Open, Single Arm, Prospective, Multicenter Study of an Investigational Extended Wear Insulin Infusion Set During Home Use in People with Type 1 Diabetes

Capillary Biomedical

Statistical Analysis Plan

Version 4.0

April 2, 2025

Based on Protocol Version 5.0

Note: The table shells are included in a separate document

Version History

Version	Author	Approvers	Revision Description	Effective Date	Study Stage	Protocol Version
1.0	Zack Reed	Craig Kollman	Original Version	10/20/2023	Protocol development and study approval	4.0
2.0	Zack Reed	Craig Kollman	Added criterion for subgroup comparisons. Removed HbA1c from some subgroup comparisons. Corrected typos.	01/05/2024	Pre-Enrollment	4.0
3.0	Zack Reed	Craig Kollman	Added subgroup analyses and tabulations for diabetes duration, taping and/or barrier wipes.	06/21/2024	Enrollment has begun	5.0
4.0	Zack Reed	Craig Kollman	Changed endpoint of CGM analysis to be the end of the Final visit day, since many are still wearing sets on that day. Rearranged multiple comparison groups to clarify grouping. Removed language about pump data being available at one-hour intervals	04/2/2025	Study is complete	5.0

Approvals

Role	Signature/Date
Author and Statistician: Zack Reed, JCHR	Zachariah Reed I agree to the terms defined by the placement of my signature in this document 2025-04-02 07:27-04:00

Senior Statistician: Craig Kollman, JCHR	Craig Kollman I am electronically signing this document 2025-04-02 15:03-04:00
Coordinating Center Director: John Lum, JCHR	John Lum I agree to the terms defined by the placement of my signature in this document 2025-04-02 08:16-04:00
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Contents

1 Study Overview

This document outlines the statistical analyses to be performed for the SteadiSet Insulin Infusion Set study.

This is an unblinded, single arm, prospective, multicenter study to assess the efficacy and safety of the SteadiSet insulin infusion set (IIS) while using a Tandem pump with t:slim X2 Control-IQ in adults with type 1 diabetes (T1D). Enrollment will proceed with a goal of 240 participants completing the trial, ~120 who will use Humalog™ (insulin lispro) and ~120 who will use NovoLog™ (insulin aspart). Participants will be recruited from up to 20 clinical sites, each contributing a maximum of 25 participants. All participants will use the SteadiSet IIS with the study pump for 12 wear periods of up to 7 days each. The efficacy analysis will include participants who complete at least 1 wear period. The safety analysis will include all enrolled participants.

2 Consistency

This SAP does not conflict with the study protocol statistics chapter (version indicated on the title page). Additional analyses and tabulations have been included in this Statistical Analysis Plan that are not included in the protocol.

3 Statistical Hypotheses

The primary outcome is percent of successfully inserted SteadiSet IIS that are not withdrawn from use prior to 7 days (168 hours) due to the reasons listed in section 5.2.

The null/alternative hypotheses are:

- Null Hypothesis: The success rate is 75%.
- Alternative Hypothesis: The success rate is different from 75% (two-sided).

4 Sample Size

The study is projected to enroll up to 300 participants such that 240 complete the trial: ~120 who will use Humalog™ (insulin Lispro) and ~120 who will use NovoLog™ (insulin aspart). Assuming N=120 participants completing the study for each insulin type, a null hypothesis stating that the success rate is 75%, a true success rate of 83%, 12 wear periods per participant, within-participant correlation of at most 0.4, and two-sided type 1 error rate of 5% we will have statistical power of 87% for the evaluation of each of the two insulin types. Note that with only 9 wear periods per participant we would still have 86% power.

5 Outcome Measures

The Primary and Key Secondary Efficacy endpoints will be analyzed by infusion set. If more than one type of insulin is used during an infusion set wear period, that wear will be excluded from analyses of the Primary and Key Secondary Efficacy endpoints. When the other Secondary outcomes or the Exploratory outcome are analyzed separately by insulin type, any wear period

during which more than one type of insulin is used will be excluded from the analysis, except where specified.

5.1 Clinical Events Committee

Clinical Primary Efficacy and Key Secondary events will be adjudicated by the Clinical Events Committee (CEC). The CEC's composition and role are described in the Clinical Events Committee SOP and Charter.

5.2 Primary Efficacy Endpoint

Percent of successfully inserted SteadiSet IIS (i.e., those not withdrawn within 8 hours of insertion) that are not withdrawn from use prior to 7 days (168 hours) due to any of the following:

1. Blood glucose value ≥250 mg/dL with ketones >1.0 mmol/L, in the absence of illness or other physiological stress.
2. Blood glucose value ≥250 mg/dL for at least 60 minutes duration, 3 hours or more following a snack or meal event AND failure to respond to up to 2 adequate corrective boluses delivered by the pump with a fall of at least 50 mg/dL. In the absence of BGM testing immediately prior to or following a corrective bolus then CGM values will be used for the primary endpoint analyses.
3. Investigator advises the infusion set should be replaced to assure participant's safety.

5.3 Key Secondary Endpoint

Proportion (%) of SteadiSet infusion sets withdrawn from use at any time following insertion prior to 7 days (168 hours) as evidenced by one or more of the following device failure modes. NOTE: infusion set removals prior to 168 hours due to miscalculation of date and/or time, along with other removals that cannot be ascribed to the investigational device performance, are excluded from this proportion calculation.

1. Infusion set failure as defined in the Primary Endpoint (including any such removals occurring during the first 8 hours following set insertion)
2. Evidence of infusion set site infection defined as requiring treatment or at the investigator's judgment
3. Cannula dislodgement from subcutaneous (SC) space (with or without liquid leakage at the cannula insertion site)
    a. Leakage at the cannula insertion site may or may not be deemed by the investigator to constitute infusion set failure following consultation with the study subject
    b. Accidental removal events (e.g., tubing caught on doorknob) are excluded from this proportion calculation
4. Occurrence of a non-resolvable pump occlusion alarm,
5. Other device malfunction (e.g., inability to pierce skin, bending, or other malformation that might impact insulin infusion, securement failure)

6. Presence of pain of sufficient severity to prompt early removal of infusion set
7. Any other event that can be ascribed to the investigational device performance that results in failure of insulin delivery

5.4 Safety Endpoints

Safety endpoints will comprise the incidence, severity, and relationship to the investigational device of all reported adverse events (serious and non-serious including DKA and severe hypoglycemia) from the day of enrollment through the day of the final study visit or the day of the first insertion + 98 days—whichever is earlier.

- Number of adverse events
- Number of adverse device effects
- Number of serious adverse events
- Number of serious adverse events that are unanticipated adverse device effects
- Number of reportable hypoglycemic events as defined in the protocol
- Number of severe hypoglycemia events as defined in the protocol
- Severe hypoglycemia event rate per 100 person-years
- Number of reportable hyperglycemic events with or without ketosis, as defined in the protocol
- Number of diabetic ketoacidosis events as defined in the protocol
- Diabetic ketoacidosis event rate per 100 person-years

5.5 Other Secondary Endpoints

- Standard glucose control measures obtained from CGM:
  - % Time in range 70–180 mg/dL
  - % Time in tight range 70–140 mg/dL
  - Mean glucose
  - % Time above 180 mg/dL
  - % Time above 250 mg/dL
  - % Time below 70 mg/dL
  - % Time below 54 mg/dL
  - Rate of hyperglycemic events using a threshold of 180 mg/dL
  - Rate of hypoglycemic events using a threshold of 54 mg/dL
- Total daily insulin dose, basal dose, bolus dose, and bolus/basal ratio, overall and by day of infusion set wear
- Participant tolerability levels for the infusion set insertion as assessed by a pain scale of 0 to 100 with zero being no pain and 100 being significant pain
- Usability, Satisfaction & Preference Survey results
- The trend in hyperglycemia in days 1–3 versus after day 3

5.6 Exploratory Endpoint

- HbA1c change from baseline to the end of study participation

5.7 Calculation of CGM Metrics

For each CGM metric, one value will be calculated for each participant at baseline and at follow-up. Dropouts will be counted as zero use for the remainder of the study.

5.7.1 Baseline

Baseline secondary CGM metrics will be calculated using CGM data from the 14 days immediately preceding screening. All the CGM readings will be weighted equally. Data will not be truncated due to protocol deviation, and there will be no imputation for missing data. A minimum of 168 hours (7 days) of data is required to calculate baseline CGM metrics.

5.7.2 Follow-up

CGM readings from periods when the participant was not wearing the investigational infusion set will be excluded from analyses.

The follow-up period begins when the first successfully inserted infusion set is inserted. Follow-up secondary CGM measurements will come from the period between the time of the first insertion and the end of the day of the Final visit. If the Final visit is missed, the last contact will be used in its place. All the CGM readings will be weighted equally. There will be no imputation for missing data. A minimum of 168 hours of data is required to calculate follow-up CGM metrics.

5.7.3 Daytime and Nighttime

Daytime readings are between 06:00 and 23:59 and nighttime readings are between 00:00 and 05:59. A minimum of 126 hours of daytime data is required to calculate baseline and follow-up daytime CGM metrics, and a minimum of 42 hours of nighttime data is required to calculate baseline and follow-up nighttime CGM metrics.

5.7.4 CGM Metrics by Study Week and Infusion Set Wear

24-hour CGM metrics will be calculated for each week of the study and each infusion set wear. A minimum of 72 hours is required to calculate CGM metrics for these periods.

5.7.5 CGM Metrics during the Final 14 Days of the Study

24-hour CGM metrics from the final 14 days of the study will be tabulated and compared with baseline. Participants must complete at least six wear periods to be included in these analyses. A minimum of 144 hours is required to calculate CGM metrics for this period.

5.7.6 Hyperglycemia Trend over Duration of Wear

The trend in hyperglycemia will be assessed with CGM metrics % time above 180 mg/dL, % time above 250 mg/dL, and mean glucose.

Hyperglycemia trend outcomes will be tabulated by day of infusion set wear. A minimum of 20 hours of data is required for a day to be included in these tabulations.

Hyperglycemia trend outcomes will also be tabulated by period of the wear (hours 0–<72 versus hours 72–168 since infusion set insertion). They will be compared between hours 0–<72 and hours 72–168. A minimum of 48 hours in both periods is required to calculate CGM metrics.

5.7.7 Prolonged Hyperglycemic Events

A CGM-measured hyperglycemic event will be defined as at least 2 sensor values >250 mg/dL that are 120 or more minutes apart plus no intervening values ≤250 mg/dL; at least 2 sensor values ≤180 mg/dL that are 15 or more minutes apart with no intervening values >180 mg/dL are required to define the end of an event, at which point the study participant becomes eligible for a new event.

5.7.8 Hypoglycemic Events

A CGM-measured hypoglycemic event <54 mg/dL will be defined as at least 2 sensor values <54 mg/dL that are 15 or more minutes apart plus no intervening values ≥54 mg/dL; at least 2 sensor values ≥54 mg/dL that are 15 or more minutes apart with no intervening values <54 mg/dL are required to define the end of an event, at which point the study participant becomes eligible for a new event.

5.8 Calculation of Insulin Metrics

For each insulin metric, one value will be calculated for each participant. Tandem pumps automatically generate basal records approximately every 5 minutes, and 20 hours of data per day will be required for a day to be considered complete. Only data from the study pump during wears of the investigational infusion set will be included; all data from a personal pump (if used during the study) will not be counted. Any dropouts will be counted as zero use for the remainder of the study.

5.8.1 Overall

Overall insulin metrics will be calculated over the entire follow-up period. A minimum of 21 complete days are required to calculate total daily insulin metrics. Baseline insulin delivery will be obtained from the Demographics CRF, which describes the week prior to the Screening visit.

5.8.2 Insulin Metrics by Study Week

Insulin metrics will be calculated for each week of the study. A minimum of 6 complete days of insulin data is required to calculate insulin metrics for a week.

5.8.3 Insulin Metrics by Day of Infusion Set Wear

Insulin metrics will also be tabulated by day of infusion set wear over the entire study. A day is each subsequent 24-hour period since the current set is inserted. Participants must provide a minimum of six complete days of insulin data to be included in the calculation for insulin metrics on that day.

6 Description of Statistical Methods

6.1 Analysis Cohorts

Analysis of the Primary Efficacy endpoint will include participants who successfully insert at least one investigational infusion set.

The analysis of the Key Secondary endpoint and the safety endpoints will include all participants who attempt to insert at least one investigational infusion set.

Analyses of all other endpoints will include participants who successfully insert at least one investigational infusion set. Intention-to-treat is not relevant since this is not a randomized trial.

6.2 Analysis of the Primary Endpoint

The proportions of successfully inserted investigational infusion sets that last at least 7 days will be tabulated overall and by infusion set location. Reasons reported for removal (main and secondary) will be tabulated. All tabulations will be done separately for each insulin type (Humalog and Novolog).

Analysis will be done separately for each insulin type. Kaplan-Meier estimates will be reported along with a curve used to estimate the proportion of infusion sets that last at least 7 days. Successfully inserted infusion sets that are removed prior to day 7 without meeting the stated failure criteria in section 5.2 (Primary Efficacy Endpoint) will be treated as censored observations at the times reported. A two-sided 95% confidence interval (95% CI) for the 7-day survival rate will be calculated with a bootstrap to account for the correlated data from having each participant wear multiple infusion sets. A corresponding bootstrap p-value will be given for the null hypothesis that the true survival probability is 75%.

There will be no imputation of missing data for the primary analysis.

6.3 Analysis of the Secondary Endpoints

If results from the Primary Efficacy and Key Secondary analyses are comparable for Humalog and Novolog, then the data will be pooled for the other Secondary, Exploratory, and Safety analyses. Otherwise, separate analyses will be done by insulin type.

6.3.1 SteadiSet IIS Success Rate

Percentage of SteadiSet infusion sets not withdrawn from use prior to 7 days (168 hours) as evidenced by the absence of device failure as defined in section 5.3 (Key Secondary Endpoint) will be analyzed using the same statistical methods as described above for the Primary Efficacy endpoint. Successfully inserted infusion sets that are removed prior to day 7 without meeting the stated failure criteria in section 5.3 will be treated as censored observations at the times reported.

6.3.2 CGM Endpoints

Baseline and follow-up secondary CGM-measured glycemic metrics will be compared. Each metric will have summary statistics appropriate to its distribution tabulated. A paired t-test will be used to compare the baseline and follow-up values from the final 14 days of the study and

from the entire duration of study set wear, and a two-sided 95% CI will be given for the mean difference. Boxplots will be drawn at baseline and follow-up, and scatter plots will be drawn for baseline versus follow-up. Participants will be included in the analysis only if they have both baseline and follow-up values. If the paired differences appear skewed, a signed rank test will be used instead.

If these analyses are performed separately by insulin type, endpoints over the entire follow-up period will be categorized according to the insulin type in use at baseline and any wear during which more than one insulin type is used will be included in the calculation. Participants must use the same insulin type as they used at baseline for the final 14 days of follow-up to be included in the comparison of the final 14 days to baseline.

6.3.2.1 Daytime and Nighttime

Baseline and follow-up summary statistics for CGM-measured outcomes will be tabulated by time of day (daytime or nighttime). 24-hr profile plots will be drawn for follow-up. If these analyses are performed separately by insulin type, endpoints over the follow-up period will be categorized according to the insulin type in use at baseline and any wear during which more than one insulin type is used will be included in the calculation.

6.3.2.2 Hyperglycemia Trend over Duration of Wear

Tables of statistics appropriate to their distributions will summarize hyperglycemia trend outcomes by day of infusion set wear.

Summary statistics will be tabulated for hours 0–<72 and hours 72–168 of infusion set wear. Boxplots will be drawn for hours 0–<72 and 72–168. A paired t-test will be used to compare the 0–<72 hour and 72–168 hour values, and a two-sided 95% CI will be given for the mean difference. Participants will be included in the analysis only if they have both 0–<72 hour and 72–168 hour values. If the paired differences appear skewed, a signed rank test will be used instead.

6.3.3 Insulin Endpoints

Summary statistics appropriate to their distributions will be tabulated at baseline and follow-up for all secondary insulin outcomes: total daily insulin, total basal insulin, total bolus insulin, and bolus/basal ratio. Boxplots will be drawn at baseline and follow-up. Insulin endpoints will also be tabulated by study week and by day of infusion set wear.

6.3.4 Pump Endpoints

Summary statistics for pump occlusion alarm rates will be reported overall and by day of infusion set wear. If tables are constructed separately by insulin type, results will be categorized according to the insulin type in use at baseline and any wear during which more than one insulin type is used will be included in the calculation.

6.3.5 Tolerability Endpoints

Pain assessment results will be tabulated overall and by infusion set wear, and appropriate summary statistics will be reported. If tables are constructed separately by insulin type, results

over the follow-up period will be categorized according to the insulin type in use at baseline and any wear during which more than one insulin type is used will be included in the calculation.

6.4 Analysis of the Exploratory HbA1c Endpoint

Summary statistics appropriate to the distributions will be tabulated for baseline and follow-up HbA1c values. A paired t-test will compare the central lab HbA1c values measured at the final study visit versus the Day 0 value, and a two-sided 95% CI will be given for the mean difference. Participants will be included in the analysis only if they have a central lab value at both times. If the paired differences appear skewed, a signed rank test will be used instead. Boxplots will be drawn at baseline and follow-up, and scatter plots will be drawn for baseline versus follow-up.

If analyses are performed separately by insulin type, results over the follow-up period will be categorized according to the insulin type in use at baseline.

6.5 Usability, Satisfaction & Preference Survey

Survey responses will be tabulated for each of the three visits, and appropriate summary statistics will be reported.

The following comparisons will be made between survey results: the 2-Week visit versus baseline, the Final visit versus baseline, and the Final visit versus the 2-Week visit. The System Usability Scale portion of the questionnaire will be scored according to published guidelines[1] and compared between surveys as a single unit. Other questions will be converted to a 0–100 scale and corresponding questions will be compared between surveys individually. Differences will be analyzed with paired t-tests or signed rank tests, as appropriate. Ninety-five percent confidence intervals will be derived from these tests.

If these analyses are performed separately by insulin type, results over the follow-up periods will be categorized according to the insulin type in use at baseline.

7 Safety Analyses

All enrolled participants will be included in the safety analyses and all their adverse events up to the end of the study will be listed.

Adverse events will be tabulated overall and by wear period, which will be from the time of insertion until the time of the next insertion. Adverse events reported after the final wear period will be assigned to the final wear period. Whether or not the adverse event occurred while the study infusion set was being used will be indicated as will the relationship of adverse events to the study device. Any AE involving hyperglycemia/ketosis will include an assessment of whether it corresponded to an infusion set failure. The circumstances of all reportable adverse events will be summarized.

8 Intervention Adherence and Retention Analyses

The following tabulations and analyses will be performed overall and by insulin type to assess intervention adherence, protocol adherence, and retention:

- Flowchart of study participants
- Number of investigational infusion sets worn
- Gaps of ≥3 hours in infusion set wears
- Tabulation of infusion set removal cases reviewed by the CEC and their determinations
- Distribution of infusion set wear per participant
- Visit completion rates for each follow-up visit
- Protocol deviations
- Numbers of and reasons for unscheduled visits and phone calls
- Participant adherence to expected BG/ketone/correction bolus procedures prior to set removals before 7 days

9 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all enrolled participants with at least one wear will be summarized in a table. For continuous variables, appropriate summary statistics will be given. For discrete variables, number and percentage will be reported for each category.

The following baseline characteristics will be included in the table:

- Age
- Sex
- Race/ethnicity
- Diabetes duration
- Education
- Household Income
- Health Insurance
- HbA1c
- BMI
- CGM metrics
    - % Time in range 70–180 mg/dL
    - % Time >180 mg/dL
    - % Time <70 mg/dL
    - Estimated HbA1c
- Insulin type—Humalog or Novolog
- Infusion set type in use at time of study screening

10 Planned Interim Analyses

No formal interim efficacy analyses are planned for this study.

11 Subgroup Analyses

The Primary Efficacy and Key Secondary outcomes as well as CGM hyperglycemia metrics (% time >180 mg/dL, % time >250 mg/dL, mean glucose), HbA1c, and insulin metrics will be explored according to the factors below.

- Hours 0–<72 versus hours 72–168 since infusion set insertion
- Infusion set location
- Whether any additional taping and/or skin adhesive barrier wipe was used to secure the infusion set on the day that it was inserted
- Units per day of insulin (<25 versus ≥25)
- Diabetes duration
- Participants who manually stop the insulin pump more often; only participants who successfully insert at least 6 infusion sets will be included, and the number of stops will be averaged over every day of the study for which data is complete as defined in 5.8.
    - Cut point will be chosen according to the distribution of the data

Hypothesis tests for differences between subgroups among the Primary Efficacy, Key Secondary, and CGM outcomes will be performed. Difference in HbA1c will be tested between subgroups based on units per day of insulin, diabetes duration, and how often participants stop the insulin pump. When subgroups are based on categorical variables, comparisons will only be made when each subgroup contains at least five members. Cut points for diabetes duration will be chosen according to the distribution of the data, but it will be treated as a continuous variable in the models.

Pump occlusion alarms will be tabulated by units per day of insulin and frequency of manual pump interruption but no formal comparisons will be made.

12 Multiple Comparisons

No correction will be made for the Primary Efficacy analysis or the Key Secondary analysis. For other analyses, the false discovery rate (FDR) will be controlled using the adaptive Benjamini-Hochberg procedure[2]. The categories for FDR correction will be:

- HbA1c and CGM outcomes
    - Entire follow-up period versus baseline
- CGM outcomes
    - Final 14 Days versus baseline
- Subgroups
    - Primary and Key Secondary outcomes
        - Hours 0–<72 versus hours 72–168
        - Infusion set location
        - <25 units/day of insulin
        - Participants who start and stop the insulin pump more often
        - Whether any additional taping and/or skin adhesive barrier wipe was used to secure the infusion set on the day that it was inserted

        - Diabetes duration
    - HbA1c (where applicable) and CGM outcomes
        - Hours 0–<72 versus hours 72–168
        - Infusion set location
        - <25 units/day of insulin (HbA1c applicable)
        - Participants who start and stop the insulin pump more often (HbA1c applicable)
        - Whether any additional taping and/or skin adhesive barrier wipe was used to secure the infusion set on the day that it was inserted
        - Diabetes duration (HbA1c applicable)
- Usability, Satisfaction & Preference Survey

13 Additional Tabulations and Analyses

The numbers and percentages of participants and wears will be reported for each insertion location.

Appropriate summary statistics will be reported for wear duration over all wears.

Numbers and percentages will be reported for whether a tape or barrier wipe was used at any point during the wear. Among wears during which additional tape or barrier wipe was used to secure the infusion set, numbers and percentages will be reported for the type(s) of tape or barrier wipe. Percentages of sets secured using additional tape, barrier wipes, or both will be reported for each of the seven days of the wear period.

14 References

1. Brooke J.: SUS-A quick and dirty usability scale. *Usability Evaluation in Industry,* 1996; 189–194.
2. Benjamini Y and Hochberg Y.: On the adaptive control of the false discovery rate in multiple testing with independent statistics, *Journal of Educational and Behavioral Statistics,* 2000; 25(1): 60–83.