Medtronic	
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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Evaluation of the MiniMed™ 780G System in Type 1 Adult and Pediatric Subjects Utilizing Insulin Fiasp® (Insulin Aspart Injection)
Clinical Investigation Plan Identifier	CIP336
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0, 23-May-2022	Not Applicable, New Document	[redacted]
2.0, 26-Aug-2022	• Clinical Investigation Plan Version removed from title page • Format updates throughout • Following sections updated per Protocol Version C: – Section 3.1: Background – Section 5: Investigational Plan – Study Design (Section Title also updated) – Section 6: Determination of Sample Size – Section 7: Statistical Methods: ○ Update pediatric age group from 2-17 to 7-17 ○ Update endpoints for updated pediatric age group ○ Update time window for analysis to reflect the newly added day 44 visit	[redacted]
3.0, 20-Sep-2023	• Local Sponsor updated in title page: Removed Europe, added Australia • Format and syntax updates throughout • Superscripts added throughout, as applicable, to associated citations • Following sections updated per Protocol Version D and Australia Local Requirements: – Section 3.1: Removed Europe; Specified 780G pump is commercial in Canada and Australia – Section 4: Updated "efficacy" to "effectiveness" – Section 5: ○ Removed references to subjects using 780G pump at screening ○ Week intervals updated to Visit #'s ○ Standard of care removed ○ Details added for Meal/Exercise Challenges – Section 6.1: Removed Europe, added Australia; Increased # of investigational centers – Section 7.1.4: Add minimal auto mode time to PP population – Section 7.2: Added details if normality is not met – Section 7.4: Added imputations methods when handling missing data – Section 7.5: Added pass/fail criteria verbiage – Section 7.9.1: Added details for Pass/Fail criteria and corresponding claims – Section 7.9.5.3: New section - Added sensitivity analysis using data after imputation – Section 9: Added references for margins used in primary safety and primary/secondary effectiveness endpoints.	[redacted]

Version	Summary of Changes	Author(s)/Title
4.0, 17-Jun-2024	• Following sections updated per Protocol Version E: – Add Protocol version to cover page – Section 3.1: Background – Section 5: Investigational Plan – Study Design • Section 7.4: Added imputation method for Visit 11 and Visit 13 • Section 7.9.5.2: Updated method of generating pseudo-site data • Section 7.9.6: Add subgroup analysis by age group	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviations	
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ID	Identification
ISO	International Organization for Standardization
ITT	Intention to Treat
NGSP	National Glycohemoglobin Standardization Program
PP	Per Protocol
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
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious 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 in the SmartGuard feature, 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 Canada, Australia, and the United States. Previous clinical investigations involved the 670G Version 4.0 pump (contains the 780G 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 Fiasp insulin. Additional details for non-clinical/clinical testing are provided in the report of prior investigations/ Investigator's Brochure (IB).

3.2 Purpose

The purpose of this study is to evaluate the safety and effectiveness of the MiniMed 780G system in type 1 adult and pediatric subjects utilizing Fiasp (insulin aspart injection) in a home setting.

4. Study Objectives

The objective of this study is to evaluate the safety and effectiveness of the MiniMed 780G system utilizing insulin Fiasp (insulin aspart injection) to support product and system labeling.

5. Investigational Plan – Study Design

This global 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 Fiasp insulin 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 should be completed in 30 days.

Companions:

Subjects will be required to have a companion who resides (or will live) in the same building (or home) during the study at night, and also to be physically present in the same building, home or location (if not at home) during the exercise and meal challenges. A companion should be present during meal challenges and for 4 hours following the start of the meal. Companions should be able to check SMBG, give glucose and/or administer glucagon.

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, either Humalog™ (insulin lispro injection) or NovoLog®/NovoRapid® (insulin aspart solution for injection). During the run-in period, study subjects with prior Automated Insulin Delivery (AID) control algorithm experience will be using the study pump with the SmartGuard feature activated (Auto Correction must remain OFF). and Medtronic Extended infusion set and reservoir. Subjects who do not have prior AID algorithm experience will use the system in Manual Mode. Before and during run-in period meal challenges, SmartGuard must be turned OFF, as noted in Meal Challenge instructional materials.
Note for subjects who have prior experience with the Auto Mode feature in Medtronic pumps (670G/770G): The term "Auto Mode" has been replaced by the term "SmartGuard" in the 780G pump.

During the run-in period, a 120 mg/dL (6.7 mmol/L) 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.

All subjects and their parents/caregivers as well as companions 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 and companions will be instructed that they should be with the subject in the same residence or building overnight.

If the MiniMed Clinical app/MiniMed Mobile app and the CareLink Clinical app are being used, parents/caregivers 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, companions, and parents/caregivers 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

as well as companions will also be instructed to check blood ketones using a ketone meter if the Accu-Chek Guide Link study meter reading is greater than 300 mg/dL (16.7 mmol/L).

As a precaution, subjects and their parents/caregivers will be told that they 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 will be instructed to insert sensors only in the locations that are specified in the User Guide materials. Reminders will be given to subjects at each office visit. Information about sensor insertions will be collected on an electronic case report form (eCRF) in the study database, i.e., insertion location.

Subjects and their parents/caregivers will be trained on all parts of the device system. This training may include access to and use of digital online learning content. A training checklist for both subjects and parents/caregivers will be implemented and completed.

The completion of emergency response training, including the use of a ketone meter, will be documented for companions. Companions may be trained in person or remotely.

After completion of training on the study devices, subjects and their parents/caregivers may attend additional visits in the days immediately following the start of system use, as needed. They may also take advantage of having access to the digital learning content.

Study Period (Visits 7-15):
All subjects will use Fiasp for the remainder of the study and will continue using the study pump, with SmartGuard feature enabled (including Auto Correction), infusion set and reservoir for approximately 90 days during the study period.

Subjects should use the system with the SmartGuard feature turned on at all times with Fiasp. 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., Suspend before low and Suspend on low).

During the first 3 weeks (between Visits 7 and 11) of the study period, a 120 mg/dL (6.7 mmol/L) 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 (5.5 mmol/L). 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 training on the SmartGuard function, subjects and their parents/caregivers may attend additional visits in the days immediately following the start of SmartGuard use, as needed. They may also take advantage of having access to the digital learning content.

Staged Enrollment:
The enrollment of subjects 7-17 years of age will not move forward until 10 subjects 18 years or older have completed 30 days of the study period and the Data Monitoring Committee (DMC) has determined that it is safe for 7-17 year olds to be enrolled into the study.

SMBG recommendations for 780G system:
With the 780G system and the Guardian 4 CGM, calibration is not required. However, a calibration is optional and will 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).

Meal and Exercise Challenges:
All subjects will be asked to participate in meal and exercise challenges during the run-in and study period.

- All challenges are at least 4 hours in duration, beginning from the time when the challenge meals or exercise are started.
- There should not be more than one meal challenge on a single day.
- Meal and exercise challenges should not be scheduled on the same day during the specified time periods.

For example: A study period regular sized or large sized meal challenge should not take place on the same day as an exercise challenge.

Subjects will be asked to check BG at the start of the meal/exercise, as well as 2 hours and 4 hours after the start of the meal/exercise and provide correction insulin as necessary.

Throughout the study, it is important for subjects to avoid additional meal/snack or exercise up to four hours after the start of the challenge. If additional meal/snack or exercise is needed within 4 hours after the start of the challenge, the subject will acknowledge that food intake or exercise occurred. Content

and timing of the meal and exercise, along with BG values, will be recorded on a log provided by the study team.

Meal challenges for all subjects (Run-in and Study period):

The following meal challenges are required during the run-in and study periods:

- Two meal challenges during the run-in period with subjects using the system in Manual Mode – between Visits 5 and 7
    - Regular sized meal with missed meal bolus at lunch
    - Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period with subjects using the system in SmartGuard, Auto Basal target set at 120 mg/dL (6.7 mmol/L) – between Visits 9 and 11 of study period
    - Regular sized meal with missed meal bolus at lunch
    - Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period with subjects using the system in SmartGuard, Auto Basal target set at 100 mg/dL (5.5 mmol/L) – between Visits 12 and 13 of study period
    - Regular sized meal with missed meal bolus at lunch
    - Large sized meal at breakfast, lunch or dinner
- One meal challenge during the study period with subjects using the system in SmartGuard, Auto Basal target set at currently set Auto Basal target – at any time after Visit 13 of study period
    - Large sized meal at breakfast, lunch or dinner

Meal challenges should only start if the following conditions are met:

- SMBG at start of meal is < 200 mg/dL (11.1 mmol/L)
- Sensor glucose is available.

Timing	Settings/Conditions	Meal Size	Meal Type	Notes
Run-in Period between visits 5 and 7	Manual Mode only **Missed meal bolus**	Regular sized meal	Lunch	Meal content, meal size and time of meal consumption should be established so that regular sized meal challenges during the study period can be matched
Run-in Period between visits 5 and 7	Manual Mode only	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should be established so that large sized meal challenges during the study period can be matched
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL [6.7 mmol/L] setpoint) **Missed Meal bolus**	Regular sized meal	Lunch	Meal content, meal size and time of meal consumption should match regular meal taken during run-in and the regular meal taken at the 100 mg/dL (5.5 mmol/L) setpoint
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL [6.7 mmol/L] setpoint)	Large sized meal	Breakfast, Lunch or Dinner	Meal content, meal size and time of meal consumption should match meal at Setpoint of 100 mg/dL (5.5 mmol/L) and run-in period meal
Study Period,	SmartGuard	Regular	Lunch	Meal content, meal size and time of

between Visits 12 and 13	(100 mg/dL [5.5 mmol/L] setpoint) **Missed meal bolus**	sized meal		meal consumption should match regular meal taken during run-in and the regular meal taken at the 120 mg/dL (6.7 mmol/L).
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL [5.5 mmol/L] setpoint)	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should match meal at Setpoint of 120 mg/dL (6.7 mmol/L) and run-in period large sized meal
Study Period Any time after Visit 13	SmartGuard (with current Auto Basal target setpoint)	Large sized meal	Breakfast Lunch or Dinner	Meal content, meal size and time of meal consumption should match large meal at Setpoint of 120 mg/dL (6.7 mmol/L)/100 mg/dL (5.5 mmol/L) and run-in period large sized meals

Regular Sized Meal Challenge with Missed Meal Bolus:

Between Visits 5 and 7 for the run-in period, while subjects are in Manual Mode with CGM, they will be asked to consume a meal without administration of a Meal Bolus at lunch. The size of the meal should be equivalent to what subjects would normally eat at this mealtime.

During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL[6.7 mmol/L] and 100 mg/dL[5.5 mmol/L]), subjects will be asked to consume the same regular sized lunch meal that they had during the run-in period. For example, if the regular sized meal was consumed without an insulin bolus for the meal at 12 pm during the run-in period, that same regular sized meal should be consumed at approximately the same time of day at each setpoint during the study period.

Large sized Meal Challenges:

On large sized meal challenge days, subjects will be instructed to eat at least 1 meal with at least 50% higher caloric intake including 50% more carbohydrates and 50% higher in fat. It is recommended that subjects eat food at restaurants or consume prepared meals. The FoodPrint™ phone app (as well as questions that will be asked by the investigational center staff during visits following meal challenges) will be used to collect information about type of food, name of restaurant (if applicable), subject confirmation that the meal eaten was different from any meal eaten within the last month and subject confirmation that meal size was at least 50% more than when subjects usually consume in terms of calories, carbohydrates and fat. The timing of the meal challenges will be at the investigator's discretion. The subject's parent/caregiver should be physically present in the same building, home or location (if not at home) during the meal challenge (and for 4 hours following the start of the meal), must be able to check SMBG (in case it is needed), and give glucose/administer glucagon as needed.

Exercise Challenge for all subjects (Study Period only):

The following exercise challenges are required during the study period:

- 2 exercise challenges at setpoint of 120 mg/dL (6.7 mmol/L, between Visits 9 and 11 of the study period)

- 2 exercise challenges at setpoint of 100 mg/dL (5.5 mmol/L, between Visits 12 and 13 of the study period)
- 1 exercise challenge at currently set Auto Basal target, at any time after Visit 13 of the study period

Conditions at start of the exercise challenges:

- SG should be present at the start of each exercise challenge
- The investigator or his/her staff will determine the minimum BG for each subject at the start of each exercise challenge. It will be noted on the subject's exercise log.

Timing	Settings/Conditions	Exercise duration	Notes
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL [6.7 mmol/L] setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 9 and 11	SmartGuard (120 mg/dL [6.7 mmol/L] setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL [5.5 mmol/L] setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period, between Visits 12 and 13	SmartGuard (100 mg/dL [5.5 mmol/L] setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period Any time after Visit 13	SmartGuard (with current Auto Basal target setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge

Exercise Challenges Details:

To fulfill the exercise challenge requirement, subjects will be asked to engage in 0.5 up to 1.5 hours of physical exercise. During this time, subjects should use either the Auto Basal setpoint target of 100 mg/dL (5.5 mmol/L) or 120 mg/dL (6.7 mmol/L) (depending on what is required at that time of the study period) unless a subject prefers to use the 150 mg/dL (8.3 mmol/L) target before, during and immediately after the exercise challenges. The FoodPrint™ phone app (as well as questions that will be asked by the investigational center staff during visits following exercise challenges) will be used to collect information about exercise type, date, time (start and finish of exercise), duration and name of the parents/caregivers/ companion present. The timing of the exercise challenge will be at the investigator's discretion. A photograph should be taken on each day of the exercise challenges to indicate where the exercise took place. Subjects may also use a Smartphone app to document their exercise. The subject's parents/caregivers/companion must be physically present in the same building, home or location (if not at home) during the exercise challenge, must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. Examples of types of exercise include, but are not limited to:

- Running
- Cycling
- Swimming
- Hiking
- Walking
- Games (e.g. Wii interactive video games)
- Indoor/outdoor playground (Pediatric subjects)
- Yoga/stretching
- Any sport activity that involves ongoing physical movement (e.g., tennis, golf, basketball, volleyball, soccer)
- Dancing
- Zumba
- Aerobics
- Spinning

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, Canada, and Australia 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	All Pediatric	Minimum 100 Subjects
	Age 7 - 13 years	Minimum 20 Subjects
	Age 14 - 17 years	Minimum 20 Subjects
Adult Age 18 - 80 years	N/A	Minimum 100 Subjects

A minimum of 10 subjects and a maximum of 40 subjects is targeted for enrollment at each investigational center to ensure that the results from the individual investigational center may be pooled for analysis.

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

[redacted]

[redacted]

[redacted]

[redacted]

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 in the listings.

7.1.4 Analysis Sets

- Intention to Treat (ITT) Population

  The ITT population will include all subjects who start the study. 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 Auto Mode ≥ 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. In addition, the mean, median, min, and max will be presented when the 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.

[redacted]

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 of primary safety, primary effectiveness and secondary effectiveness endpoints for age 18-80 and age 7-17. The pass/fail criteria (see section 7.9.1) are established independently for each age cohorts.

7.5.1 Age 18-80

For the following endpoints from age 18-80, the procedure test hierarchically the ordered hypotheses in sequence 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%[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 [3.9 -10.0 mmol/L]) will be estimated and compared to a threshold of 73.7% by a non-inferiority test with a margin of 7.5%[5,6] and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 18-80: The mean % of time in hypoglycemia (< 54 mg/dL [3.0 mmol/L]) will be estimated and compared to a threshold of 0.86% by a non-inferiority test with a margin of 2%[7] and a significance level of 0.025 (one-sided).
- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) 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 hierarchically the ordered hypotheses in sequence 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%[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 [3.9 -10.0 mmol/L]) will be estimated and compared to a threshold of 65.3% by a non-inferiority test with a margin of 7.5%[5,6] and a significance level of 0.025 (one-sided).

Secondary Effectiveness Endpoints

- Age 7-17: The mean % of time in hypoglycemia (< 54 mg/dL [3.0 mmol/L]) will be estimated and compared to a threshold of 0.71% by a non-inferiority test with a margin of 2%[7] and a significance level of 0.025 (one-sided).
- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL [3.9 -10.0 mmol/L]) 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 goal of the study for each age cohort (age 18-80 and age 7-17) is to evaluate both primary safety and primary/secondary effective endpoints according to the predefined threshold per cohort. Once all effective endpoints are met, the claim of superiority will be made.
- The goal of study for each age cohort (age 18-80 and age 7-17) will be also considered met when the evaluation criteria of both primary safety and effective endpoints meets the predefined threshold per cohort. However, the claim of non-inferiority will not be made.

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%[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 utilizing insulin Fiasp (insulin aspart injection) 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%[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 utilizing insulin Fiasp (insulin aspart injection) 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%[5,6]. 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 utilizing insulin Fiasp (insulin aspart injection) 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%[5,6]. 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 utilizing insulin Fiasp (insulin aspart injection) for age 7-17 will be concluded if null hypothesis is rejected.

7.9.4 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%[7]. 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 utilizing insulin Fiasp (insulin aspart injection) 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 utilizing insulin Fiasp (insulin aspart injection) 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%[7]. 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 utilizing insulin Fiasp (insulin aspart injection) 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 utilizing insulin Fiasp (insulin aspart injection) for age 7-17 will be concluded if null hypothesis is rejected.

7.9.7 Safety Data Summarized

- 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

7.9.8 Device Deficiencies

Descriptive summary will be used to characterize Device Deficiencies:

- All reports of device issues.

[redacted]

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

[redacted]

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

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