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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Safety and Effectiveness Evaluation of the MiniMed™ 780G System Used in Combination with the DS5 CGM
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviations	
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
ICF	Informed Consent Form
ID	Identification
PC	Personal Computer
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SAP	Statistical Analysis Plan
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
TIR	Time in Range
TS	Technical Support
UADE	Unanticipated Adverse Device Effect

3. Introduction

3.1 Background

In patients with insulin dependent diabetes mellitus, glycemic control is influenced by numerous factors such as insulin dosage, insulin absorption, timing, physiological/ lifestyle factors such as exercise, food intake, hormones and illness. These factors may contribute to significant variability in insulin requirements, which makes self-management of type 1 diabetes challenging.

Patients who are using continuous glucose monitoring (CGM), including sensor-augmented pump therapy, experience improvements in glycemic control. Advanced sensor-augmented insulin pumps are now being used in clinical practice including closed loop systems that automatically adjust the amount of insulin delivered to maintain glucose levels near the target value set by the user.[1]

The MiniMed 780G system is a closed loop insulin system. In addition to automatically adjusting the amount of insulin delivered based on sensor glucose (SG) readings while operating with the SmartGuard feature activated, the MiniMed 780G insulin pump can also automatically deliver correction boluses when the system has been delivering at the maximum allowable basal rate and SG remains elevated. This pump is currently in commercial distribution in Europe and is under review by the United States Food and Drug Administration (FDA). Previous clinical investigations involved the 670G Version 4.0 pump (contains the 780G Advanced Hybrid Closed Loop [AHCL] algorithm) used in combination with the Guardian Sensor (3) glucose sensor, Guardian Link (3) transmitter, Humalog, and Novolog insulin. This investigation is intended to confirm safety and effectiveness of the 780G insulin pump used in combination with the DS5, which combines the glucose sensor and transmitter into one disposable device. Additional details for non-clinical/clinical testing are provided in the report of prior investigations.

3.2 Purpose

The purpose of this study is to confirm the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM in type 1 diabetes adult and pediatric subjects in a home setting.

4. Study Objectives

The objective of this study is to evaluate the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM.

5. Investigation Plan

This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes on the MiniMed 780G system using DS5 as well as Medtronic Extended infusion set and reservoir. The run-in period and study period will be approximately 120 days long.

The period from Visit 1 (consent and screening) through Visit 6 must be completed in 30 days.

Run-in Period (Visits 2-6):
The run-in period begins at Visit 2 and ends once Visit 7 occurs.

The intent of the run-in period will be to allow subjects to become familiar with new study devices while using their own insulin: Humalog™ (insulin lispro injection), NovoLog® (insulin aspart solution for injection), or Admelog® (insulin lispro injection). During the run-in period, study subjects will be using the study pump with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard™ feature is turned OFF), DS5, Medtronic Extended infusion set and reservoir.

SmartGuard (with Auto Correction OFF) during the run-in period will be permitted for study subjects who are using the Auto Mode feature in a Medtronic pump prior to screening. In the 780G study pump, the term "Auto Mode" has been replaced with "SmartGuard". All others are to use the system in Manual Mode during the run-in period.

Therapy at Screening	Pump Setting During Run-in Period
Continuous Subcutaneous Insulin Infusion (CSII)	Manual Mode
SAP (no closed loop)	Manual Mode
SAP (with closed loop) in non-Medtronic pump	Manual Mode
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction OFF

During the run-in period and only for subjects with Auto Mode experience through the use of a Medtronic insulin pump, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is set to 4 hours.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

Subjects who do not have experience with Medtronic insulin pumps, as specified above, will use the system in Manual Mode.

All subjects and their parents/caregivers (if applicable) will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training regarding the need to have access to and how to use glucose and glucagon in case of hypoglycemia.

Parents/caregivers (if applicable) will be instructed that they should be with the subject in the same residence or building overnight.

If the MiniMed Clinical app and the CareLink Clinical app are being used, parents/caregivers (if applicable) will be instructed that subjects should be connected to CareLink via the appropriate Smartphone app for data uploading and push notifications for low or high blood sugar when they are apart, e.g., at school, other activities. Instructions on the appropriate operation of the apps will be provided.

For study purposes, subjects and parents/caregivers (if applicable) will be trained and/or instructed to perform self-monitoring of blood glucose (SMBG) if subjects are experiencing a severe hypoglycemic event, severe hyperglycemic event or diabetic ketoacidosis (DKA). Subjects and their parents/caregivers (if applicable) will also be instructed to check subject blood ketones using a Precision Xtra ketone meter or other approved ketone meter if the Accu-Chek Guide Link study meter reading is greater than 300 mg/dL.

As a precaution, subjects and their parents/caregivers (if applicable) will be told that subjects should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe, or insulin pen) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e., infusion set occlusion with high glucose).

Subjects and their parents/caregivers (if applicable) will be instructed to insert the DS5 into subjects only in the locations that are specified in the User Guide. Reminders will be given to subjects and their parents/caregivers (if applicable) at each office visit. Information about sensor insertions will be collected at each study visit on an electronic case report form (eCRF) in the study database, e.g., insertion location.

Subjects and their parents/caregivers (if applicable) will be trained on all parts of the device system. This will involve live training conducted by the investigational center staff. A training checklist for both subject and parents/caregivers (if applicable) will be implemented and completed. Parents/caregivers (if applicable) should be available for relevant parts or all of this training, either in person or virtually. After completion of training on the study devices, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of system use, as needed.

Study Period (Visits 7-15):
All subjects will continue using the study pump with SmartGuard feature enabled (including Auto Correction), Humalog/ NovoLog/ Admelog, DS5, infusion set and reservoir. During the study period, each subject will be encouraged to continue on the same brand of insulin with which they started. All SmartGuard™ features will be activated and should be used for the duration of the study period.

Subjects should use the system with the SmartGuard feature turned on at all times. When prompted by the pump, subjects should take appropriate measures and follow directions on the pump to remain in or return to the SmartGuard feature. During times when subjects are not able to use the SmartGuard feature, they should use the system in Manual Mode (e.g., with Suspend before low or Suspend on low activated).

Therapy at Screening	**Pump Setting During Study Period**
Continuous Subcutaneous Insulin Infusion (CSII)	SmartGuard feature with Auto Correction ON
SAP (no closed loop)	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in non-Medtronic pump	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction ON

During the first 3 weeks (between Visits 7 and 11) of the study period, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is initially set to 4 hours and then titrated towards 2-3 hours or at the investigator's discretion.

During the next 3 weeks (between Visits 11 and 13) of the study period, the Auto Basal target setting should be set to 100 mg/dL. Active Insulin Time is recommended to be set to 2-3 hours or at investigator's discretion.

During the remaining weeks of the study (any time after Visit 13) of the study period, the Auto Basal target as well as Active Insulin Time should be set to what is best for the individual subject, at investigator's discretion.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

After completion of live training on the SmartGuard function, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of SmartGuard use, as needed.

SMBG recommendations for 780G system:
Calibration is not required with the MiniMed 780G system using the DS5. However, a calibration is optional and it will automatically occur any time a blood glucose (BG) is entered. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in the SmartGuard feature. Subjects will be instructed to perform SMBG if their symptoms do not match the sensor glucose (SG) value (i.e., they develop symptoms of hypoglycemia or hyperglycemia, but the SG value does not correlate with their symptoms).

5.1 Duration
The study is anticipated to last approximately 18 months from first investigational center initiation to study completion. Individual subject participation is expected to be approximately 120 days through the study period.

5.2 Rationale
The accuracy of the DS5 has been evaluated in previous clinical trials and has been confirmed to provide performance that meets the previously established requirements for glucose sensors used with the MiniMed 780G pump. This investigation is required to provide additional confirmation of the safety of the pump used in combination with the DS5.

6. Determination of Sample Size

6.1 Sample Size and Investigational Centers
A total of up to 250 subjects with insulin-requiring type 1 diabetes age 7-80 will be enrolled at up to 25 investigational centers across the United States in order to have 200 subjects enter the study period. Up to 125 subjects will be enrolled in the pediatric age group (7-17 years of age), up to 125 in the adult age group (18 years or older):

Subject Age Group	Sub-groups	Enrollment Goal (N)
Pediatric Age 7 – 17 years	Age 7 - 13 years	Minimum 20 Subjects
	Age 14 - 17 years	Minimum 20 Subjects

Investigational centers will be encouraged to enroll a study population that represents a wide variety of backgrounds.

6.2 Sample Size Considerations/Sample Size Justification

6.2.1 Age 18-80

- Sample size for the primary safety endpoint: the overall mean change in HbA1c from baseline to end of 3-month study period, non-inferiority test

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 HCL age 18 to 75, N = 101) study was -0.50%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 0.4%) with a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), non-inferiority test

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8.8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 7.5%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL), non-inferiority test

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 HCL age 18 to 75, N = 104) study was 0.86%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.79%, SAS power and sample size calculator with one sample T

test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 2%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), simple superiority test

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is 76%, with a standard deviation of 7.2%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the simple superiority with a significance level of 0.025 (one-sided).

6.2.2 Age 7-17

- Sample size for the primary safety endpoint: the overall mean change in HbA1c from baseline to end of 3-month study period, non-inferiority test

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was -0.38%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 0.4%) with a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), non-inferiority test

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 7.5%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL), non-inferiority test

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 0.71%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.60%, SAS power and sample size calculator with

one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 2%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), simple superiority test

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is 67.6% , with a standard deviation of 7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the simple superiority with a significance level of 0.025 (one-sided).

6.2.3 Expected Drop-out Rates

Incorporating the expected drop-out rates, a total of up to 250 subjects will be enrolled, in order to have 200 subjects enter the study period.

7. Statistical Methods

7.1 Study Subjects

7.1.1 General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected on eCRFs, subject questionnaires, and electronically by uploading the various devices. Data and analysis will be summarized in a Clinical Study Report. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

7.1.2 Disposition of Subjects

The number of subjects enrolled, completed, and early terminated in the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

7.1.3 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented as Listings.

7.1.4 Analysis Sets

- Intention to Treat (ITT) Population

  The ITT population will include all subjects who start the study period. Primary safety, primary effectiveness, secondary effectiveness and descriptive endpoints will be evaluated for ITT population.

- Per Protocol (PP) Population

  The PP population will include all subjects who complete the study period, are in SmartGuard feature ≥ 80% of the time and without any major deviations. Primary safety, primary

effectiveness and secondary effectiveness endpoints will be evaluated for PP population as the sensitivity/supplementary analyses.

- Safety Population

  The Safety Population will include all enrolled subjects (subjects who signed Informed Consent Form (ICF)). Safety adverse events data summary will be evaluated for safety population.

7.2 General Methodology

Summary statistics for continuous variables will be represented by number of subjects(n), mean, median, standard deviation and categorical variables will be represented by counts and percentages. P-values for hypothesis testing will be evaluated based on one-sided testing using significance level of 0.025. Confidence intervals if needed will be reported as two-sided 95% confidence intervals. For primary safety, primary effectiveness and secondary effectiveness endpoints, normality will be verified for appropriate statistical methodology. Comparisons between the outcomes in study period and the threshold will be performed using one sample T-test for testing the statistical significance of the difference if normality assumption is met or Wilcoxon signed rank test if normality assumption is not met.

The templates for Tables, Listings and Figures (TLFs) will be available in the TLFs document.

7.3 Center Pooling

Data will be pooled for analysis. Additional sensitivity analysis will be performed for site effect in section 7.9.4.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Data entry error or non-reasonable values will be resolved before data analysis. No imputations will be done for missing data. Analysis will be done by all available data.

For partial date entered in Medical History CRF, the first day of the month or the first day of the year will be used.

7.5 Adjustments for Multiple Comparisons

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity. Safety and effectiveness endpoints will be evaluated independently between age 18-80 and age 7-17.

Fixed sequential testing will be applied in the following order: primary safety, primary effectiveness and secondary effectiveness endpoints for age 18-80 and age 7-17.

7.5.1 Age 18-80

For the following endpoints from age 18-80, the procedure test will be applied hierarchically in sequence of the ordered hypotheses at level α =0.025 until a first hypothesis is non-rejected.

Primary Safety Endpoint

- Age 18-80: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.5% in reducing HbA1c from baseline to end of 3-month study period.

Primary Effectiveness Endpoint

- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 18-80: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.86% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided).
- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a simple superiority test and a significance level of 0.025 (one-sided).

7.5.2 Age 7-17

For the following endpoints from age 7-17, the procedure test will be applied hierarchically in sequence of the ordered hypotheses at level α =0.025 until a first hypothesis is non-rejected.

Primary Safety Endpoint

- Age 7-17: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.38% in reducing HbA1c from baseline to end of 3-month study period.

Primary Effectiveness Endpoint

- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 7-17: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.71% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided).
- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a simple superiority test and a significance level of 0.025 (one-sided).

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, Body Mass Index (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 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

Not applicable.

7.9 Evaluation of Objectives

Safety and effectiveness endpoints will be evaluated independently between age 18-80 and age 7-17.

7.9.1 Pass/Fail Criteria

The study pass/fail criteria is based on statistical hypothesis of the primary endpoints. The study for each age cohort (age 18-80 and age 7-17) will be considered a success when the evaluation criteria of both primary safety and effective endpoints meets the predefined threshold per cohort.

Justification for Exclusion of Particular Information from the testing of the Hypothesis:
Not Applicable.

7.9.2 Primary Safety Endpoint

Age 18-80:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared by a non-inferiority test to the threshold of -0.50% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\Delta\mu_{780G} \geq -0.50\% + 0.4\%$

  H_a: $\Delta\mu_{780G} < -0.50\% + 0.4\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared by a non-inferiority test to the threshold of -0.38% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\Delta\mu_{780G} \geq -0.38\% + 0.4\%$

H_a: $\Delta\mu_{780G} < -0.38\% + 0.4\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 7-17 will be concluded if null hypothesis is rejected.

7.9.3 Analysis of Effectiveness Endpoint

All effectiveness endpoints will be analyzed using the data from the Visit 13 to the end of the study.

7.9.3.1 Primary Effectiveness Endpoint

Age 18-80:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) will be estimated and compared by a non-inferiority test to the threshold of 73.7% with a margin of 7.5%. A significance level of 0.025 (one-sided) will be used. The 7.5%, which is approximately 100 minutes increase in TIR per day, was also observed from the HCL pivotal trials. It is loosely correlated to ~0.5% reduction in A1c as well. Analysis will be performed on the ITT and PP populations.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\mu_{780G} \leq 73.7\% - 7.5\%$

  H_a: $\mu_{780G} > 73.7\% - 7.5\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) will be estimated and compared by a non-inferiority test to the threshold of 65.3% with a margin of 7.5%. A significance level of 0.025 (one-sided) will be used. The 7.5%, which is approximately 100 minutes increase in TIR per day, was also observed from the HCL pivotal trials. It is loosely correlated to ~0.5% reduction in A1c as well. Analysis will be performed on the ITT and PP populations.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\mu_{780G} \leq 65.3\% - 7.5\%$

  H_a: $\mu_{780G} > 65.3\% - 7.5\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 7-17 will be concluded if null hypothesis is rejected.

7.9.3.2 Analysis of Secondary Effectiveness Endpoints

Age 18-80:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL [3.0 mmol/L]) will be estimated and compared by a non-inferiority test to the threshold of 0.86% with a margin of 2%. A significance level of 0.025 (one-sided) will be used. Analysis will be performed on the ITT and PP populations. The 2% came from not more than 30 minutes increase in hypoglycemia per day to establish a non-inferiority test.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\mu_{780G} \geqslant 0.86\% + 2\%$

  H_a: $\mu_{780G} < 0.86\% + 2\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 18-80 will be concluded if null hypothesis is rejected.

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) will be estimated and compared by a simple superiority test with a significance level of 0.025 (one-sided). Analysis will be performed on the ITT and PP populations.

  The hypothesis of superiority is mathematically expressed as:

  H_0: $\mu_{780G} \leq 73.7\%$

  H_a: $\mu_{780G} > 73.7\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Superiority of MiniMed 780G system used in combination with the DS5 CGM for age 18-80 will be concluded if null hypothesis is rejected.

Age 7-17:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL [3.0 mmol/L]) will be estimated and compared by a non-inferiority test to the threshold of 0.71%

with a margin of 2%. A significance level of 0.025 (one-sided) will be used. The 2% came from not more than 30 minutes increase in hypoglycemia per day to establish a non-inferiority test. Analysis will be performed on the ITT and PP populations.

The hypothesis of non-inferiority is mathematically expressed as:

H_0: $\mu_{780G} \geq 0.71\% + 2\%$

H_a: $\mu_{780G} < 0.71\% + 2\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Non inferiority of MiniMed 780G system used in combination with the DS5 CGM for age 7-17 will be concluded if null hypothesis is rejected.

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) will be estimated and compared by a simple superiority test with a significance level of 0.025 (one-sided). Analysis will be performed on the ITT and PP populations.

The hypothesis of superiority is mathematically expressed as:

H_0: $\mu_{780G} \leq 65.3\%$

H_a: $\mu_{780G} > 65.3\%$

The null hypothesis will be tested against the alternative hypothesis using one sample t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Superiority of MiniMed 780G system used in combination with the DS5 CGM for age 7-17 will be concluded if null hypothesis is rejected.

7.9.4 Sensitivity Analysis for Primary safety, primary effectiveness and secondary effectiveness endpoints

7.9.4.1 Sensitivity Analysis 1: PP population

Primary safety, primary effectiveness and secondary effectiveness endpoints will be evaluated for PP population as the sensitivity/supplementary analyses.

7.9.4.2 Sensitivity Analysis 2: Site effect evaluation with ITT population

To address the pooled sites in statistical analysis, sensitivity analysis 2 will be conducted if the site effect is significant (with a significance level of 0.1) in primary safety, primary effectiveness and secondary effectiveness endpoints.

The site effect will be evaluated by a linear mixed model. The final estimate will be a weighted average of the estimate for each site, where the weight of each site is the inverse of the variance of each site estimate (which equals to the inverse of the square of the standard error of each site estimate).

Note: During the site effect test, sites with less than 6 subjects per age group will be pooled into 'Pseudo-sites' of at least 10 subjects per pseudo-site. Pseudo-site will be pooled by ranking those sites with less than 6 subjects by the site number and pooling those sites in order until the subjects reach at least 10.

7.9.5 Descriptive Endpoints

Time windows for the following endpoints are visit 2 – visit 7, visit 7- visit 11, visit 11- visit 13, and visit 13 to the end of study (EOS) or exit.

- Time spent in the SmartGuard feature versus time spent in Manual Mode
- Change in mean glucose value from baseline to EOS
- Time in different ranges (% of SG): SG < 70 mg/dL, 70 mg/dL ≤ SG ≤ 140 mg/dL, SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54 mg/dL and 70 mg/dL
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS
- Change of weight from baseline to EOS

Subgroup analysis will be performed for:

- Setpoint
  - 100 mg/dL
  - 110 mg/dL
  - 120 mg/dL
  - 150 mg/dL (Temp Target Usage)
- Age
  - Age 18-80
  - Age 7-17
  - Age 7-13
  - Age 14-17

7.9.6 Safety Data Summarized

Safety data will be summarized based on the following time windows: visit 1 - visit 2, visit 2 - visit 7, visit 7 - the end of study (EOS) or exit, and visit 13 to the end of study (EOS) or exit.

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA

7.9.7 Device Deficiencies

Descriptive summary will be used to characterize DDs:

- All reports of device issues.

7.9.8 Subject Feedback

Descriptive summary will be used to characterize study survey/questionnaire results. A total score, and the scores for each subscale of the INSPIRE questionnaires will be calculated and reported. Refer to CIP337 Survey/Questionnaire Guide for administration details.

7.10 Safety Evaluation

The safety of the study will be evaluated and summarized per all enrolled subjects, including but not limited to the following:

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects
- Unanticipated Serious Adverse Device Effect
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA

7.11 Health Outcomes Analyses

Descriptive summary will be used to characterize study questionnaire results. A total score, and the scores for each subscale of the INSPIRE questionnaires will be calculated and reported. Refer to CIP337 Questionnaire Guide for administration details.

7.12 Changes to Planned Analysis

Not applicable.

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

1. Beato-Víbora PI, Gallego-Gamero F, Lázaro-Martín L, Romero-Pérez MDM, Arroyo-Díez FJ. Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority over Predictive Low-Glucose Suspend Technology. *Diabetes Technology and Therapeutics.* 2020;22(12):912-919.
2. Cryer PE. Defining and reporting hypoglycemia in diabetes: A report from the American diabetes association workgroup on hypoglycemia. *Diabetes Care.* 2005;28(5):1245-1249.
3. Hyperglycemic Crises in Diabetes. *Diabetes Care.* 2004;27(SUPPL. 1):S94-S102.