Statistical Analysis Plan	
Clinical Investigation Plan Title	Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adult and Pediatric Subjects
Clinical Investigation Plan Identifier	CIP321
Clinical Investigation Plan Version	Version D
Sponsor/Local Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Document Version	Version 3.0

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]
2.0	Updated, corresponding to the CIP Version B.1	[redacted]
3.0	Updated, corresponding to the CIP Version D • Update the following sections to reflect the use of the 780G system in continued access period. ▪ Background ▪ Purpose ▪ Objectives ▪ Endpoints ▪ Investigation Plan ▪ General Methodology • Update the font, spacing and format to achieve the consistency for following sections. ▪ Endpoints ▪ Handling of Missing, Unused, and Spurious Data and Dropouts ▪ Health Outcomes Analyses ▪ Changes to Planned Analysis ▪ Validation Requirements	[redacted] Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
CGM	Continuous Glucose Monitoring
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HbA1c	Glycosylated hemoglobin
SAE	Serious Adverse Event

SADE	Serious Adverse Device Events
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
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, including sensor-augmented pump therapy, experience improvements in glycemic control. Advanced features of sensor-augmented pump therapy are now being used in clinical practice; these include automatic suspension of insulin delivery when a pre-set glucose threshold is reached (low glucose suspend) or is predicted to be reached (predictive low glucose suspend). Both approaches have shown that a significant reduction in the risk and burden of hypoglycemia can be achieved, especially in patients who are prone to experiencing hypoglycemia.

Parallel to these approaches to mitigate the risk of hypoglycemia, more progressive advancements in technology can link insulin delivery directly to glucose levels. Closed-loop insulin delivery is different from conventional pump therapy and low glucose management technology because it uses a control algorithm to automatically adjust insulin delivery based on subcutaneous sensor data to improve diabetes management. Manual meal-time announcement and prandial insulin boluses still need to be carried out by patients in order to overcome the delay in insulin action of currently available insulin analogues. The 'hybrid' closed-loop approach is in contrast to a 'fully' closed-loop approach, in which user input to the control algorithm related to meals would not be required.

Medtronic has conducted numerous studies to evaluate hybrid closed loop technology. After completing a variety of feasibility studies with the hybrid closed loop algorithm, 2 separate pivotal trials were initiated to show that the use of hybrid closed loop technology (MiniMed™ 670G system) is safe in both adults and children over the age of 2.

In the young adult/adult pivotal study, patients aged 14 to 75 years with type 1 diabetes were recruited from 10 centers (9 in the United States, 1 in Israel)

The pediatric pivotal study was conducted as an at-home, multi-center study, which enrolled 162 participants ages 2-13 years of age. Patients were recruited at 11 centers (10 in the United States, 1 in Israel). The study was identical in design to the young adult/adult pivotal study.

Study results in the pediatric study mirrored data from the pivotal trial of the system in adults and adolescents (14 and above), showing patients spent more time in euglycemic range, experienced less glycemic variability, had less exposure to hypoglycemia and hyperglycemia and significantly reduced HbA1c compared to baseline data where they used sensor-augmented pumps. No episodes of severe hypoglycemia or diabetic ketoacidosis and no serious device-related adverse events were reported.

The Advanced Hybrid Closed Loop system (AHCL) is based on the MiniMed™ 670G hybrid closed loop system currently in commercial distribution in the United States, Canada and Europe but includes enhancements intended to reduce the frequency of Auto Mode exits and decrease the time spent in hyperglycemia relative to the current MiniMed™ 670G system. Additionally, patients using the AHCL system will not be required to confirm sensor glucose using SMBG measurement before making therapy adjustments based on displayed sensor glucose values. This investigation is designed to confirm that these enhancements to the system's closed loop algorithm and the elimination of the requirement for confirmatory SMBG measurements do not have any adverse impact on safety and efficacy.

During the continued access period, subjects will be using the 780G insulin pump, which may include a new transmitter (Guardian™ 4 transmitter) that contains a new sensor algorithm that converts raw signals into sensor glucose values without the need for entry of fingerstick calibration values. The accuracy of the sensor glucose values provided using this new algorithm was characterized by applying the algorithm to raw data collected during a prospective investigation that included frequent sample testing with either YSI or SMBG reference values. In silico modeling confirmed that glycemic outcomes during 780G Auto Mode operation using sensor values produced by the new sensor algorithm were similar to the outcomes when using the current algorithm which requires at least two calibrations per day.

The algorithm in the 780G insulin pump is functionally equivalent to the algorithm in the 670G, version 4.0 AHCL, insulin pump. Aside from a number of differences in the user interface, the method of telemetry is different in the 780G system, because it utilizes Bluetooth communication between devices and to upload pump data to CareLink™ via a smartphone device. The user experience is enhanced through the availability of smartphone apps that allow for uploading of pump data to CareLink™ and the remote monitoring of data that has been uploaded to CareLink™.

3.2 Purpose

The purpose of this study is to evaluate the safety of the Advanced Hybrid Closed Loop system (AHCL) in type 1 diabetes adult and pediatric subjects in a home setting. In addition, during the continued access period, all remaining subjects will receive the 780G insulin pump system to evaluate subject safety.

4. Study Objectives

4.1 Objectives

Primary Objective(s)

The objective of the study is to collect in-home data using the AHCL system. For the initial part of the study, the 670G insulin pump system, version 4.0 AHCL, is being used; during the continued access period the 670G system will be replaced by the 780G insulin pump system.

4.2 Endpoints

4.2.1 Descriptive Endpoints – During Study Period

- The mean change in HbA1c will be presented from baseline to end of study
- Change of Total Daily Dose (TDD) of insulin from baseline to end of study
- Change of weight from baseline to end of study
- Time spent in Auto Mode versus time spent in Manual Mode
- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, SG > 140, 180, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL
- Change in BG values during meal challenge (BG prior and BG 2 hours after meal)
- Change in % of time in euglycemia (70-180 mg/dL) during meal challenge, prior and 2 hours after meal
- Difference in AUC during meal challenge prior and 2 hours after meal
- Subgroup analysis will be performed for:
    - Age
        - 7-13
        - 14-75
    - Setpoint
        - 100 mg/dL
        - 120 mg/dL

- Temp Target usage
  - Yes
  - No

4.2.2 Descriptive Endpoints – During Continued Access Period

Descriptive Endpoints for Continued Access

- Time in Target Range (TIR, 70 – 180 mg/dL)
- Time Below Range (TBR, SG < 70 mg/dL)
- Time Above Range (TAR, SG > 180 mg/dL)
- Time in different range (% of SG): SG < 54, 60 mg/dL, SG > 140, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54, 60, and 70 mg/dL
- Time spent in Auto Mode versus time spent in Manual Mode
- The mean change in HbA1c , if applicable
- Change of Total Daily Dose (TDD) of insulin

4.2.3 Safety Endpoint – During Study Period and Continued Access

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

4.2.4 Device Deficiencies – During Study Period and Continued Access

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

4.2.5 Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP321 AHCL Questionnaire Guide for administration details.

5. Investigation Plan

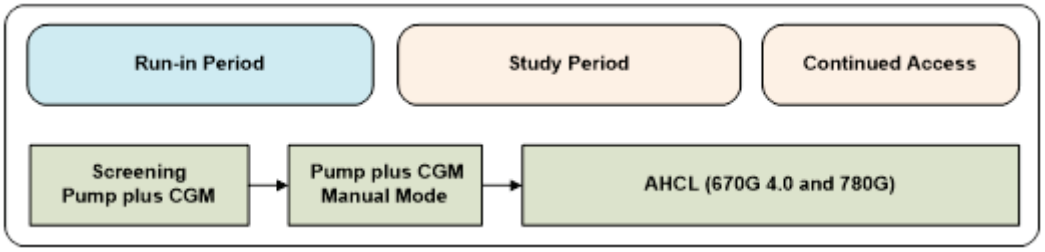
This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes. The study period will be approximately 90 days long. It will be followed by a continued access period, during which subjects who have completed the entire study period will be given the opportunity to continue using investigational study devices until those devices are approved by the FDA for commercial use and are commercially available. They will be provided with a revised consent form and will sign it prior to continuing. Subjects who have already completed the study period will be given the opportunity to re-enter the study, if they elect to continue using the system. They will also sign the revised consent form.

A total of up to 350 subjects (aged 7-75) will be enrolled at up to 30 investigational centers in the US in order to achieve the following:

- N=125 subjects 14-75 years of age with type 1 diabetes who will complete the study
- N=125 subjects 7-13 years of age with type 1 diabetes who will complete the study

Staged enrollment:

- Subjects 7-13 years of age may be enrolled after N=15 subjects 14 -75 years with type 1 diabetes have finished 30 days of the study period. The Data Monitoring Committee (DMC) will review the subjects' data. Enrollment of subjects 7-13 years of age may begin after DMC approval.



Overview of the Run-in and Study Periods:

Run-in Period:

The run-in period will be used to allow subjects to become familiar with new study devices. During the run-in period study subjects will be using the Study Pump (MiniMed™ 670G, version 4.0 AHCL) with only the Sensor Augmented Pump function activated (i.e. SmartGuard™ Auto Mode is turned OFF). All subjects and their caregivers 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 oral glucose and glucagon in case of hypoglycemia.

For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hypoglycemic event, severe hyperglycemic event or Diabetic Ketoacidosis (DKA). As a precaution, subjects 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) 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 will be instructed to insert glucose 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.

Regular Sized Dinner Challenge with Missed Meal Bolus:

On the day prior to attending Visit 5, while subjects are in manual mode with CGM, they will be asked to consume dinner without administration of a Meal Bolus. The size of the meal should be their standard amount. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the meal and provide correction as necessary. Content and timing of the meal, along with BG values, will be recorded on the Meal Challenge log. This missed dinner bolus challenge should only start if the following conditions are met:

- SMBG at start of meal is $\leq$ 200 mg/dL
- Sensor glucose is available.

Study Period:

Having met all criteria, subjects will proceed to the study period, which begins at Visit 5. All subjects will continue using the study pump and will use Auto Mode for 90 days during the study period.

Subjects should use the system in Auto Mode at all times. If subjects are exited from Auto Mode, they should try to mitigate and return to Auto Mode as soon as possible. During times when subjects are not able to use Auto Mode, they should use the remaining SmartGuard™ features (i.e. Suspend before Low).

Setpoint in the study pump:

The sponsor will provide guidance on the starting setpoint for subjects based on cohorts listed below:

- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.

- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period

The investigator has the discretion to start subjects at either the 100 mg/dL or 120 mg/dL setpoints, while the Sponsor will ensure that the required minima for each setpoint are being met. Regardless of which setpoint is being set at the beginning of the study period, subjects should attempt to change the setpoint after 45 days (+/- 5 days) of the study period. For example: A subject who starts at the 100 mg/dL setpoint, should attempt to change the setpoint to 120 mg/dL after 45 days.

Meal challenges (Run-in and Study period):

The table below summarizes all meal challenges in the study.

- All meal challenges should only start if the following conditions are met:
  - SMBG at start of meal is ≤ 200 mg/dL
  - Sensor glucose is available.

Run-in period; Regular sized meal with missed Meal Bolus challenge				
Timing	**Type of challenge**	**Day**	**Meal(s)**	**Notes**
Run-in	Missed Meal Bolus (regular sized meal)	Day prior to V5	Regular sized Dinner	If the subject qualified to stay in Auto Mode during the Run-In Period, they must turn off Auto Mode for at least 6 hours prior to the start of the Missed Meal Bolus Challenge.
Study period; Meal challenges				
Setpoint	**Type of challenge**		**Meal(s)**	**Notes**

Study Period (100 mg/dL setpoint)	Large sized meals	Day 1	Large sized Breakfast **and** Large sized Dinner	Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.**
Study Period (100 mg/dL setpoint)	Large sized meals	Day 2	Large sized Breakfast **and** Large sized Dinner	Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.**
Study Period (100 mg/dL setpoint)	Large sized meal	Day 3	Large sized Breakfast	Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.**
	Missed Meal Bolus		Regular sized dinner meal	Meal composition, meal size and time of meal consumption should match **Run-in period** meal
Study Period (100 mg/dL setpoint)	Missed Meal Bolus with Large sized meal	Day 4	Large sized Dinner	Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.**
Study Period (120 mg/dL setpoint)	Large sized meals	Day 1	Large sized Breakfast **and** Large sized Dinner	Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.**
Study Period (120 mg/dL setpoint)	Large sized meals	Day 2	Large sized Breakfast **and** Large sized Dinner	Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.**
Study Period (120 mg/dL setpoint)	Large sized meal	Day 3	Large sized Breakfast	Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.**
	Missed Meal Bolus		Regular sized dinner meal	Meal composition, meal size and time of meal consumption should match **Run-in period** meal
Study Period (120 mg/dL setpoint)	Missed Meal Bolus with Large sized meal	Day 4	Large sized Dinner	Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.**

- **Regular Sized Dinner Challenge with Missed Meal Bolus**

During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL and 100 md/dL) on Day 3 of the multi-day meal challenge, subjects will be asked to consume the ***same regular sized dinner that they had during the run-in period***. For example, if the dinner meal was consumed without an insulin bolus for the meal at 5 pm during the run-in period, that same dinner meal should be consumed at approximately the same time on Day 3 at each setpoint during the study period. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the start of the meal and provide correction as necessary. Details should be recorded, along with BG values, on the Meal Challenge log.

- **Large sized Meal Challenges:**

  On large sized meal challenge days, all 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 than what the subject reports that he/she usually eats. It is recommended that subjects eat food at restaurants or consume prepared meals (e.g. things like turkey and stuffing), which have not been eaten during the last month. A log will be used to collect information about type of food, name of restaurant (if applicable), confirmation that the meal eaten was different from any meal eaten within the last month and confirmation that meal size was at least 50% more than when subjects usually consume in terms of calories, carbohydrates and fat. The log should also contain the time and date of the meal, as well as confirmation that a BG was taken at the start of the meal, 2 hours after the start of the meal and 4 hours after the start of the meal. The timing of the meal challenges will be at the investigator's discretion. The subject's companion must 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. This challenge will include a missed Meal Bolus on Day 4. See Table above.

Exercise Challenges (Study Period):

The following exercise challenges should occur during the study period:

- 3 consecutive days of exercise challenge at setpoint of 100 mg/dL
- 3 consecutive days of exercise challenge at setpoint of 120 mg/dL

- **Exercise Challenges Details**

  On exercise challenge days, all subjects will be required to engage in 1-2 hours of physical exercise each day. During this time, subjects should use the Auto Basal setpoint target of

100 mg/dL or 120 mg/dL (depending on what is required at that time of the study period), unless a subject prefers to use the 150 mg/dL target before, during and immediately after the exercise challenges. For the remainder of days, the temporary target will be set at the Investigator's discretion. A log will be used to collect information about exercise type, date, time (start and finish of exercise), duration and name of the companion. The log should also contain confirmation that SMBG was done at the beginning of exercise, as well as 2 and 4 hours after the start of the exercise. The timing of the exercise challenge will be at the investigator's discretion. A photograph should be taken on each day of the exercise to indicate that exercise took place. Subjects may also use a Smart Phone application to document their exercise. The subject's 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 which involves ongoing physical movement (i.e., tennis, golf, basketball, tee ball or volleyball)
- Dancing
- Zumba
- Aerobics
- Spinning

Continued Access period:

At the end of the study period, subjects will have the opportunity to continue using the AHCL system at home until the Sponsor receives FDA approval to commercialize the products and system is commercially available. During the continued access period, subjects will be asked to use the system as intended and to upload device data on a weekly basis. See Visit Schedule tables for frequency of device uploading. Office visits will be required at 3 month intervals.

Continued Access Period expansion:

During the continued access period, all participating subjects will transition from the 670G system, version 4.0 AHCL, to the 780G system which features Bluetooth® connectivity. The CGM used with 780G will be Guardian™ 4 Transmitter with the Guardian™ Sensor (4). Subjects will continue to use the 780G system at home until the sponsor notifies sites to end subjects' study participation. The MiniMed™ Clinical App and the Medtronic CareLink™ Clinical App will be used by subjects when they are available.

SMBG recommendations:
Typically, one SMBG is required every 12 hours for calibration. Routine SMBG is not required. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in Auto Mode. For study purposes, subjects will be instructed to perform SMBG if they are feeling low (but sensor glucose is not low) and if they are experiencing a severe hypoglycemic event, a severe hyperglycemic event or DKA.

Companions:
Subjects will be required to have a companion who resides (or will live) in the same building (or home) during the proposed 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 (in case it is needed), give glucose or administer glucagon.

5.1 Duration

The study is anticipated to last no longer than 18 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 6 months to complete subject enrollment. Subjects can expect to participate for approximately 4-5 months between the run-in period and study period. The continued access period may lengthen the overall duration of the study considerably.

5.2 Rationale

The design of this study as a single arm trial with safety and effectiveness endpoints represents the next step in the development of a closed loop insulin delivery system. Iterative changes in the control algorithm, which include additional levels of automation, require a study design equivalent to the design that was approved in the study of the predecessor MiniMed™ 670G system.

6. Determination of Sample Size

A total of up to 350 subjects (aged 7-75) will be enrolled at up to 30 investigational centers in the US in order to reach 250 subjects who will complete the study (125 for 14-75 years old and 125 for 7-13 years old).

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects enrolled in the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

- Intention to Treat (ITT) Population

  The Intention to Treat (ITT) population will include all subjects who start the study period (which means subjects must enter auto mode).

- Per Protocol (PP) Population

  The Per Protocol (PP) population will include all subjects who complete the study period, are in Auto Mode ≥ 80% of the time and without major deviations.

- Efficacy Population

  The primary analysis will be performed on the ITT population. Sensitivity analysis will be performed on PP population.

- Safety Population

  The Safety Population will include all enrolled subjects (subjects who signed inform consent form).

7.2 General Methodology

7.2.1 Descriptive Endpoints – During Study Period

- The mean change in HbA1c will be presented from baseline to end of study
- Change of Total Daily Dose (TDD) of insulin from baseline to end of study

- Change of weight from baseline to end of study
- Time spent in Auto Mode versus time spent in Manual Mode
- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, SG > 140, 180, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL
- Change in BG values during meal challenge (BG prior and BG 2 hours after meal)
- Change in % of time in euglycemia (70-180 mg/dL) during meal challenge, prior and 2 hours after meal
- Difference in AUC during meal challenge prior and 2 hours after meal
- Subgroup analysis will be performed for:
    - Age
        - 7-13
        - 14-75
    - Setpoint
        - 100 mg/dL
        - 120 mg/dL
    - Temp Target usage
        - Yes
        - No

7.2.2 Descriptive Endpoints – During Continued Access Period

Descriptive Endpoints for Continued Access

- Time in Target Range (TIR, 70 – 180 mg/dL)
- Time Below Range (TBR, SG < 70 mg/dL)
- Time Above Range (TAR, SG > 180 mg/dL)
- Time in different range (% of SG): SG < 54, 60 mg/dL, SG > 140, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54, 60, and 70 mg/dL
- Time spent in Auto Mode versus time spent in Manual Mode
- The mean change in HbA1c , if applicable
- Change of Total Daily Dose (TDD) of insulin

7.2.3 Safety Endpoint – During Study Period and Continued Access

- Serious Adverse Events (SAE)

- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

7.2.4 Device Deficiencies – During Study Period and Continued Access

Descriptive summary will be used to characterize all reports of device issues.

7.2.5 Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP321 AHCL Questionnaire Guide for administration details.

7.3 Center Pooling

Data will be pooled for analysis.

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

No imputation will be applied. Analysis will be done by all available data.

7.5 Adjustments for Multiple Comparisons

Not applicable.

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, 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 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

Not applicable.

7.9 Evaluation of Objectives: Exploratory Analysis

7.9.1 Analysis of Primary Safety Endpoint

The overall mean difference of the change in HbA1c from baseline to end of 3-month study period. The goal is to show simple superiority in reducing HbA1c from baseline to end of 3-month study period.

7.9.2 Analysis of Primary Effectiveness Endpoint

The primary effectiveness endpoint is change in % of time in euglycemia (70 – 180 mg/dL).

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

7.9.3 Analysis of Secondary Effectiveness Endpoint

The secondary effectiveness endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study period.

Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

Secondary Endpoint: % of Time in Hyperglycemia (> 140 mg/dL)

The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

7.9.4 A Suspected Missed Meal Analysis

A suspected Meal event with missed meal Bolus during home use will be detected by an algorithm, developed by Medtronic. The impact of a missed meal bolus will be analyzed.

7.9.5 Sample Size Justification for Exploratory Analysis

7.9.5.1 Sample Size for Primary Safety Endpoint

The overall mean change in HbA1c from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of % of change in HbA1c (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in HbA1c is less than 0%.

Assuming the mean difference of change in HbA1c from baseline to the 3-month visit is 0.4%, the standard deviation of change in HbA1c is 1.1%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition

7.9.5.2 Sample Size for Primary Effectiveness Endpoint: % of Time in Euglycemia (70- 180 mg/dL)

The overall mean change in % of time in euglycemia (70- 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \leq 0\%$

Ha: $\mu > 0\%$

Where μ is the mean of change in % of time in time in euglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% lower confidence limit of the mean change in % of time in Time in Range is greater than 0%.

Assuming the mean of change in time in time in euglycemia (%) from baseline to the 3-month visit is 4.0%, the standard deviation of change in percentage time in Time in Range is 11.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

7.9.5.3 Sample Size for Secondary Effectiveness Endpoint

7.9.5.3.1 Sample Size for Secondary Effectiveness Endpoint: % of Time in >180 mg/dL

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hyperglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hyperglycemia is less than 0%.

Assuming the mean of change in time in hyperglycemia from baseline to the 3-month visit is 3.0%, the standard deviation of change in percentage time in hyperglycemia is 8.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

7.9.5.3.2 Sample Size for Secondary Effectiveness Endpoint: % of Time in >140 mg/dL

The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hyperglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hyperglycemia is less than 0%.

Assuming the mean of change in time in hyperglycemia from baseline to the 3-month visit is 4.0%, the standard deviation of change in percentage time in hyperglycemia is 10.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

7.9.5.3.3 Sample Size for Secondary Effectiveness Endpoint: % of Time in <70 mg/dL

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hypoglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hypoglycemia is less than 0%.

Assuming the mean of change in time in hypoglycemia from baseline to the 3-month visit is 3.5%, the standard deviation of change in percentage time in hypoglycemia is 10.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

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 (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

7.11 Health Outcomes Analyses

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

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

American Diabetes Association. Hyperglycemic Crises in Diabetes. Diabetes Care. 2004; 27(1):S94-S102.

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Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697–703.