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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Post Approval Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System Supplemented with Commercial Patient Data
Clinical Investigation Plan Identifier	CEP266
Clinical Investigation Plan Version	Version E
Sponsor/Local Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325
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1 Version History

Version	Summary of Changes	Author(s)/Title
1.0 **15-FEB-2018**	Please reference CBP10050 Version A: BP for CEP266 Post Approval Study of the Threshold Suspend (TS) Feature with a Sensor-Augmented Pump (SAP) System approved via Agile. Adopted new template for Harmonization to MDT SOPs.	[redacted]
2.0 **01-MAR-2018**	Corrected formatting errors noted after previous approval	[redacted]

2 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
MDR	Medical Device Reporting
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

3 Introduction

The approval of the MiniMed® 530G Pump model (MMT-751, MMT-551) occurred on 27th September 2013. Prior to submitting the IDE for a device that incorporates the Threshold Suspend (TS) feature in the United States, Medtronic evaluated and released the Medtronic MiniMed® Paradigm Veo pump in Europe and other part of the world. One of the first steps towards approval of a similar device in the United States was taken with the CEP 235 study. The study was completed in 2011 and the study report has been submitted.

This Statistical Analysis Plan (SAP) was created using CEP266, Protocol version E. Please refer to the Reference section for other documents used to create this SAP.

This SAP dictates the contents in the final study report only.

4 Study Objectives

The purpose of the study is to provide ongoing surveillance of the TS feature with a sensor augmented pump system over a 12-month period.

The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration. This objective will be demonstrated in several ways using two sub-studies:

1) Sub-study 1: Multi-Center Trial

- Comparison of A1C measurement from baseline to end of study in the CEP266 study population

2) Sub-study 2: Commercial Data Evaluation
   - CareLink® data from the commercial MiniMed 530G users
   - Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR)
   - Review of published data on the TS feature
   - Review of unpublished data on the TS feature, as available

5 Investigation Plan

5.1 Study Design

The evaluation of Threshold Suspend(TS) feature is conducted by two sub-studies: 1) Commercial Data Evaluation; 2) Prospective Multi-Center Trial.

5.1.1 Multi-Center Trial

The Multi-center trial was initiated to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump (Medtronic MiniMed® 530G insulin pump) in patients 16 and older with insulin requiring diabetes over a period of one year.

In addition, additional data from commercial use will be analyzed/summarized to support the Multi-center trial as the enrolled population is lower (N=426) than the anticipated N=1000 subjects.

5.1.2 Commercial Data Evaluation

Additional dataset:

- CareLink® data from the commercial MiniMed 530G users
- Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR)
- Review of published data on the TS feature
- Review of unpublished data on the TS feature, as available

5.2 Study Population of Multi-Center Trial

A total of 426 subjects have been enrolled in the study.

40 Investigational centers were activated across the United States. Selection was based on Investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures and the investigator's ability to recruit subjects into the study.

5.3 Inclusion Criteria

1. Subject is age 16 or older at time of screening
2. Subject has been diagnosed with diabetes mellitus for at least one year prior to screening.
3. Subject is currently on pump therapy.
4. Subject is transitioning to the 530G insulin pump system with the TS feature turned ON.
5. Subject is willing to complete all study related activities
6. Subject is willing to upload data every 21 days from the study pump

7. Subject must have Internet access and access to a computer system that meets the requirements for uploading the pumps. This may include use of family or friend's computer system with Internet access.
8. Subject is able (by insurance or financial means) to cover the initial investment and ongoing cost of the 530G insulin pump and consumables, CGM, CONTOUR NEXT LINK RF enabled meter and supplies for the length of the study- 1 year.

5.4 Exclusion Criteria

1. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study devices in the last 2 weeks.
2. Subject is a woman of child-bearing potential who has a positive pregnancy test at screening or plans to become pregnant during the course of the study
3. Subject is being treated for hyperthyroidism at time of screening
4. Subject has an abnormality (>1.8mg/dL) in creatinine at time of screening visit
5. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit. If TSH is out of range, Free T3 and Free T4 will be tested. Subject may be included with TSH out of range as long as Free T3 and Free T4 are in normal reference range.
6. Subject has taken any oral, injectable, or IV steroids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV steroids during the course of the study
7. Subject is currently abusing illicit drugs
8. Subject is currently abusing prescription drugs
9. Subject is currently abusing alcohol
10. Subject has sickle cell disease or hemoglobinopathy
11. Subject has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening or plans to receive red blood cell transfusion or erythropoietin over the course of study participation
12. Subject diagnosed with current eating disorder such as anorexia or bulimia
    Subject has been diagnosed with chronic kidney disease that results in chronic anemia

6 Determination of Sample Size

6.1 Sample Size for Primary Endpoint

The overall mean change in A1C from baseline to the end of study will be estimated and compared by a non-inferiority test with an A1C margin of 0.4% and a significance level of 0.025 (one-sided) with the CEP 266 study population. The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in A1C is less than 0.4%

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of change in A1C (%).

Assuming the mean of change in A1C from baseline to the 12-month follow-up visit is zero, the standard deviation of change in A1C is 1%, SAS power and sample size calculator shows that a total of 100 subjects will provide over 95% power to detect the non-inferiority with a margin of 0.4% and with one-sided type I error of 0.025.

6.2 Sample Size for Adverse Event

Based on previous STAR3 IDE study (G060159), the serious adverse event rate for DKA and severe hypoglycemia was 14.79% (1.27% for DKA and 13.52% for severe hypoglycemia). Assuming a one-year serious adverse event rate for DKA and severe hypoglycemia of 14.5%, a sample size of 480 would produce a one-sided 95% upper confidence limit around 17.5%. The actual one-sided 95% upper confidence limit for DKA incidence rate and severe hypoglycemia incidence rate will also be report separately.

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects enrolled, completed the trial and those that discontinued early will be provided along with the reasons for early discontinuation. The number of subjects completing each scheduled visit overall will be provided in addition to stratification by protocol in which they were enrolled under.

An enrolled subject is one that has signed consent to be included in the study. A subject is deemed as a participating subject if they have completed the eligibility assessment and are not exited as a screen failure. Subjects will be categorized by demographic information for both the categories of Enrolled subjects and Participating subjects. See section 7.2.1.2 Descriptive Statistics.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented.

7.1.3 Analysis Sets

7.1.3.1 Intention to Treat (ITT) Population

The Intention to Treat (ITT) population will include all enrolled subjects.

7.1.3.2 Completed Case (CC) Population

The Completed Cases (CC) population is all subjects who complete the trial.

7.1.3.3 Efficacy Population

The primary efficacy analysis will be performed on the CC population.

7.1.3.4 Safety Population

The Safety Population will be the ITT population (include all enrolled subjects).

7.2 General Methodology

7.2.1 Primary Efficacy Analysis

A mixed effects model will be used to produce the estimate and confidence interval of the overall mean change in A1C while accounting for inter-site variability: The 97.5% upper confidence interval of A1C will be calculated and compared to the 0.4% non-inferiority margin with the CEP 266 study population. As for endpoint analysis, the proposed mixed effects model using all A1C measurements has more power than the model only using Change in A1C from baseline to one-year visit.

$$Y_{ij} = X_{ij}\beta + B_i + B_{ij} + \varepsilon_{ij}$$

where

$Y_{ij} = (Y_{ij1}, \ldots, Y_{ij5})'$ is the A1C measurement vector for the jth subject in the ith site;

$$= \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 \end{pmatrix}$$ is a the covariate vector for the jth subject in the ith site;

$$\beta = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{pmatrix}$$ is the coefficient vector, β_0 estimate the mean A1C at baseline, β_4 estimate the mean change of A1C from baseline to one-year visit;

$B_i = (b_i, \ldots b_i)'$ is the random effect vector for the ith site;

$B_{ij} = (b_{ij}, \ldots b_{ij})'$ is the random effect vector for the jth subject in the ith site;

$\varepsilon_{ij} = (\varepsilon_{ij1}, \ldots, \varepsilon_{ij5})'$ is the random error term;

"The mean of baseline A1C measurement is estimated by β_0, mean of 3-month A1C measurement estimated by $\beta_0 + \beta_1$, …, mean of 12-month A1C measurement estimated by $\beta_0 + \beta_4$, i.e., β_4 estimate the mean change of A1C from baseline to one-year visit; the 97.5% upper confidence interval of β_4 will be calculated and compared the 0.4% non-inferiority margin."

7.2.1.1 Sensitivity Analysis

Sensitivity analysis will be performed on the ITT population with multiple imputations. The missing data in A1C measurements will be handled by the multiple imputation approach using imputation regression

method, where the independent variables in the regression model are age, gender, baseline A1C and BMI. In each imputed dataset, the missing A1C data will be imputed by $\hat{y} + z\hat{\sigma}$, where $\hat{y}$ is the predicted value from regression, z is a standard normal random variable, $\hat{\sigma}$ is the estimated standard deviation of the random residual from the regression model. The imputation will be performed five times using the MI procedure and the analysis results will be combined to form one inference using the MIANALYZE procedure in SAS 9.3.

7.2.1.2 Descriptive Statistics

The primary endpoint will also be summarized (descriptive statistics) and stratified by:

- Investigational Site
- Age
  - Adults age 22 and older
  - Adolescents age 16-21
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject refused
- Race
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum less than 80%
  - Native Hawaiian/Other Pacific Islander
  - Asian
  - Other
  - Subject refused
- Baseline BMI according to WHO criteria [World Health Organization, 2011]
  - Underweight subjects (BMI less than 18.5 kg/m
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²):
  - Overweight subjects (BMI 25.00 to 29.99 kg/m)
  - Obese subjects (BMI 30.00 to 39.99 kg/m)
  - Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)
- Gender
  - Male
  - Female
- Diabetes Classification
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes
- Duration of Diabetes
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- Hypoglycemic Unawareness Questionnaire
  - Patients with intact hypoglycemic awareness (95% confidence interval will be provided)

- Patients who have impaired hypoglycemic awareness (95% confidence interval will be provided)
- Transition Groups
  - Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 7 days or less prior to screening
  - Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 8 to 365 days prior to screening

7.2.2 Safety Analysis for Multi-Center Trial

All adverse events reported by the site per protocol for enrolled subjects will be summarized. The summary will include all adverse events and adverse events by: Insulin Pump Infusion set; Insulin administration and pump use; Sensor Use; Severe Hypoglycemia; Severe Hyperglycemia; Diabetic Ketoacidosis; Adverse Device Event; Serious Adverse Event and Unanticipated Adverse Device Effect. Adverse Events by Investigator will also be provided. No formal statistical analysis will be carried out.

In addition, data will be collected for a descriptive summary of device disposition; adverse events; device performance and user acceptance. Safety analysis will include a summary of the following:

All Adverse events to be collected include the following:

- Adverse Events related to the study device
- Adverse Events related to study procedures
- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of Diabetic Ketoacidosis (DKA)

Adverse Events will be stratified by

- Age
  - Adults age 22 and older
  - Adolescents age 16-21
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject refused
- Race
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum less than 80%
  - Native Hawaiian/Other Pacific Islander)
  - Asian
  - Other
  - Subject Refused
- Baseline BMI according to WHO criteria [World Health Organization, 2011]
  - Underweight subjects (BMI less than 18.5 kg/m)

- Normal weight subjects (BMI 18.5 to 24.99 kg/m²)
- Overweight subjects (BMI 25.00 to 29.99 kg/m)
- Obese subjects (BMI 30.00 to 39.99 kg/m)
- Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)

- Gender
  - Male
  - Female
- Diabetes Classification
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes
- Duration of Diabetes
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- Hypoglycemic Unawareness Questionnaire
  - Patients with intact hypoglycemic awareness (95% confidence interval will be provided)
  - Patients who have impaired hypoglycemic awareness (95% confidence interval will be provided)
- Frequency and average duration of hypoglycemic event (based on two weeks prior to the adverse event)
- The actual one-sided 95% upper confidence limit of severe adverse event incidence rate (DKA and severe hypoglycemia) will be calculated. Individual one-sided 95% confidence limit for DKA only and severe hypoglycemia only will also be provided. Please note: the planned analysis may not be adequate since we did not meet the defined minimum sample size requirement.

7.2.3 Secondary Endpoint for Multi-Center Trial

The mean change in A1C from baseline to 3-month, 6-month, 9-month and 12-month will be summarized individually for each of the three baseline A1C cohorts:

- A1C less than 7.0%;
- A1C between 7.0% to 9.0%;
- A1C greater than 9.0%

7.2.4 Descriptive Endpoints for Multi-Center Trial

Descriptive Summary Statistics will be provided.

7.2.4.1 A1C Change:

- The percentages of subjects with increased A1C and decreased A1C from baseline will be presented for each baseline A1C subgroup (less than 7%, 7% – 9% and greater than 9%) and overall.
- The distribution of subjects' changes in A1C will also be summarized by histogram for each baseline A1C subgroup and overall.

7.2.4.2 TS Metrics – Hypoglycemia Endpoints:

Hypoglycemic Event Incidence, where an event is identified by the following criteria within 4 hours that TS is activated:

- CGM value less than or equal to 70 mg/dL continuously for greater than 20 minutes
- The rate of change (defined by the change between two consecutive sensor glucose measurements) will be examined during the 10-minute time interval before reaching a sensor glucose value of less than or equal to 70 mg/dL. If any rate of change in sensor glucose is >5 mg/dl/minute, the event will not be counted
- When the time between two successive events is less than 30 minutes, they will be combined as one event

The above information will be repeated for hypoglycemia threshold at 40, 50, 60, 65 and 70 mg/dL with and without TS activation and will be summarized by Day (8:00am – 10:00pm) /Night (10:00pm – 8:00am) and TS Threshold Settings.

The hypoglycemic event incidence, duration and the percentage of time spent (below TS threshold setting) within 4-6 hours of suspend will also be summarized. The hypoglycemic event is identified as:

- CGM value below the TS threshold continuously for at least 20 minutes
- No evidence of patient intervention which includes meter BG, meal marker and insulin delivery change during the first 20 minutes when CGM value is below the TS threshold.
- When the time between two successive events is less than 30 minutes, they will be combined as one event

Data will be summarized for each baseline A1C subgroup (less than 7%, 7%-9% and greater than 9%) and overall.

7.2.4.3 TS Metrics – Hyperglycemia Endpoints:

Hyperglycemic Event Incidence, where an event is identified by the following criteria within 4 hours that TS is activated:

- CGM value greater than or equal to 180 mg/dL continuously for greater than 20 minutes.
- The rate of change (defined by the change between two consecutive sensor glucose measurements) will be examined during the 10-minute time interval before reaching a sensor glucose value of greater than or equal to 180 mg/dL. If any rate of change in sensor glucose is >5 mg/dl/minute, the event will not be counted
- When the time between two successive events is less than 30 minutes, they will be combined as one event

The above information will be repeated for hyperglycemia threshold at 180, 250, 300, 350 and 400 mg/dL with and without TS activation and will be summarized by Day (8:00am – 10:00pm) /Night (10:00pm – 8:00am) and TS Threshold Settings. The hypoglycemic event incidence, duration and the percentage of time spent (below TS threshold setting) within 4-6 hours of suspend will also be summarized. The data will be summarized for each baseline A1C subgroup (less than 7%, 7%-9% and greater than 9%) and overall.

7.2.4.4 Device Utilization:

- We will provide descriptive summary statistics of suspend event including frequency, mean change of SG values before and after the suspense.
- TS Setting ON/OFF
- TS Threshold Setting
- Number of occurrences and time of Insulin Delivery Suspension by TS suspension/manual suspension (unrelated to the threshold suspend feature)
  - Manual suspension
  - Temporary basal set to zero
  - Threshold Suspend without user acknowledgement
  - Threshold Suspend acknowledged by user and cancelled
  - Threshold Suspend acknowledged by user and confirmed
  - Threshold Suspend first acknowledged by subject and confirmed, the followed by a second Threshold suspend not acknowledged by the subject after the hypoglycemia repeat time has elapsed.
- Subject response to insulin suspension
  - Confirmatory SMBG compliance during TS (within 2 hours of alarm) by length of time after the alarm (every 30 min up to 4 hours from TS activation)
  - Length of time to acknowledge TS alert by day and night
  - Comparison of time of alarm, time to SMBG and effects on glycemia
  - Therapeutic change in basal insulin (within 2 hours of alarm)
  - Frequency of basal increase/decrease/no change;
  - Summary statistics of amount of basal increase/decrease
- Frequency of Sensor Dislodgement / Suspected Occlusion
- Early infusion set change (before 3 days)
- Frequency of infusion set changes
- Frequency of Infusion Set occlusion alarms
- Total suspend time including manual suspends, times when the subject sets a temporary basal rate of zero, and threshold suspends separately and together during the nighttime, daytime, and 24 hour periods.
- Frequency of repeated threshold suspends with 1) ≤15 minutes and 2) ≤60 minutes of basal insulin delivery between suspends.
- Repeated threshold suspends with total suspend durations of ≤1 hour, 1-≤2 hours, 2-≤4 hours, 4-≤6 hours, etc. Please calculate “total suspend durations” as the sum of the durations of repeated suspensions with 1) ≤15 and 2) ≤ 60 minutes between suspends (intervening basal delivery time should not be included).

7.2.4.5 CGM Metric:

- CGM Adherence – average sensor-wear per week
- Comparison between CGM data and Glucose Meter data

7.2.4.6 Device Performance

- All complaints that are reported via the 24-hour HelpLine will be summarized and reported.

7.2.4.7 Effectiveness of educational materials

- Subject Questionnaire at Screening
- Subject Questionnaire After Training Session and Device Placement

7.2.4.8 Human Factors:

- Frequency of subject acknowledging the alarm and continuing the suspend, when the suspend occurred automatically (without subject interaction)
- Frequency of subject not continuing the Threshold Suspend and instead manually suspending insulin delivery or setting a temporary basal rate of zero

7.2.4.9 Questionnaires:

The following will be performed on each questionnaire:

- EQ-5D and EQ-5D-Y
  - Summary of changes in score from baseline to end of study will be performed.
- Low Blood Sugar Survey (Adult, Parent and Child)
  - Summary of changes in score from baseline to end of study will be performed.
- Subject Questionnaire at Screening and Subject Questionnaire after Training Session and Device Placement (training evaluation questionnaire)
  - Summary of answers that will be provided no more than 2 hours before and 2 hours after placement of 530 G pump in order to assess effectiveness of training materials.
- Hypoglycemia Unawareness Questionnaire
  - Summary of changes in score from baseline to end of study will be performed.

7.3 Center Pooling

Data will be pooled for analysis.

7.4 Handling of Missing Data

For ITT population, the missing data in A1C measurements will be handled by the multiple imputation approach using imputation regression method, where the independent variables in the regression model are age, gender, baseline HbA1C and BMI. The imputation will be performed five times using the MI procedure and the analysis results will be combined to form one inference using the MIANALYZE procedure in SAS 9.4. The primary analysis population for the change in A1C endpoint will be the ITT population with multiple imputations.

All available device data will be used for the analysis. No imputation will be applied for the device data.

7.5 Adjustments for Multiple Comparisons

No adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, ethnicity, diabetes History, height, weight, BMI and baseline HbA1C will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

7.7 Health Outcomes Analyses

Descriptive summary will be used to characterize data from questionnaires that are given to subjects to record feedback.

7.8 Commercial Data Evaluation: Carelink Database Analysis

Analysis from the Carelink database with patients on the MiniMed 530G system intends to provide a large heterogeneous source of data taken from the actual commercial use with MiniMed 530G. The focus of this analysis is to provide a robust data set on the safety of this system. To this end, our analysis will not only provide a summary of glucose control and correlation with the use of the Threshold Suspend (TS) feature but will provide a focused analysis on key aspects of the MiniMed 530G system as it relates to the safety of the system.

Datasets will come from MiniMed 530G patients and insulin pumps sold and uploaded within date windows.

7.8.1 Primary Safety Endpoint

The difference in self-reported first A1C and subsequent A1C collected from StartRight program. The mean difference in A1C will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided).

The overall difference in A1C will be estimated and compared by a non-inferiority test with an A1C margin of 0.4% and a significance level of 0.025 (one-sided). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean difference in A1C is less than 0.4%

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of difference in A1C (%).

Primary safety endpoint will be presented and tested using pair t-test on those subjects with both first and subsequent A1c.

Descriptive subgroup analysis of A1c data will be performed on demographic cohorts (age, gender, duration of diabetes and years on insulin), and first A1c (less than 7.0%, 7.0-9.0%, greater than 9.0%)

This analysis addresses the primary and secondary safety endpoint per conditions of approval in FDA 530G approval letter

7.8.2 Primary Efficacy Endpoint

Two primary efficacy endpoints are defined below. The study will be considered successful if both endpoints are met. Therefore, alpha is kept at a significance level of 0.025 (one sided).

Primary efficacy endpoint will be presented and tested using pair t-test on those subjects with both TS feature ON and TS feature OFF within date windows.

7.8.2.1 Co-Primary Efficacy Endpoint:

The difference in percent time spent <70 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent <70 mg/dL (TS feature ON and TS feature OFF) will

be estimated and compared by a superiority test with a significance level of 0.025 (one-sided). The goal is to show superiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}}$

Ha: $\mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}}$

where μ (TS feature ON) is the subject mean of percent time with SG below 70 mg/dL during TS feature ON, μ (TS feature OFF) is the subject mean of percent time with SG below 70 mg/dL during TS feature OFF.

7.8.2.2 Co-Primary Efficacy Endpoint:

The difference in percent time spent >180 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent >180 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided) and a margin of 5%. The goal is to show non-inferiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}} + 5\%$

Ha: $\mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}} + 5\%$

where μ (TS feature ON) is the subject mean of percent time with SG > 180 mg/dL during TS feature ON, μ (TS feature OFF) is the subject mean of percent time with SG > 180 mg/dL during TS feature OFF.

7.8.3 Descriptive Endpoint

- Adverse Events collected via Outreach program. Adverse events (Hospitalized High BG and Hospitalized Low BG) collected during Outreach program will be summarized and presented. Adverse event rates in 100 patient years will also be reported. Adverse events will be further stratified by device component (pump, sensor, sensor serter, infusion set, infusion set serter, reservoir or accessories), age, gender duration of diabetes and years on insulin.
- The difference in estimated A1C ((average sensor glucose + 36.9) / 28.0) from TS feature ON and TS feature OFF [Nathan D, etc. 2008]. Subgroup analysis of A1c data will be performed on demographic cohorts (age, gender, duration of diabetes and years on insulin), and first A1c (less than 7.0%, 7.0-9.0%, greater than 9.0%). This analysis addresses the primary and secondary safety endpoint per conditions of approval in FDA 530G approval letter
- TS Feature Utilization: TS feature utilization will be calculated using the available SG with TS feature 'turned on', divided by the period of MiniMed 530G device use (i.e. 288 * Number of days with TDD > 0 units) * 100.

Validation of correct TS feature activation (i.e., insulin suspension) with fingerstick when available will be provided including:

1. Total number of insulin suspensions from TS feature activations
2. Total number of insulin suspensions which were accompanied by fingerstick glucose. (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)

3. Total number of insulin suspensions with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Hypoglycemic Event Incidence, duration and percentage of time spent (SG less than or equal to 50 and 70 mg/dL): with and without TS feature ON, with or without fingerstick glucose. A hypoglycemic event is defined by SG less than the defined threshold for at least 20 minutes. Validation of CGM with fingerstick when available will be provided including:

  1. Total number of hypoglycemic events
  2. Total number of hypoglycemic events that were accompanied by fingerstick glucose (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)
  3. Total number of hypoglycemic event with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Hyperglycemic Event Incidence, duration and percentage of time spent (SG greater than or equal to 180, 250, 300, and 400 mg/dL) with and without TS feature ON; with fingerstick or not. A hyperglycemic event is defined by SG greater than the defined threshold for at least 20 minutes. Provision of fingerstick data when available will provide a separate and important reference to CGM data. Validation of CGM with fingerstick when available will be provided including:

  1. Total number of hyperglycemic events
  2. Total number of hyperglycemic events that were accompanied by fingerstick glucose (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)
  3. Total number of hyperglycemic event with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Characteristics of patient behavior for each cohort (e.g. Cohort 1-5 below) will be provided. The provision of this data will help to better understand the profile of patients using this device.

Cohort Description:

- Cohort 1: 0-24% TS feature utilization
- Cohort 2: 25-49% TS feature utilization
- Cohort 3: 50-74% TS feature utilization
- Cohort 4: 75-100% TS feature utilization
- Cohort 5: Data from all 530G uploads regardless of TS feature utilization

7.8.3.1 CGM Adherence – average sensor-wear per week

Logic used: sensor utilization will be calculated using the available SG, divided by the period of 530G device use (i.e. 288 * Number of days with TDD > 0 units) * 100

In studies such as the JDRF1, higher utilization was associated with improved glucose control. Compliance to sensor wear or fingerstick testing gives insight into the type of patient using the system. However this assessment is limited by the fact that patient may not be wearing a sensor because they have a change in insurance or financial status that does not allow them to wear sensor.

CGM adherence will be stratified by

- Age:
  - Adults age 22-and older
  - Adolescents age 16-21
- Gender
  - Male
  - Female
- Years on Insulin
  - Years on Insulin less than 20 years
  - Years on Insulin greater than or equal to 20 years
- Age at diabetes onset or Duration of Diabetes:
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- Baseline A1c
  - < 7%
  - 7-9%
  - >9%

7.8.3.2 Fingerstick monitoring

In the DCCT2,3 the higher amount of times the patient checked their glucose was correlated with overall glucose control. For example, if the patient checked glucose more frequently they had better glucose control. Compliance to sensor wear or fingerstick testing gives insight into the type of patient using the system. However, this assessment is limited by the fact that a patient may not be checking their glucose because their insurance limits the amount of fingerstick glucose strips or their copays have increased.

Logic used: Fingerstick utilization will be calculated using the number of available SMBGs, divided by the period of 530G device use (i.e. Number of days with TDD > 0 units) * 100

7.8.3.3 Infusion set changes – how often

Compliance to infusion set changes gives insight into the type of patient using the system. However, this assessment is limited by the patient's ability to pay (copay) for their infusion sets and extends the wear of the infusion set.

Logic used: Infusion set utilization will be calculated using the average days between available infusion set change surrogate (i.e., rewind event to rewind event).

7.8.4 Adverse Event Reporting

Adverse events (Hospitalized High BG and Hospitalized Low BG) collected during Outreach program will be summarized and presented. Adverse event rates in 100 patient years will also be reported.

Adverse events will be further stratified by device component (pump, sensor, sensor serter, infusion set, infusion set serter, reservoir or accessories), age, gender duration of diabetes and years on insulin.

7.8.5 Data Completeness

Missing demographic measures (Age, gender, Age at Diabetes Onset, Years on Insulin and baseline A1C at entry) for Carelink dataset will be summarized and presented.

7.8.6 Sample Size Calculation

7.8.6.1 Sample Size for Primary Safety Endpoint

The difference in self-reported first A1C and subsequent A1C collected from StartRight program. The mean difference in A1C will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided).

The overall change in A1C from baseline will be estimated and compared by a non-inferiority test with an A1C margin of 0.4% and a significance level of 0.025 (one-sided). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean difference in A1C is less than 0.4%

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of difference in A1C (%).

Assuming the mean different in A1C from baseline to subsequent is zero, the standard deviation of change in A1C is 1%, SAS power and sample size calculator shows that a total of 200 subjects will provide over 95% power to detect the non-inferiority with a margin of 0.4% and with one-sided type I error of 0.025.

7.8.6.2 Sample Size for Co-Primary Efficacy Endpoint

The difference in percent time spent <70 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean difference in percent time spent <70 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a superiority test with a significance level of 0.025 (one-sided). The goal is to show superiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}}$

Ha: $\mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}}$

Sample size estimates for time in hypoglycemic range is based on paired t test with a one-sided type I error rate of 2.5%. Assume in TS feature ON, the mean is 5% with standard deviation of 4%, In TS feature OFF, mean is 9% with standard deviation of 6%, SAS power and sample size calculator shows that a total of 200 subjects will provide over 90% power to detect the superiority of TS feature ON compared to TS feature OFF.

7.8.6.3 Sample Size for Co-Primary Efficacy Endpoint

The difference in percent time spent >180 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean difference in percent time spent >180 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided) and a margin of 5%. The goal is to show non-inferiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{TS\ Feature\ ON} \geq \mu_{TS\ Feature\ OFF} + 5\%$

Ha: $\mu_{TS\ Feature\ ON} < \mu_{TS\ Feature\ OFF} + 5\%$

Sample size estimates for time in hyperglycemic range is based on paired t test with a one-sided type I error rate of 2.5%. Assume in TS feature ON, the mean is 21% with standard deviation of 9%, In TS feature OFF, mean is 25% with standard deviation of 10%, SAS power and sample size calculator shows that a total of 200 subjects will provide over 90% power to detect the non-inferiority of TS feature ON compared to TS feature OFF, with a margin of 5%.

8 Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9 References

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