight
- Questionnaires

This does not apply to the CGM metrics which are calculated as described above.

Data from follow-up visits occurring in the following windows will be included in analysis:

Visit (Target Date)	Metrics[a]	From Day[b]	Thru Day[b]
2 week (14 days)	I	9	21
13 week (91 days)	H,I,B,Q	78	105
26 week (182 days)	H,I,B,Q	162	203

a – H = HbA1c, I = Insulin metrics, B=BMI (height & weight), Q = Questionnaires.
b – Days from randomization, inclusive.

5. Description of Statistical Methods

5.1. General Approach:

- All analyses comparing the CLC arm with SAP arm will follow the intention-to-treat (ITT) principle with each participant analyzed according to the treatment assigned by randomization.
- All randomized participants will be included in the primary and secondary analyses of CGM metrics.
- 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 an alternate transformation, nonparametric, or MM estimation methods will be used instead for the primary and secondary outcomes. Previous experience suggests that no transformation, nonparametric, or MM estimation analyses will be necessary for % time in range 70-180 mg/dL, % above 180 mg/dL, mean glucose, or HbA1c.Other outcomes like % below 70 mg/dL over 26 weeks are skewed; however the differences from baseline are expected to follow a normal distribution and there may be no need for transformation, nonparametric, or MM estimation.

5.2 Analysis Cohorts

Primary and Secondary Analyses:

- All randomized participants will be analyzed according to the ITT principle as described above.
- All randomized subjects with a lab or local HbA1c measurement at 13 or 26 weeks will be included in HbA1c analyses. Similar approaches will be followed for the other secondary outcomes like insulin, weight, and questionnaires analyses.

Per Protocol (PP) Analyses:

Four different per protocol analyses will be considered:

- If more than 5% of subjects in a treatment group have fewer than 168 hours of post-randomization CGM data, the primary and secondary hierarchical analyses will be replicated excluding such subjects.
- If more than 5% of subjects in a treatment group have fewer than 2,184 hours of post-randomization CGM data, the primary and secondary hierarchical analyses will be replicated excluding such subjects.
- The primary and secondary hierarchical analyses will be replicated only with participants from CLC group who used the system in CL mode for >3,494 hours overall and with participants from SAP group who used the sensor for >3,494 hours overall.
- The first 2 weeks in the CLC group involve system training. The primary and secondary hierarchical CGM analyses will be repeated excluding CGM data prior to the 2-week visit date (or Day 14 post-randomization, if the 2 week visit is missing). Only subjects with at least 24hr of CGM data following the first 2 weeks will be included in this analysis.

Safety Analyses:

- Safety outcomes will be reported for all randomized participants by treatment arm. Separately, any reported adverse events during the pre-randomization phase will be tabulated.

Sensitivity Analysis:

- Covariate adjustment: As noted below in Section 6, the primary and secondary hierarchical analyses will include a pre-specified list of covariates. Imbalances between groups in important covariates (as specified below in Section 11) are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated by additionally including factors potentially associated with the outcome for which there is an imbalance between groups (assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value).
- Missing Data: As noted below in Section 6, all subjects will be included in primary analyses and any missing post-randomization data will be handled using direct likelihood. It is also worth emphasizing that any statistical method for handling missing data makes a number of untestable assumptions. The goal will be to minimize the amount of missing data in this study so that results and conclusions 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 and secondary hierarchical analysis when using different methods. The following methods will be applied:

- Direct likelihood
- Rubin's multiple imputation
- Available cases only

6. Primary Analysis

This study primary outcome is CGM measured % time in range 70-180 mg/dL over 26 weeks.

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM-measured % in range 70-180 mg/dL and for differences from pre-randomization by treatment group.

Primary analysis will be done using direct likelihood. A longitudinal linear regression model will be fit with the percent of time in range at baseline and follow-up as the dependent variable. This model will adjust for age, prior CGM use and pump use as fixed effects and site as a random effect. Primary analysis will report the point estimate, 95% confidence interval and p-value for the treatment group difference at follow-up. This model adjusts for baseline time in range by forcing the treatment groups to have the same mean value at baseline. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed even after the transformation, then a transformation or robust statistical method (e.g., non-parametric or MM estimation) will be used instead. It is expected that the residual values for CGM-measured % in range 70-180 mg/dL will follow an approximate normal distribution.

7. Analysis of the Secondary Endpoints

7.1. Hierarchical Analyses

To preserve the overall type 1 error for selected key secondary endpoints, a hierarchical testing procedure will be used. If the primary analysis for time in range described above results in a statistically significant result ($p < 0.05$), then testing (similar to the model described above for the primary outcome) will proceed to the next outcome metric in the following order:

- CGM-measured % in range 70-180 mg/dL (primary outcome)
- CGM-measured % above 180 mg/dL
- CGM-measured mean glucose
- HbA1c at 26 weeks
- CGM-measured % below 70 mg/dL
- CGM-measured % below 54 mg/dL

This process continues iteratively moving to the next variable down on the list until a non-significant result ($p \geq 0.05$) is observed, or all six variables have been tested. If a non-significant

result is encountered, then formal statistical hypothesis testing is terminated and any variables below on the list are not formally tested and analysis of these variables become exploratory.

For example, in the hypothetical scenario depicted in the table below, the first four outcome variables both have a significant result so testing continues to the fifth variable (CGM % below 70 mg/dL). The result is not significant for that fifth variable ($p = 0.06$) so testing stops. No formal hypothesis test is conducted for the sixth variable on the list in this example scenario.

Table 3. Example Hierarchical Test Results

HIERARCHICAL ORDER	OUTCOME VARIABLE	TREATMENT ARM P-VALUE	SIGNIFICANT?	ACTION
1st	CGM % 70-180 mg/dL (primary outcome)	0.001	Yes	Test next variable
2nd	CGM % above 180 mg/dL	0.02	Yes	Test next variable
3rd	CGM mean glucose	0.007	Yes	Test next variable
4th	HbA1c at 26 weeks	0.03	Yes	Test next variable
5th	CGM % below 70 mg/dL	0.06	No	Stop formal testing
6th	CGM % below 54 mg/dL	Not tested	Unknown	N/A

Regardless of the results of the hierarchical testing, summary statistics appropriate to the distribution will be tabulated by treatment arm for each hierarchical outcome. A 95% confidence interval for the treatment arm difference will also be calculated for all five 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 reach statistical significance.

7.1.1 CGM Metrics

Analysis for each of the CGM metrics listed above for the hierarchical analysis will parallel the analysis described for the primary outcome in Section 6. The p-value used for the hierarchical analysis will be based on the treatment arm comparison at 26 weeks.

7.1.2 HbA1c

For the HbA1c analysis, a longitudinal model the primary analyses will be fit using values at baseline, 13 and 26 weeks adjusting for age, prior CGM use and pump use as fixed effects and site as a random effect. Missing data will be handled by direct likelihood in this longitudinal model. This model implicitly adjusts for baseline HbA1c by forcing the treatment groups to have the same mean value at baseline. Local HbA1c values measured at the site will be included as an auxiliary variable (analogous to imputing any missing lab values). The p-value used in the hierarchical analysis above will be based on the laboratory values at 26 weeks. Regression diagnostics will be employed analogous to as described in Section 6 for the primary outcome.

7.2. Other CGM Secondary Analyses

The analyses for the other secondary CGM-measured outcomes will parallel those mentioned above for the primary outcome. These will be done using CGM data over the entire 6 months of follow-up and repeated restricting to the first 3 months of follow-up (see Section 4.3).

7.3. HbA1c Analyses

The analysis of HbA1c as a continuous outcome at 26 weeks is described above in Section 7.1.2. A similar treatment arm comparison will also be done at 13 weeks. Summary statistics will be given by treatment arm at 13 and 26 weeks.

For the binary HbA1c outcomes listed in Section 4, risk-adjusted percentages by treatment group will be computed at 26 weeks from a logistic regression model. The logistic regression will adjust for baseline HbA1c, age, prior CGM and pump use as fixed effects, and clinical site as a random effect.

7.4. Insulin Analyses

Summary statistics appropriate to the distribution for total daily insulin and the bolus:basal ratio will be given by treatment group at 2, 13 and 26 weeks. A longitudinal regression model will be fit for both of these metrics using direct likelihood. A point estimate and confidence interval will be given for the treatment arm difference at 13 and 26 weeks. Regression diagnostics will be as described above for the primary outcome.

7.5. Weight and Body Mass Index Analyses

Summary statistics appropriate to the distribution for weight and BMI will be given by treatment group at 13 and 26 weeks. A longitudinal regression model will be fit for both of these metrics incorporating the baseline value using direct likelihood. These models will adjust for age, gender, prior CGM and pump use as fixed effects and site as a random effect. This model implicitly adjusts for the baseline value by forcing the treatment groups to have the same mean value at baseline. A point estimate and confidence interval will be given for the treatment arm difference at 13 and 26 weeks. Regression diagnostics will be as described above for the primary outcome.

7.6. Questionnaires

For each questionnaire, mean ± SD values or percentiles appropriate to the distribution will be given by randomization group for the total score and each subscale at baseline, 13 and 26 weeks.

For participants <18 years of age, some questionnaires will be administrated to both parents and participants. Separate analyses will be conducted for:

- Participants <18 years of age,
- Parents of participants <18 years of age, and
- Participants ≥18 years of age

For questionnaires administered to both randomization groups, comparisons will be made using similar direct likelihood longitudinal models as described above for the primary outcomes. Separate models will be run for the total score and each of the subscales listed above, and the models will adjust for baseline questionnaire score. A point estimate, confidence interval and p-value will be given for the treatment arm difference at 13 weeks and 26 weeks.

8. Safety Analyses

All enrolled participants will be included in these analyses and all their safety events up to the final 26-week visit will be reported. (Note: a separate Extension Study will start when a participant completes the randomized trial and its analyses will be detailed in a separate Protocol and Statistical Analysis Plan.)

The circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Ketone events defined as a calendar day with ketone level >1.0 mmol/L
- CGM-measured hypoglycemic events (≥15 minutes with glucose concentration <54 mg/dL)
- CGM-measured hyperglycemic events (≥15 minutes with glucose concentration >300 mg/dL)
- BG-measured hypoglycemic events (one BG record <54 mg/dL)
- BG-measured hyperglycemic events (one BG record >350 mg/dL)
- Worsening of HbA1c from baseline to 26 weeks by >0.5%
- Serious adverse events with a possible or greater relationship to a study device (including anticipated and unanticipated adverse device effects)
- Other serious adverse events not related to a study device
- Adverse device effects (ADE) that do not meet criteria for SAE

For the following outcomes, mean ± SD or summary statistics appropriate to the distribution will be tabulated by treatment group:

- Number of SH events and SH event rate per 100 person-years
- Number of DKA events and DKA event rate per 100 person-years
- Any adverse event rate per 100 person-years

If there are at least 10 events across both treatment arms, the numbers will be compared between the two treatment arms using a robust Poisson regression and the percentage of subjects with at least one event will be compared using logistic regression. The regression will adjust for the participant-reported number of events 12 months prior to the start of the study and site as random effect. The amount of follow up will be included as an offset covariate to compare the rates.

The analyses for the two continuous CGM-measured outcomes will parallel those mentioned above for the primary outcome.

For subjects participating in the Extension Study, the comparison of safety outcomes between the two treatment groups only include those events occurring on or after randomization until the 26 week visit. For subjects not participating in the Extension Study or dropouts, the comparison of safety outcomes between the two treatment groups only include those events occurring on or after randomization.

Any pre-randomization adverse events will be tabulated separately.

9. Device Issues

Reported device issues for each type of study device (e.g., closed loop system, CGM, blood glucose meter)

10. Protocol Adherence and Retention

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

- Listing of all protocol deviations
- Tabulation of protocol-specified visits and phone contacts completed in window, out of window and missed for each visit/phone contact
- Flow chart accounting for all enrolled participants up to randomization

- Flow chart of all randomized participants at all scheduled visits and phone contacts to assess visit, and phone completion, and study completion rates
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped treatment (CLC or CGM) and reasons

11. Baseline Descriptive Statistics

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

Will include:

- Age
- Gender
- Race/ethnicity
- Income, education, and/or insurance status
- Diabetes duration
- Insulin method before enrollment (pump vs. MDI)
- CGM use before enrollment
- Daily SMBG for CGM users and non-users
- HbA1c
- BMI
- C-peptide
- Scores for quality of life, hypoglycemia awareness, and fear questionnaires
- Participant-reported number of SH and DKA 12 months prior to the start of the study

12. Other Tabulations

Individual listings for each participant will include the following:

- Treatment group, age , gender, race/ethnicity, duration, height, weight, and BMI
- Study related information (like enrollment and randomization dates, enrollment and randomization HbA1c, randomization C-peptide, status, run-in requirement)

- Previous insulin method, CGM, SMBG, non-insulin medications, device months used and manufacturer
- Past SH and DKA events
- Physical exam results
- Income, education, and insurance
- Pre-existing medical conditions other than diabetes
- Medication at enrollment
- Baseline glucose metrics

The following tabulations and analyses will be performed by treatment group:

- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria)
- % time CGM data available - overall and by month

The following tabulations and analyses will be performed by treatment group to assess intervention adherence for the study:

- Sensor use – hours per week and percent time of use – overall and by month
- The daily frequency of downloaded BGM use - overall and by month

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

- Performance metrics, describing the Control-IQ system and its components like:
  - % time CGM data were available to the Control-IQ system – overall and by month
  - % time in different operational modes - overall and by month
  - Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by month
- Technology Expectations Survey score at baseline and Technology Acceptance Survey score at 26 weeks

13. Planned Interim Analyses

No formal interim analyses are planned for this study.

The DSMB will review safety data collected for the study. The data to be reviewed will include information regarding all of the following:

- Status of randomized participants

- Recruitment rates by month and by site
- Baseline demographic and clinical characteristics
- Dropped participants and reasons for discontinuing
- Protocol deviations
- Device issues
- Scheduled and unscheduled visits and contacts
- Frequency of CGM and system use over time and by site
- Reportable adverse events as described in section 8 of the protocol
- CGM-based hypo- and hyper-glycemic events during the 2-week baseline and all available post randomization data

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 the protocol).

14. Subgroup Analyses

In exploratory analyses, all primary outcomes found significant according to the hierarchical rules outlined above will be assessed separately in various subgroups and for continuous variables according to the baseline value as defined below. Tests for interaction with treatment group will be performed and further explored if an interaction will be found in the first place.

Interpretation of subgroup analyses will be viewed with caution, particularly in the absence of an overall significant difference a. For continuous variables, results will be displayed in subgroups based on cutpoints although the analysis will utilize the variable as continuous, except for age which will be analyzed both as a continuous variable and in two age groups. 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 and generally based on means or medians.

- Baseline HbA1c
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Baseline CGM time 70-180 mg/dL
- Device use before the enrollment: pump/MDI, CGM/no CGM, and combinations of both
- Age (<25 vs. ≥25)
- Sex
- Race

- Clinical site
- Body mass index
- Income, education, and/or insurance status
- Baseline scores for quality of life, hypoglycemia awareness and fear questionnaires
- C-peptide level

15. Multiple Comparison/Multiplicity

Primary Analysis

Since there will be a single comparison for the primary outcome (CGM-measured % 70-180 mg/dL), no adjustment is needed.

Secondary Hierarchical Analyses

The hierarchical testing procedure described above in Section 7.1 will be used to control the overall type 1 error for the primary outcome plus five key secondary outcomes identified above.

All Other Secondary Analyses

For comparison of other efficacy endpoints considered exploratory, the false discovery rate (FDR) will be calculated using the Benjamini-Hochberg method adapted using the two-stage test. FDR adjusted p-values will be calculated separately for the following categories:

- CGM metrics over 24hr
- CGM metrics during awake periods
- CGM metrics during nighttime periods
- CGM metrics during the first three months
- HbA1c analyses
- Insulin, weight, BMI
- Questionnaires
- Subgroup analyses (separately for each primary and secondary hierarchical outcomes found significant)

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

16. Exploratory analyses

No p-values will be calculated for these analyses.

The following metrics will be reported with the appropriate statistics by the associated CL mode:

- % below 70 mg/dL
- % above 180 mg/dL
- % time in range 70-180 mg/dL
- mean glucose
- coefficient of variation

17. Additional Tabulations and Analyses

- 24 hours profiles with mean (or medians) and quartiles lines and 4-week interval boxplots by treatment arms for:
    - % below 70 mg/dL
    - % above 180 mg/dL
    - % time in range 70-180 mg/dL
    - mean glucose
    - coefficient of variation
- Subjects in the CLC arm will enter their bedtimes in the system. Summary statistics for the same outcome metrics listed in the previous bullet will be given stratified by sleep and awake times.
- It is expected to collect most of the continuous insulin data in the two treatment groups over 26 weeks. The two insulin analyses (total daily insulin per kg and basal: bolus insulin ratio based on the subject-reported values) will be repeated using 2 weeks of system and/or pump data at 2, 13, and 26 weeks.

The International Diabetes Closed Loop Protocol 3 (DCLP3) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology

Addendum to Statistical Analyses Plan Version 1.0:

DCLP3 SAP V1.0
10_12_2018.pdf

May 8, 2019

Lead Statistician and Author: Dan Raghinaru
I am the author of this document
2019-05-08 12:16-04:00

Senior Statistician Approver: Craig Kollman
I am approving this document
2019-05-08 16:34-04:00

Addendum

1. On January 31, 2019 it was found out that most insulin summary metrics displayed in t:connect for the Control-IQ study pump are not correct.
For the CLC group, since some sites used this incorrect information to record insulin data on CRF forms at 2, 13, and 26 weeks, the insulin information entered on the CRF forms for the CLC group will not be used in any analyses. The 2 weeks of actual insulin data uploaded from the pump at 2, 13, and 26 weeks will be used instead.
For the SAP group, the CRF data will be used.
The above insulin analyses will replace the ones mentioned in sections 7.4 and 17 of the Statistical Plan.

2. In section "*5.4 Analyses Windows*", it was implied that BMI (height and weight) will be collected at 2, 13, and 26 weeks. Because there is no collection of height and weight at 13 weeks, the analyses mentioned in section "*7.5. Weight and Body Mass Index Analyses*" will not include the 13-week time point.

3. In section "*4.3 Calculation of CGM Metrics*" it was stated that: "*If an enrolled subject can show CGM use at least 11 out of the 14 days prior to enrollment, then he/she can proceed directly to randomization*". Since screening and the associated CGM use assessment may occur later than the enrollment date in some cases, the above sentence will be changed to: "*If an enrolled subject can show CGM use at least 11 out of the 14 days prior to* ***screening****, then he/she can proceed directly to randomization*"

4. On March 4, 2019 the Closed-Loop feature was suspended studywide due to an Unanticipated Problem with the Closed-Loop feature delivering insulin when not needed; the Closed-Loop feature was resumed on March 29, 2009.
All primary and secondary analyses described in the SAP will continue to be conducted according to the intent-to-treat principle and will not exclude any data during this suspension period.

New sensitivity analyses will be added for the primary, secondary hierarchical CGM outcomes, and for % time in different operational mode outcomes that will exclude data during the above-mentioned suspension period.

5. On lines 285-288 we wrote: "*Residual values will be examined for an approximate normal distribution. If residuals are highly skewed* ***even after the transformation****, then a transformation*

or robust statistical method (e.g., non-parametric or MM estimation) will be used instead." Typo - "*even after the transformation*" does not belong in the sentence and will be removed from the final draft. Here is the final version: "*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*."