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Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	IMPACT2: In-Home Study with MiniMed™ 780G Pump Automated Control in Type 2 – Evaluation of the AHCL System in Adults with Insulin-requiring Type 2 Diabetes
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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, 17-SEP-2022	• Deleted "Clinical Investigation Plan Version" • Updated "Background" to align with protocol version C • Deleted endpoints from "Study Objectives" • Updated "Investigation Plan" to align with protocol version C • Updated "Duration" to align with protocol version C • Added "General Aspects of Analysis" • Updated "Analysis Sets" • Updated "Handling of Missing, Unused, and Spurious Data and Dropouts" • Updated "Evaluation of Objectives" • Updated "Descriptive Endpoints" to align with protocol version C • Updated "Safety Evaluation" • Added "Continued Access Period" throughout • Administrative changes throughout	[redacted]
3.0, 27-APR-2023	• Updated "List of Abbreviations and Definitions of Terms" to align with protocol version D • Updated "Introduction" to align with protocol version D • Updated "Study Objectives" to align with protocol version D • Updated "Investigation Plan" to include both phases and to align with protocol version D • Updated "Determination of Sample Size" to include both phases • Updated "Statistical Methods" to align with protocol version D • Administrative changes, including formatting, throughout	[redacted]

Version	Summary of Changes	Author(s)/Title
4.0, 11-APR-2024	• Updated "List of Abbreviations and Definitions of Terms" to align with protocol version F • Updated "Introduction" to align with protocol version F • Updated "Investigation Plan" to align with protocol version F • Updated "Determination of Sample Size" to align with protocol version F • Updated "Disposition of Subjects" • Updated "Statistical Methods" to align with protocol version F	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AID	Automatic Insulin Delivery
AUC	Area Under Curve
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HHS	Hyperglycemic Hyperosmolar syndrome (HHS)
PP	Per Protocol
SADE	Serious Adverse Device Events
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
TIR	Time in Range
UADE	Unanticipated Adverse Device Effect

3. Introduction

3.1 Background

Type 2 diabetes mellitus, formerly known as non-insulin dependent diabetes and mature-onset diabetes, is characterized by a lack of insulin (reduced secretion that can reach an absolute lack) or insulin resistance (reduced insulin sensitivity of insulin receptors in cell membranes). In adults, type 2 diabetes accounts for 90–95% of all diagnosed cases of diabetes. [1] The exact cause of type 2 diabetes remains unknown, although both genetics (race/ethnicity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism) and environmental factors (obesity and lack of exercise) appear to play roles. [2, 3] Type 2 diabetes usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. The pancreas initially responds by increasing insulin production but over time this excess production cannot be maintained, leading to a decrease in insulin production and a lack of insulin.

Algorithm driven closed-loop systems enable automated subcutaneous delivery of insulin in response to real-time continuous glucose sensor readings. Prior Medtronic studies to date have assessed the safety and effectiveness of closed-loop insulin delivery in patients with type 1 diabetes. For some patients with type 2 diabetes whose treatment consists of diet or non-insulin glucose-lowering medications, an episode of severe illness could result in elevated glucose levels that may make it necessary to provide insulin in order to improve and optimize glucose control. Other type 2 patients are using pumps, but do not yet have access to the benefits of closed loop control. Medtronic has conducted a study of pump systems in Type 2 patients, which found that Insulin Pump therapy has a sustained, durable, effect on glycemic control in uncontrolled type 2 diabetes. [4]

The MiniMed 780G system is an advanced hybrid 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 Europe, Australia, and the United States. Previous clinical investigations involved the 670G Version 4.0 pump (contains the 780G AHCL (Advanced Hybrid Closed Loop) algorithm) used in combination with the Guardian Sensor (3) glucose sensor, Guardian Link (3) transmitter, and Humalog or Novolog. The MiniMed 780G insulin pump has also been used in combination with Guardian 4 glucose sensor and Guardian 4 transmitter.

This investigation is intended to confirm safety and effectiveness of the MiniMed 780G system in patients with type 2 diabetes. The study began with investigation of the MiniMed 780G system with the Guardian 4 Sensor/Transmitter in the type 2 diabetes population. The introduction of the 780G BLE 2.0 system with disposable sensor DS5 into the study is intended to confirm safety and effectiveness of the 780G insulin pump used in combination with the DS5; the DS5 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 system in type 2 adults in a home setting, which will support a future regulatory submission for labeling expansion.

4. Study Objectives

The objective of this study is to assess the safety and effectiveness of the MiniMed 780G system when used by adults with insulin-requiring type 2 diabetes.

5. Investigation Plan

This study is a multi-center, single arm study in adult subjects with insulin-requiring type 2 diabetes, conducted in 2 phases. Phase 1 has been completed. Subjects who participated in Phase 1 have been transitioned to Phase 2, if they consented to do so. New subjects will only participate in Phase 2.

Phase 1: MiniMed™ 780G insulin pump with Guardian 4 Sensor

Phase 1 studied the MiniMed™ 780G insulin pump with Guardian 4 Sensor. This phase is now complete.

Run-in Period (Visits 2-8):

The run-in period begins at Visit 2 and ends once Visit 9 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/NovoRapid (insulin aspart solution for injection), or Admelog (insulin lispro injection).

During the run-in period of the study, subjects will be using the study pump in Manual Mode, with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard feature turned OFF). The "Suspend before Low" and "Suspend on Low" features may be used.

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 [i.e., AID]) in non-Medtronic pump	Manual Mode
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction OFF

All subjects will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training by investigational center staff regarding the need to have access to and how to use glucose and glucagon in case of hypoglycemia.

Companions/care partners will be instructed that they should be with the subject in the same residence or building complex overnight.

If the MiniMed Clinical app and the Carelink Clinical app are being used, companions/care partners 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 work, other activities. Instructions on the appropriate operation of the apps will be provided.

For study purposes, subjects will be instructed to perform self-monitoring of blood glucose (SMBG) if they are experiencing a severe hypoglycemic event, severe hyperglycemic event, hyperglycemic hyperosmolar syndrome (HHS), or diabetic ketoacidosis (DKA).

- Blood ketones will be measured by all subjects using a ketone meter when:
  - the subject is symptomatic for high blood glucose or
  - the sensor glucose value is >300mg/dL, the BG is checked by fingerstick and, if BG is >300mg/dL, blood ketones should be checked

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, or insulin pen) in the event they are asked to revert back to their own therapy during the study or experience study device issues (e.g. infusion set occlusion with high glucose).

Subjects will be instructed to insert sensors only in the locations that are specified in the User Guide. Subjects should be reminded about appropriate sensor placement at each office visit. Information about predominant location of sensor insertions will be collected on an electronic case report form (eCRF) at the end of a subject's participation.

Subjects will be trained on all parts of the device system. Companions/care partners should be trained on how to respond to high or low glucose events. This should involve live training conducted by investigational center staff. A training checklist for each subject should be completed by investigational center-based trainers. Companions/care partners should be available for relevant parts or, if desired, all of this training, either in person or virtually.

After completion of training on the study devices, subjects will be asked to attend additional visits in the days immediately following the start of system use, as needed. They may also take advantage of having continued access to the digital learning content, provided it is available at study start.

Study Period (Visits 9-18):
The study period begins at Visit 9 and ends at the conclusion of Visit 18.

Subjects will continue using the study pump and study sensor and will use the SmartGuard feature for approximately 90 days during the study period. Subjects should use the system with the SmartGuard feature (with Auto Correction ON) 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, SmartGuard. During times when subjects are not able to use SmartGuard, they should use the system in Manual Mode (e.g., using Suspend before low and Suspend on low settings).

Pump Settings:

During the first 3 weeks (between Visits 9 and 14) 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 at the investigator's discretion.

During the next 3 weeks (between Visits 14 and 16) of the study period, a 100 mg/dL Auto Basal Target should be set. Active Insulin Time is recommended to be set to 2-3 hours or at investigator's discretion. During the remaining weeks (any time after Visit 16) 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.

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

After completion of training on SmartGuard functions, subjects 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 digital learning content, provided it is available at study start.

Staged Enrollment:
The study period will start with subjects who have a total daily insulin (TDD) requirement of 125 units or less. After 10 subjects have completed 6 weeks of the study period, the Data Monitoring Committee (DMC) will assess if it is safe to proceed with subjects using SmartGuard who have a TDD of greater than 125 units. Upon DMC approval, subjects with TDD greater than 125 units may use SmartGuard.

SMBG recommendations for 780G system:
With the 780G system and the study sensor, calibration is not required. 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 SmartGuard. 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.

- 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 size meal challenge should not take place on the same day as an exercise challenge

It is important for subjects to avoid additional meal/snack or exercise up to 4 hours after the start of each challenge. If additional meal/snack is consumed or exercise is done within 4 hours after the start of the challenge, the subject will acknowledge this on the challenge log. Subjects will be asked to check BG at the start of the meal/exercise, as well as 2 hours and 4 hours after the meal/exercise and take bolus correction as necessary. Content and timing of the meal and exercise, along with answers to challenge questions, 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 (between Visits 7 and 9) with subjects using the system in **Manual Mode** (SmartGuard must be turned off at least 6 hours prior to the meal challenge for subjects using it during the run-in period)
    - One Regular sized meal with *missed meal bolus* at lunch
    - One Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period (between Visits 12 and 14) with subjects using the system in SmartGuard, Auto Basal target set at 120 mg/dL
    - One Regular sized meal with *missed meal bolus* at lunch
    - One Large sized meal at breakfast, lunch or dinner
- Two meal challenges during the study period (between Visits 15 and 16) with subjects using the system in SmartGuard, Auto Basal target set at 100 mg/dL
    - One Regular sized meal with *missed meal bolus* at lunch
    - One 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 investigator's discretion – at any time after Visit 16
    - One 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
- Sensor glucose is available.

Timing	Settings/Conditions	Meal Size	Meal Type	Notes
Run-in Period between visits 7 and 9	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 7 and 9	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 12 and 14	SmartGuard (120 mg/dL 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 setpoint
Study Period between Visits 12 and 14	SmartGuard (120 mg/dL 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 and run-in period meal
Study Period between Visits 15 and 16	SmartGuard (100 mg/dL 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 120 mg/dL.
Study Period between Visits 15 and 16	SmartGuard (100 mg/dL 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 and run-in period large sized meal
Study Period Any time after Visit 16	SmartGuard (Auto Basal target setpoint at investigator's discretion)	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 /100mg/dL and run-in period large sized meals

Details about Regular Meal Challenges 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 patients would normally eat at this mealtime. 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 a log provided by the study team.

During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL and 100 md/dL), 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. 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 log.

Details about Large sized Meal Challenges:

On large sized meal challenge days, subjects will be instructed to eat one 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. A log will be used to collect information about the food that was eaten, the name of the restaurant (if applicable), and confirmation that meal size was at least 50% more in terms of calories, carbohydrates and fat. The log will also be used to record the time and date of the meal and check box 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/care partner 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). They must be able to check SMBG (in case it is needed) and give glucose/administer glucagon if required.

Exercise Challenge for all subjects (during Study Period only):

The following exercise challenges are required during the study period:

- 2 exercise challenges at setpoint of 120 mg/dL, between Visits 12 and 14
- 2 exercise challenges at setpoint of 100 mg/dL, between Visits 15 and 16
- 1 exercise challenge at investigator's discretion, at any time after Visit 16

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 12 and	SmartGuard (120 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge

14			
Study Period between Visits 12 and 14	SmartGuard (120 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period between Visits 15 and 16	SmartGuard (100 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period between Visits 15 and 16	SmartGuard (100 mg/dL setpoint)	Min 30 minutes, up to 1.5 hours	Challenge must take place on days without meal challenge
Study Period Any time after Visit 16	SmartGuard (Auto Basal target setpoint at investigator's discretion)	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 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 temp target before, during and immediately after the exercise challenges. A log will be used to collect information about exercise type, date, time (start and finish of exercise) and duration. The log should also ask a 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 challenges to indicate where the exercise took place. The subject's companion/care partner 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.

Subjects should have carbohydrates available during and after exercise, if needed for safety reasons.

If, during exercise, subjects experience any physical discomfort (e.g. chest pain, palpitations, shortness of breath, dizziness, etc.), exercise should be stopped immediately and subject should seek medical attention, if required. Subjects should contact the investigational center to report incidences of discomfort that lead to the cessation of exercise.

Examples of types of exercise include, but are not limited to:

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

Companions:

Subjects will be required to have a companion (may be care partner) 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 (Phase 1). Companions should be able to check SMBG, give glucose and/or administer glucagon.

Continued Access Period (from the end of Visit 18):

Phase 1 subjects will have the opportunity to transition into Phase 2 upon completion of Phase 1 – Study Period or at their next continued access period visit. The continued access period for Phase 1 of the study will end as soon as subjects transition to Phase 2 or exit the study.

Phase 2: MiniMed™ 780G BLE 2.0 insulin pump with Disposable Sensor 5 (DS5)

Phase 2 will study the MiniMed™ 780G BLE 2.0 insulin pump with the disposable sensor DS5.

Run-in Period (Visits 2-8):

The run-in period begins at Visit 2 and ends once Visit 9 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/NovoRapid (insulin aspart solution for injection), or Admelog (insulin lispro injection).

During the run-in period of the study, subjects will be using the study pump in Manual Mode, with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard feature turned OFF). The "Suspend before Low" and "Suspend on Low" features may be used.

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 (i.e., Automatic Insulin Delivery (AID) in non-Medtronic pump	Manual Mode
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction OFF

All subjects will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training by investigational center staff regarding the need to have access to and how to use glucose and glucagon in case of hypoglycemia.

Companions/care partners will be instructed that they should be with the subject in the same residence or building complex overnight.

If the MiniMed Clinical/MiniMed Mobile app and the Carelink Clinical app are being used, companions/care partners 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 work, other activities. Instructions on the appropriate operation of the apps will be provided.

For study purposes, subjects will be instructed to perform self-monitoring of blood glucose (SMBG) if they are experiencing a severe hypoglycemic event, severe hyperglycemic event, hyperglycemic hyperosmolar syndrome (HHS), or diabetic ketoacidosis (DKA).

- Blood ketones will be measured by all subjects using a ketone meter when:
    - the subject is symptomatic for high blood glucose or
    - the sensor glucose value is >300mg/dL, the BG is checked by fingerstick and, if BG is >300mg/dL, blood ketones should be checked

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, or insulin pen) in the event they are asked to revert back to their own therapy during the study or experience study device issues (e.g.,infusion set occlusion with high glucose).

Subjects will be instructed to insert study sensors only in the locations that are specified in the User Guide. Subjects should be reminded about appropriate study sensor placement at each office visit. Information about predominant location of study sensor insertions will be collected on an electronic case report form (eCRF) at the end of a subject's participation.

Subjects will be trained on all parts of the device system. Companions/care partners should be trained on how to respond to high or low glucose events. This should involve training conducted by investigational center staff. A training checklist for each subject should be completed by investigational center-based trainers. Companions/care partners should be available for relevant parts or, if desired, all of this training, either in person or virtually.

After completion of training on the study devices, subjects will be asked to attend additional visits in the days immediately following the start of system use, as needed. They may also take advantage of having continued access to the digital learning content, provided it is available at study start.

Study Period (Visits 9-18):
The study period begins at Visit 9 and ends at the conclusion of Visit 18.

Subjects will continue using the study pump and study sensor and will use the SmartGuard feature for approximately 90 days during the study period. Subjects should use the system with the SmartGuard feature (with Auto Correction ON) 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, SmartGuard. During times when subjects are not able to use SmartGuard, they should use the system in Manual Mode (e.g., using Suspend before low and Suspend on low settings).

Pump Settings:
During the first 3 weeks (between Visits 9 and 14) of the study period, a 120 mg/dL Auto Basal Target should be used. It is recommended that Active Insulin Time is initially set to 4 hours and then titrated towards 2-3 hours at the investigator's discretion.

During the next 3 weeks (between Visits 14 and 16) of the study period, a 100 mg/dL Auto Basal Target setting should be used. Active Insulin Time is recommended to be set to 2-3 hours or at investigator's discretion.

During the remaining weeks (any time after visit 16) 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.

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

After completion of training on SmartGuard functions, subjects 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 digital learning content, provided it is available at study start.

SMBG recommendations for 780G BLE 2.0 system:

With the 780G BLE 2.0 system and the study sensor, calibration is not required. 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 SmartGuard. 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).

Companions:
Subjects will be required to have a companion (may be care partner) who resides (or will live) in the same building (or home) during the study at night. Companions should be able to check SMBG, give glucose and/or administer glucagon.

Subjects who transitioned from Phase 1 to Phase 2
Phase 1 subjects were given the opportunity to transition into Phase 2 upon completion of the Phase 1 study period or at a subsequent continued access period visit. Transitioning subjects were expected to complete all required Visit 1 – Phase 2 activities prior to entering Visit 9 – Phase 2 and did not need to complete Visit 2 through Visit 8 of Phase 2.

5.1 Duration

For each phase, individual subject participation is expected to be approximately 135 days through the study period.

5.2 Rationale

Previous clinical investigations have confirmed the safety and clinical performance of the 780G insulin pump when used in a type 1 population in subjects 7 years of age or older. This investigation is intended to provide confirmation of the safety and clinical performance of the 780G system in a type 2 population in subjects 18-80 years of age.

6. Determination of Sample Size

A total of up to 575 subjects with insulin-requiring type 2 diabetes age 18-80 will be enrolled collectively in Phase 1 and Phase 2 at up to 40 investigational centers across the United States with at least 300 subjects entering the study period of Phase 2.
A maximum of 40 subjects may be enrolled, not inclusive of screen failures, at each investigational center.

The following sample sizes support the evaluation of the MiniMed™ 780G insulin pump with Guardian 4 Sensor and the MiniMed™ 780G BLE 2.0 insulin pump with Disposable Sensor 5 (DS5), separately.

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

7. Statistical Methods

7.1 Study Subjects

7.1.1 General Aspects of Analysis

For each phase, 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. For each phase, data and analyses will be summarized in a Clinical Study Report. Any deviations from the original statistical plan and the rationale will be described in the Clinical Study Report.

7.1.2 Disposition of Subjects

For each phase, 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 by period.

7.1.3 Clinical Investigation Plan (CIP) Deviations

For each phase, all protocol deviations will be presented in listings.

7.1.4 Analysis Sets

For each phase, the following populations will be analyzed.

- Intention to Treat (ITT) Population

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

- Per Protocol (PP) Population

  The Per Protocol (PP) population will include all subjects who complete the study period, are in SmartGuard ≥ 80% of the time, and without major deviations. Primary safety, primary effectiveness, and secondary effectiveness endpoints will be evaluated for the PP population as the sensitivity/supplementary analyses.

- Safety Population

  The Safety Population will include all enrolled subjects (subjects who signed the informed consent form). Safety adverse events data summary will be evaluated for the safety population.

7.2 General Methodology

The following will be evaluated by phase.

For each phase, summary statistics will be represented by number of subjects (n), mean, median, and standard deviation for continuous variables and by counts and percentages for categorical variables. P-values for hypothesis testing will be evaluated based on one-sided testing using a 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. For testing the statistical significance of the difference, comparisons between the outcomes in the study period and the threshold will be performed using a one-sample t-test if the normality assumption is met or a Wilcoxon signed rank test if the normality assumption is not met.

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

7.2.1 Center Pooling

For each phase, data will be pooled for analysis at the subject level. Additional sensitivity analysis will be performed for site effect in section 7.3.1.4.

[redacted]

7.2.3 Adjustments for Multiple Comparisons

For each phase, a fixed-sequence statistical strategy will be applied for primary and secondary endpoints to adjust for multiplicity and the order of the tests will be as follows: 1. Primary effectiveness and safety endpoints and 2. Secondary effectiveness endpoint. Further testing stops as soon as there is a failure of an endpoint in the sequence to show significance at level alpha (e.g., $\alpha = 0.025$).

7.2.4 Demographic and Other Baseline Characteristics

For each phase, 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.

7.2.5 Treatment Characteristics

Not applicable.

[redacted]

7.3 Evaluation of Objectives

The following endpoints will be evaluated for each of the phases, separately.

Phase 1: MiniMed™ 780G insulin pump with Guardian 4 Sensor

Phase 2: MiniMed™ 780G BLE 2.0 insulin pump with DS5

All effectiveness endpoints will be analyzed using the data from Visit 16 to the end of the study period (Auto Basal target set at investigator's discretion).

7.3.1 Study Period

7.3.1.1 Primary Safety Endpoint

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% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used.

The hypothesis of non-inferiority is mathematically expressed as:

$H_0: \Delta\mu_{780G} \geq 0\% + 0.4\%$
$H_a: \Delta\mu_{780G} < 0\% + 0.4\%$

Note: Phase 1 subjects transitioned into Phase 2 will not be included in this analysis for Phase 2.

The null hypothesis will be tested against the alternative hypothesis using a one sample t test if the normality assumption is met or a Wilcoxon signed rank test if the normality assumption is rejected. The overall mean change in HbA1c from baseline to end of 3-month study period is less than 0% with a margin of 0.4% will be concluded if the null hypothesis is rejected.

7.3.1.2 Primary Effectiveness Endpoint

The mean % of time in range (TIR 70-180 mg/dL), μ_{780G}, will be estimated and compared by a non-inferiority test to the threshold of 70% with a margin of 7.5%. A significance level of 0.025 (one-sided) will be used.

The hypothesis of non-inferiority is mathematically expressed as:

$H_0: \mu_{780G} \leqslant 70\% - 7.5\%$

$H_a: \mu_{780G} > 70\% - 7.5\%.$

The null hypothesis will be tested against the alternative hypothesis using a one sample t test if the normality assumption is met or a Wilcoxon signed rank test if the normality assumption is rejected. The mean % of time in range is greater than 70% with a margin of -7.5% will be concluded if the null hypothesis is rejected.

7.3.1.3 Secondary Effectiveness Endpoint

The mean % of time in range (TIR 70-180 mg/dL), μ_{780G}, will be estimated and compared by a simple superiority test with a significance level of 0.025 (one-sided).

The hypothesis of superiority is mathematically expressed as:

H_0: $\mu_{780G} \leq 70\%$

H_a: $\mu_{780G} > 70\%$

The null hypothesis will be tested against the alternative hypothesis using a one sample t test if the normality assumption is met or the Wilcoxon signed rank test if the normality assumption is rejected. Mean % of time in range is greater than 70% will be concluded if the null hypothesis is rejected.

7.3.1.6 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

7.3.1.7 Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP341 Questionnaire Guide for administration details.

7.3.1.8 Safety Data Summarized

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

7.3.2 Run-in Period

7.3.2.1 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

7.3.2.2 Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP341 Questionnaire Guide for administration details.

7.3.2.3 Safety Data Summarized

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

Note: For subjects participating in both Phase 1 and Phase 2, if there is an AE within the time between Phase 2 consent and Phase 2 study period, it will be attributed to the Phase 2 run-in period.

7.3.3 Continued Access Period

Only applicable for Phase 1.

7.3.3.1 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

7.3.3.2 Safety Data Summarized

- Serious Adverse Events (SAE)

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

7.4 Health Outcomes Analyses

For each phase, descriptive summary will be used to characterize data from questionnaire results.

7.5 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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