# The International Diabetes Closed Loop Protocol 3 (DCLP3X) Trial: A Pivotal Study of t:slim X2 with Control-IQ Technology

# Extension Study

## Statistical Analysis Plan

## Version 1.0

## September 9, 2019

## Based on Protocol Version 6.0

I have compared this SAP with the protocol version listed above and confirmed they are consistent.

*Note: The table shells will be included in a separate document*

# Version History

| Version | Author | Approvers | Effective Date | Study Stage | Protocol Version |
|---|---|---|---|---|---|
| 1.0 | Dan Raghinaru | Craig Kollman | 9/9/2019 | Follow-up post the initial 3months. Interim safety analyses for October 4, 2019 DSMB meeting in progress. | 6.0 |

| Version | Revision Description |
|---|---|
| 1.0 | Original Version |

# Approvals

| Role | Digital Signature or Handwritten Signature/Date |
|---|---|
| **Author and Statistician:** Dan Raghinaru, JCHR | |
| **Senior Statistician:** Craig Kollman, JCHR | |
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# 1. Study Overview

The following table gives an overview of the DCLP3X 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 - Extension Study |
| **Précis** | An extension study for participants who completed a prior 6-month randomized controlled trial (RCT) of a closed loop system (Control-IQ) vs. sensor-augmented pump (SAP). |
| **Investigational Device** | t:slim X2 with Control-IQ and Dexcom G6 system |
| **Objectives** | The objectives of the study are<br>(1) Among individuals who used CLC in the original RCT, to compare continued use of CLC (t:slim X2 with Control-IQ Technology) for 3 months versus switching to a Predictive Low-Glucose Suspend (PLGS) system (t:slim X2 with Basal-IQ Technology) for 3 months.<br>(2) Among individuals who used SAP in the original RCT, to obtain additional safety data by initiating use of the Control-IQ system for 3 months.<br>(3) For all participants, use of the CLC system between the end of 3-month period and the point that the system becomes commercially available in order to gather additional safety data |
| **Study Design** | Objective 1: RCT with 1:1 randomization to intervention with CLC vs. PLGS for 3 months.<br>Objective 2: Observational study of initiation and use of CLC for 3 months.<br>Objective 3: Observational study of initiation and use of CLC for 3 months following use of PLGS for 3 months; use of CLC by all participants between end of 3-month period and the point that the system becomes commercially available in order to gather additional safety data. |
| **Number of Sites** | Seven US clinical sites |
| **Primary Endpoint** | Objective 1: The primary efficacy outcome for the RCT is time in target range 70-180 mg/dL measured by CGM in CLC group vs. PLGS group over 3 months. Safety outcomes also will be assessed<br>Objective 2: The primary outcome is safety outcomes. Efficacy also will be assessed as a pre-post within participant analysis<br>Objective 3: The primary outcome is safety outcomes. Efficacy also will be assessed as a pre-post within participant analysis |
| **Population** | **Key Inclusion Criteria**<br>• Successfully completed the original 6-month RCT within the prior 14 days<br>**Key Exclusion Criteria**<br>• Use of any non-insulin glucose-lowering agents except metformin |
| **Sample Size** | Sample size is based on the number in the original RCT who successfully complete six months and sign consent to participate in this study (up to approximately 168 total). |
| **Treatment Groups** | Objective 1<br>• Group 1: t:slim X2 with Control-IQ Technology and Study CGM<br>• Group 2: t:slim X2 with Basal-IQ Technology and Study CGM |

| PARTICIPANT AREA | DESCRIPTION |
|---|---|
| | |
| **Participant Duration** | 3 months |
| **Protocol Overview/Synopsis** | Eligible participants in the original RCT who agree to be part of the Extension Study will sign the informed consent form.<br>• Participants assigned to the original RCT SAP group will initiate use of the CLC system for 3 months.<br>• Participants assigned to the original RCT CLC group will be randomly assigned 1:1 to either continue CLC or switch to PLGS for 3 months.<br>• After 3 months, all participants will be given the opportunity to use the CLC system until the point that the system becomes commercially available |

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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**

| | 0 Weeks | 1w | 2w | 13w | 26w, then every 13 weeks until end | Final Visit |
|---|---|---|---|---|---|---|
| **Visit (V) or Phone (P)** | **V** | **P[1]** | **P[1]** | **V** | **V** | **V** |
| **Comment** | **Screen/Enroll and Rand/Assign** | | | | | |
| **Eligibility Assessment** | X | | | | | |
| **HbA1c (DCA Vantage or similar point of care device, or local lab)** | X[2] | | | X | X | X |
| **HbA1c (Central lab)** | X[2] | | | X | | |
| **Pregnancy test (females of child-bearing potential)** | X | | | X | X | |
| **Device Data download(s)** | | X | X | X | X | X |
| **Review diabetes management and AEs** | | X | X | X | X | X |
| **Questionnaires** | X[2] | | | X | X[3] | X |
| **Follow-up Phone Call** | | | | | | P |

[1] Only performed for those participants who switched from SAP in the original 6-month RCT to CLC in the Extension Study, or from CLC in the original RCT to PLGS in the Extension Study

[2] Will use results obtained at Final Visit of preceding 6-month RCT

[3] 26-Week visit only

## 2. Objective 1

Among individuals who used CLC in the preceding 6-month RCT, to compare continued use of CLC (t:slim X2 with Control-IQ Technology) for 3 months versus switching to a Predictive Low-Glucose Suspend (PLGS) system (t:slim X2 with Basal-IQ Technology) for 3 months.

- Design and Primary Outcome: RCT with 1:1 randomization to intervention with CLC vs. PLGS for 3 months. All analyses (treatment group comparisons) will be considered exploratory/hypothesis-generating. Consequently, there will not be an attempt to adjust for multiplicity. Time-in-range 70-180 mg/dL will be considered the primary exploratory outcome.
- Sample Size: The sample size will depend on how many subjects complete the preceding 6-month RCT and consent to participate in the extension. However, it is expected that about 100 subjects will be enrolled and randomized for Objective 1.

### 2.1 Outcome Measures

#### 2.1.1 Endpoints

*CGM Metrics*

- Overall Control and Hyperglycemia
  - CGM-measured % in range 70-180 mg/dL.
  - CGM-measured % above 180 mg/dL
  - CGM-measured mean glucose
  - % >250 mg/dL
  - % >300 mg/dL
  - high blood glucose index
  - % in range 70-140 mg/dL
- Hypoglycemia
  - % below 70 mg/dL
  - % below 54 mg/dL
  - % below 60 mg/dL
  - low blood glucose index
  - hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- Glucose variability
  - Coefficient of variation (CV)
  - Standard deviation (SD)

- CGM metrics by time of day. Calculate all CGM metrics listed above (including the primary outcome) for:
    - All 24 hours of the day
    - Daytime only (06:00AM to 11:59AM)
    - Nighttime only (00:00AM to 05:59AM)

*HbA1c*

- HbA1c at 13 weeks
- HbA1c <7.0% at 13 weeks
- 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

*Questionnaires*:

- Fear of Hypoglycemia Survey (HFS-II) at 13 weeks – total score and 3 subscales:
    - Behavior (avoid)
    - Behavior (maintain high BG)
    - Worry
- Hyperglycemia Avoidance Scale at 13 weeks – total score and 4 subscales:
    - Immediate action
    - Worry
    - Low BG preference
    - Avoid extremes
- Diabetes Distress Scale at 13 weeks – total score and 4 subscales:
    - Emotional burden
    - Physician-related distress
    - Regimen-related distress
    - Interpersonal distress
- Hypoglycemia Confidence Scale at 13 weeks – total score
- Clarke Hypoglycemia Awareness Scores at 13 weeks

- INSPIRE survey scores at 13 weeks
- System Usability Scale (SUS) at 13 weeks and final visit – barriers, benefits, and total score
- Technology Expectations Survey at baseline (only for participants who had been assigned to SAP during the preceding 6-month RCT) – barriers, benefits, efficacy, and total scores
- Technology Acceptance Survey at 13 weeks – barriers, benefits, efficacy, and total scores

*Other*

- Insulin at 13 weeks
    - Total daily insulin (units/kg)
    - Basal: bolus insulin ratio
- Weight and Body Mass Index (BMI) at 13 weeks

**2.1.2. Calculation of CGM Metrics**:

- Baseline: CGM data from the last 13 weeks of the preceding 6-month RCT (i.e. 90 days prior to the final visit of the preceding RCT) will be used to calculate baseline metrics. At least 168 hours of CGM data will be required for the calculation. Baseline CGM metrics will be treated as missing for any participants who have fewer than 168 hours of data in the last 13 weeks of the preceding RCT.
- Follow-up: CGM metrics will be calculated by pooling all data starting with randomization day in the current study (or enrollment day, for subjects not randomized) and up through previous midnight of the earlier of day 98 from enrollment/randomization or the 13-week visit date, will be included. At least 168 hours of CGM data will be required for the calculation.
- All CGM metrics at baseline and during follow-up will be calculated giving equal weight to each sensor reading for each participant.
- Daytime and nighttime
    - CGM metrics above will also be calculated for daytime period (06:00AM to 11:59PM) and overnight period (00:00AM to 05:59AM) separately.
    - Minimum 126 hours of CGM data will be required to calculate daytime metrics and minimum 42 hours of CGM data will be required to calculate overnight metrics.
    - If <168 hours of CGM data available for combined day and night, then CGM metrics will not be calculated separately for daytime and overnight periods.

**2.1.3 HbA1c**

- Baseline: Local and lab HbA1c values collected at the 26-week visit in the preceding 6-month RCT will serve as baseline.
- Follow-up: Local and lab HbA1c values collected at the 13-week visit will serve as follow-up values.
- For continuous outcome models, both local and lab values will be used. For binary outcomes, lab values will be used (if lab value is missing, the local value will be used instead).

### 2.1.4 Questionnaires

The questionnaires administered at the 26-week visit in the preceding 6-month RCT will serve as baseline, in addition to the Technology Expectations Survey at baseline of the current study for participants who had been assigned to SAP during the preceding 6-month RCT.

All questionnaires will be administered online and participants/parents 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 data, 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.

### 2.1.5 Analysis Windows

Analysis windows apply to the following outcomes measured at baseline (26-week visit in the preceding 6-month RCT) and at the follow-up 13-week visit:

- HbA1c
- Insulin metrics
- Weight/BMI
- 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] |
|---|---|---|---|
| 26-week visit of preceding RCT | H,I,B,Q | -14 | 0 |
| 13-week visit of current study (91 days) | H,I,B,Q | 78 | 105 |

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

## 2.2 General Approach

- 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 M estimation methods 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 % time in range 70-180 mg/dL, % above 180 mg/dL, mean glucose, or HbA1c. Other outcomes like % below 70 mg/dL over 13 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 M estimation.

- All analyses comparing the CLC arm with PLGS 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.
- All treatment group comparisons analyses will be considered exploratory/hypothesis-generating. Consequently, there will not be an attempt to adjust for multiplicity.
- 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.

## 2.3. Analysis Cohorts

### 2.3.1 Per-Protocol Analyses

- All randomized participants will be analyzed according to the ITT principle as described above.
- Safety outcomes will be reported for all enrolled and randomized participants.
- If more than 5% of participants have fewer than 50% data (or <1,092hr) of post-randomization CGM data, then selected CGM analyses will be replicated excluding such participants.
- Selected CGM and HbA1c analyses will be replicated including only those participants from the CLC and PLGS groups who used the system for >80% overall.

### 2.3.2 Sensitivity Analyses

- Covariate adjustment: As noted below, primary analyses will include a pre-specified list of covariates. 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 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 above, 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 analysis when using different methods. The following methods will be applied:
    - Direct likelihood
    - Rubin's multiple imputation
    - Available cases only

## 2.4. Primary and other CGM Metrics Analyses

This study primary outcome is CGM measured % time in range 70-180 mg/dL over 13 weeks.

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM metrics and for differences from pre-randomization by treatment group.

The analyses will be done using direct likelihood. A longitudinal linear regression model will be fit with the metric at baseline and follow-up as the dependent variable. This model will adjust for age as fixed effect and site as a random effect. The analyses will report the point estimate, 95% confidence interval and p-value for the treatment group difference at follow-up. 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.

## 2.5. HbA1c Analyses

Summary statistics (mean ± SD or n(%)) will be reported for the central lab HbA1c (continuous variable) at randomization and 13-weeks by treatment group. A longitudinal model will be fit using values at randomization and 13 weeks adjusting for age as fixed effect 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). Regression diagnostics will be employed as described earlier.

For the binary HbA1c outcomes listed above, risk-adjusted percentages by treatment group will be computed from a logistic regression model. The logistic regression will adjust for the same factors mentioned above for the analysis with HbA1c as a continuous factor.

## 2.6. Questionnaires, Insulin, Weight, and BMI Analyses

For questionnaires, insulin, weight, and BMI metrics comparisons between treatment arms will be made using similar methods as described above for the primary analysis.

## 2.7. Safety Analyses

All enrolled and randomized participants will be included in these analyses and all their safety events up to the 13-week visit will be reported.

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 (defined as at least 15 consecutive minutes <54 mg/dL)
- CGM-measured hyperglycemic events (defined as at least 120 consecutive minutes >300 mg/dL)
- Worsening of HbA1c from randomization to 13 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 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 and the worsening in HbA1c will parallel the binary HbA1c models mentioned above.

### 2.8. Device Issues

Reported device issues for each type of study device (e.g., closed-loop system, PLGS system, CGM) by treatment group.

### 2.9. 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 and randomized participants up to week 13
- 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 PLGS) and reasons

## 2.10. 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 at randomization
- Gender
- Race/ethnicity
- Diabetes duration at randomization
- HbA1c at the end of preceding 6-month RCT
- BMI at the end of preceding 6-month RCT

## 2.11. Other Tabulations

Individual listings for each randomized participant will include the following:

- Treatment group, age, gender, race/ethnicity, duration, height, weight, and BMI at randomization
- Pre-existing medical conditions other than diabetes
- Medication at enrollment/randomization
- 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 to the system

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

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

## 2.12 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
- 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 the protocol
- CGM-based hypo- and hyper-glycemic events during 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).

## 2.13. Subgroup Analyses

In exploratory analyses, selected outcomes (CGM-measured % time in range 70-180 mg/dL, % time below 70 mg/dL, % time above 180 mg/dL, mean glucose, and HbA1c) for which analyses suggest a treatment group difference 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. 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.

- Baseline HbA1c
- Baseline CGM time spent <70 mg/dL
- Baseline CGM time spent >180 mg/dL
- Baseline CGM time 70-180 mg/dL
- Age at randomization
- Sex
- Race
- Clinical site
- Body mass index at randomization
- Income, education, and/or insurance status
- Baseline scores for quality of life, hypoglycemia awareness and fear questionnaires

## 2.14. Multiple Comparison/Multiplicity

All treatment group comparisons analyses will be considered exploratory/hypothesis-generating. Consequently, there will not be a formal adjustment for multiplicity.

## 2.15. Additional Tabulations and Analyses

Twenty-four hours profiles with medians and quartiles lines and 4-week interval boxplots and tabulations by treatment arms for:

- % below 70 mg/dL
- % above 180 mg/dL

- % time in range 70-180 mg/dL
- mean glucose

Among women who consent to collection of the menstrual information, an analysis that compares outcomes at different times during the menstrual cycle will be performed overall and by contraception type for selected CGM and insulin metrics.

## 3. Objective 2

Among individuals who used SAP in the original RCT, to asses efficacy and to obtain additional safety data by initiating use of the Control-IQ system for 3 months.

### 3.1 Outcome Measures

The outcome measures for this objective will be the same as those listed above in Section 2.1.

### 3.2 General Approach

- 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 M estimation methods 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 % time in range 70-180 mg/dL, % above 180 mg/dL, mean glucose, or HbA1c. Other outcomes like % below 70 mg/dL over 13 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 M estimation.
- All enrolled participants with non-missing baseline and post-enrollment data will be included in the primary and secondary analyses.
- All before/after comparisons analyses will be considered exploratory/hypothesis-generating. Consequently, there will not be an attempt to adjust for multiplicity.

### 3.3. Analysis Cohorts

#### 3.3.1 Per-Protocol Analyses

- Safety outcomes will be reported for all enrolled participants.
- If more than 5% of participants have fewer than 50% data (or <1,092hr) of post-enrollment CGM data, then selected CGM analyses will be replicated excluding such participants.
- Selected CGM and HbA1c analyses will be replicated including only those participants who used the CLC system for >80% overall.

### 3.4. Primary and other CGM Metrics Analyses

This study primary outcome is CGM measured % time in range 70-180 mg/dL over 13 weeks.

Summary statistics (mean ± SD or median (quartiles)) will be reported for the CGM metrics and for differences from pre-enrollment.

The before/after values will be compared using paired t-tests. Paired differences will be examined for an approximate normal distribution. If the differenced are highly skewed, then a Wilcoxon signed-rank test will be used instead.

### 3.5. HbA1c Analyses

Summary statistics (mean ± SD or n(%)) will be reported for the central lab HbA1c (continuous variable) at randomization and 13-weeks. If the central lab values are missing, then the local values will be used instead. The before/after values will be compared using paired t-tests. Paired differences will be examined for an approximate normal distribution. If the differenced are highly skewed, then a Wilcoxon signed-rank test will be used instead.

For the binary HbA1c outcomes listed above, a McNemar test will be used.

### 3.6. Questionnaires, Insulin, Weight, and BMI Analyses

For questionnaires, insulin, weight, and BMI metrics comparisons between before/after will be made using similar methods as described above in Section 3.4 for the primary analysis.

### 3.7. Safety Analyses

The safety metrics will be the same as those listed above in Section 2.7 and will be analyzed in a similar manner except that there are no treatment groups for this objective and no formal statistical comparisons.

### 3.8. Device Issues

Same as above in Section 2.8, except no randomization and no treatment groups.

### 3.9. Protocol Adherence and Retention

Same as above in Section 2.9, except no treatment groups.

### 3.10. Baseline Descriptive Statistics

Same as above Section 2.10, except no treatment groups.

### 3.11. Other Tabulations

Same as above Section 2.11, except no treatment groups.

### 3.12 Planned Interim Analyses

The DSMB will review data as described above in Section 2.12.

### 3.13. Subgroup Analyses

No subgroup analyses will be performed for this objective.

### 3.14. Multiple Comparison/Multiplicity

No formal correction will be done for multiple comparisons.

### 3.15. Additional Tabulations and Analyses

Similar as described above in Section 2.15 with no stratification by treatment group.

### 4. Objective 3

To obtain additional safety data by continuing use of the Control-IQ system until it becomes commercially available

- Design and Outcomes: Observational study of initiation and use of CLC for 3 months following use of PLGS for 3 months. For all participants, use of the CLC system between the end of 3-month period and the point that the system becomes commercially available in order to gather additional safety data. All safety outcomes will be tabulated and certain exploratory analyses will be conducted, analyzing metrics as change from baseline (using PLGS) to study period (using CLC).
- The sample size will depend on how many subjects complete the preceding 6-month RCT, consent to participate in the extension, and continue in the study after the initial 3 months of the extension until the system becomes commercially available.

## 4.1 Outcome Measures

### 4.1.1 Endpoints

*CGM Metrics*

- Overall Control and Hyperglycemia
  - CGM-measured % in range 70-180 mg/dL.
  - CGM-measured % above 180 mg/dL
  - CGM-measured mean glucose
  - % >250 mg/dL
  - % >300 mg/dL
  - high blood glucose index
  - % in range 70-140 mg/dL
- Hypoglycemia
  - % below 70 mg/dL
  - % below 54 mg/dL
  - % below 60 mg/dL
  - low blood glucose index
  - hypoglycemia events (defined as at least 15 consecutive minutes <70 mg/dL)
- Glucose variability
  - Coefficient of variation (CV)
  - Standard deviation (SD)

- CGM metrics by time of day. Calculate all CGM metrics listed above (including the primary outcome) for:
    - All 24 hours of the day
    - Daytime only (06:00AM to 11:59AM)
    - Nighttime only (00:00AM to 05:59AM)

*HbA1c*

- HbA1c at 26, weeks, every 13 weeks until the end, and/or at the final visit
- HbA1c <7.0% at 26weeks, every 13 weeks until the end, and/or at the final visit
- HbA1c <7.5% at 26weeks, every 13 weeks until the end, and/or at the final visit

*Questionnaires*:

- System Usability Scale (SUS) at final visit – barriers, benefits, and total score
- Control-IQ Patient-Reported Outcomes Questionnaire at final visit

*Other*

- Insulin at 26weeks, every 13 weeks until the end, and/or at the final visit
    - Total daily insulin (units/kg)
    - Basal: bolus insulin ratio

### 4.1.2 Calculation of CGM Metrics:

- Baseline: CGM data between enrollment or randomization and 13-week visit will be used to calculate baseline metrics. At least 168 hours of CGM data will be required for the calculation. Baseline CGM metrics will be treated as missing for any participants who have fewer than 168 hours of data.
- Follow-up: CGM metrics will be calculated by pooling all data starting after 13-week visit date. At least 168 hours of CGM data will be required for the calculation.
- All CGM metrics at baseline and during follow-up will be calculated giving equal weight to each sensor reading for each participant.
- Daytime and nighttime
    - CGM metrics above will also be calculated for daytime period (06:00AM to 11:59PM) and overnight period (00:00AM to 05:59AM) separately.
    - Minimum 126 hours of CGM data will be required to calculate daytime metrics and minimum 42 hours of CGM data will be required to calculate overnight metrics.
    - If <168 hours of CGM data available for combined day and night, then CGM metrics will not be calculated separately for daytime and overnight periods.

### 4.1.3 HbA1c

- Baseline: Lab HbA1c values collected at the 13-week visit will serve as baseline. If the lab is missing, then the local value will be used instead.
- Follow-up: Local HbA1c values collected at the 26-,week, every 13 weeks until the end, and/or at the final visit will serve as follow-up values.

### 4.1.4 Analysis Windows

Analysis windows apply to HbA1c outcomes measured at baseline (13-week visit) and to HbA1c, insulin, and questionnaires outcomes at the follow-up 26-week, every 13 weeks until the end, and/or at the final visits.

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] |
|---|---|---|---|
| 13-week visit (91 days) - Baseline | H | 78 | 105 |
| 26-week visit of (182 days)– Follow-up | H,I | 169 | 196 |
| every 13 weeks until the end (273, 364, and so on days)– Follow-up | H,I | 260, 351, and so on | 287, 378, and so on |

a – H = HbA1c, I = Insulin metrics.
b – Days from randomization/enrollment, inclusive.

## 4.2 General Approach

Same as described above in Section 3.2.

## 4.3. Analysis Cohorts

Same as described above in Section 3.3.

## 4.4. Primary and other CGM Metrics Analyses

Analyses will be similar to those described above in Section 3.4 except that p-values will be calculated only for before/after PLGS/CLC comparisons.

## 4.5. HbA1c Analyses

This analysis will be similar to that described above in Section 3.5 except that p-values will be calculated only for before/after PLGS/CLC comparisons and the "after" HbA1c value will be the local value at the final visit.

## 4.6. Questionnaires and Insulin Analyses

Same as above in Section 3.6.

## 4.7. Safety Analyses

Same as above Section in 3.7.

## 4.8. Device Issues

Same as above in Section 3.8.

## 4.9. Protocol Adherence and Retention

Same as above in Section 3.8.

## 4.10. Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all 13-week participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed for the PLGS/CLC cohort and overall.

Will include:

- Age at 13-week
- Gender
- Race/ethnicity
- Diabetes duration at 13-week
- HbA1c at 13-week

## 4.11. Other Tabulations

Individual listings for each 13-week participant will include the following:

- Age, gender, race/ethnicity, duration, and HbA1c at 13-week
- New medications

The following tabulations and analyses will be performed:

- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria)
- % time CGM data available to the system

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

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

## 4.12 Planned Interim Analyses

Same as above in Section 2.12.

## 4.13. Subgroup Analyses

No subgroup analyses will be performed for this objective.

## 4.14. Multiple Comparison/Multiplicity

No formal correction will be done for multiple comparisons.

## 4.15. Additional Tabulations and Analyses

Same as above in Section 3.15.