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APPROVALS

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[redacted]	Biostatistician	07/26/2024 11:38:03
[redacted]	Clinical Study Manager (CSM)	07/26/2024 11:38:59
[redacted]	Biostatistician	07/26/2024 11:54:12
[redacted]	Statistics Programmer	07/26/2024 14:50:50
[redacted]	Clinical Leadership	08/01/2024 20:07:13

Medtronic

LENNY - Statistical Analysis Plan

Clinical Investigation Plan Title	EvaLuation of thE MiNiMed 780 System iN Young Paediatric Subjects (2-6 years old) with Type 1 Diabetes in a Home Setting (LENNY)
Clinical Investigation Plan Identifier	342
Clinical Investigation Plan Version	Version E, 30 OCT 2023
Statistical Analysis Plan Version Date	Version 2.0 22 JUL 2024
Sponsor/Local Sponsor	Medtronic International Trading Sàrl [redacted]

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 23 APR 2024	Not Applicable, New Document	[redacted] / Sr Statistician
2.0 22 JUL 2024	**Par 7.1.3:** • Updated the Per Protocol population set definition to exclude participants with major protocol deviations, including now non-compliance with randomization assignment • Added definition and sensitivity purpose of "As Treated population set" for continuation phase **Par 7.10:** Specified that safety reporting will be performed by both assigned randomization treatment and actual treatment received	[redacted] Prin Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviations	
ADE	Adverse Device Effect
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AIT	Active Insulin Time
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
CV	Coefficient of Variation
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
EDC	Electronic Data Capture
HbA1c	Glycosylated hemoglobin
ICF	Informed Consent Form
ITT	Intention to Treat

Abbreviations	
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SBL	Suspend Before Low
SD	Standard Deviation
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TAR	Time above Range
TBR	Time below Range
T1D	Type 1 diabetes
TDD	Total Daily Dose
TIR	Time in Range
USADE	Unanticipated Serious Adverse Device Effect

3. Introduction

The global incidence of newly diagnosed cases of type 1 diabetes (T1D) in children and adolescents is increasing. In 2019, the International Diabetes Federation (IDF) indicated that every year, 98,200 children and adolescents aged 0–14 years are diagnosed with T1D worldwide [1].

In T1D, 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. The use of sensor-augmented pump therapy with predictive low-glucose suspend features, available in the commercialized MiniMed 640G System, in which the pump stops insulin delivery when an algorithm predicts glucose levels to drop below the prespecified low-glucose threshold, is accompanied by improvements in glycemic control in children, but the management of the therapy remains challenging in the young children due to high variability of insulin requirements, marked insulin sensitivity and unpredictable eating and activity patterns.

In 2020, a sensor-augmented pump system, called the MiniMed 780G system, with an advanced hybrid closed loop (AHCL) algorithm became commercially available in Europe. The system features SmartGuard technology which allows the pump to automatically adjust the amount of insulin delivered based on sensor glucose (SG) readings. The system can also automatically deliver correction boluses and has multiple adjustable glucose targets (100 mg/dL, 110mg/dL, 120 mg/dL and 150 mg/dL) (5.5 mmol/L, 6.1 mmol/L, 6.7 mmol/L and 8.3 mmol/L).

Several studies have been completed and are ongoing on the AHCL MiniMed 780G system to demonstrate its safety and effectiveness in children, adolescents, and adults. In a pivotal study, it was demonstrated

that the MiniMed 780G system helped children over 7 years old to reach better time in range (TIR) and better mealtime glycaemia without increasing time below range (TBR), severe hypoglycemia or ketoacidosis [2]. Furthermore, real-life data analysis in 3,211 users, reporting age <15, demonstrated a GMI of 6.8±0.3%, TIR of 73.9±8.7%, and TBR (70 mg%) of 3.2%, while spending 92.7% of time in AHCL [3].

These studies and real-life usage of the MiniMed 780G system has been shown to improve glycemic control and reduce the burden of management of T1D in children and adolescents. However, studies involving very young children remain limited, and therefore this randomized trial is being conducted to evaluate safe usage of the MiniMed 780G system in comparison with the currently available standard sensor-augmented pump therapy for young children 2 to 6 years old.

This Statistical Analysis Plan (SAP) Version is based on Protocol E 3' OCT 2023, and it has been designed to document, before data is analyzed, the planned statistical analyses for both study and continuation phases and will be used to support the clinical reports. This SAP does not limit the analysis in reports, and additional analyses of the study data beyond this plan might be conducted. However, this document provides the basis for the statistical sections of the clinical reports. Analyses not planned in the SAP and incorporated into the final report will be referred to as "not prespecified". Moreover, in case any analyses will be done differently than planned in the CIP or SAP, an explanation will be provided in the final reports.

4. Study Objectives

4.1 Primary Objective

The objective of the study is to evaluate the safety and performance of the MiniMed™ 780G system in Auto Mode firstly in comparison to the MiniMed™ 780G system in Manual Mode with Suspend before low activated (currently available standard therapy) in the study phase and secondly in comparison to the new MiniMed™ 780G BLE 2.0 system with DS5 sensor in Auto Mode among paediatric population (2-6 years old) in the continuation phase.

4.1.1 Study Phase Primary Endpoint

The primary endpoint for LENNY study phase is the between-treatment difference (MiniMed™ 780G system in Auto Mode vs MiniMed™ 780G system in Manual Mode) in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L) during the study phase period. This endpoint will be assessed for non-inferiority with an absolute margin of 7.5% TIR.

4.1.2 Continuation Phase Primary Endpoint

The primary endpoint for LENNY continuation phase is the between-treatment difference (MiniMed™ 780G BLE 2.0 system with DS5 in Auto Mode vs MiniMed™ 780G system in Auto Mode) in the mean HbA1c

(%) at the end of 12-week continuation phase period 2. This endpoint will be assessed for non-inferiority with an absolute margin of 0.4% HbA1c.

4.2 Secondary Endpoints

4.2.1 Study Phase Secondary Endpoint

The secondary endpoints for LENNY study phase will be the between-treatment (MiniMed™ 780G system in Auto Mode vs MiniMed™ 780G system in Manual Mode) difference in the study phase for:

- Mean HbA1c at the end of each 12-week period, non-inferiority test with an absolute margin of 0.4% HbA1c.
- % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]), simple superiority test.
- Mean HbA1c at the end of each 12-week period, simple superiority test.

4.2.2 Continuation Phase Secondary Endpoint

The secondary endpoints for LENNY continuation phase will be the between-treatment (MiniMed™ 780G BLE 2.0 system with DS5 in Auto Mode vs MiniMed™ 780G system in Auto Mode) difference in the continuation phase period 2 for:

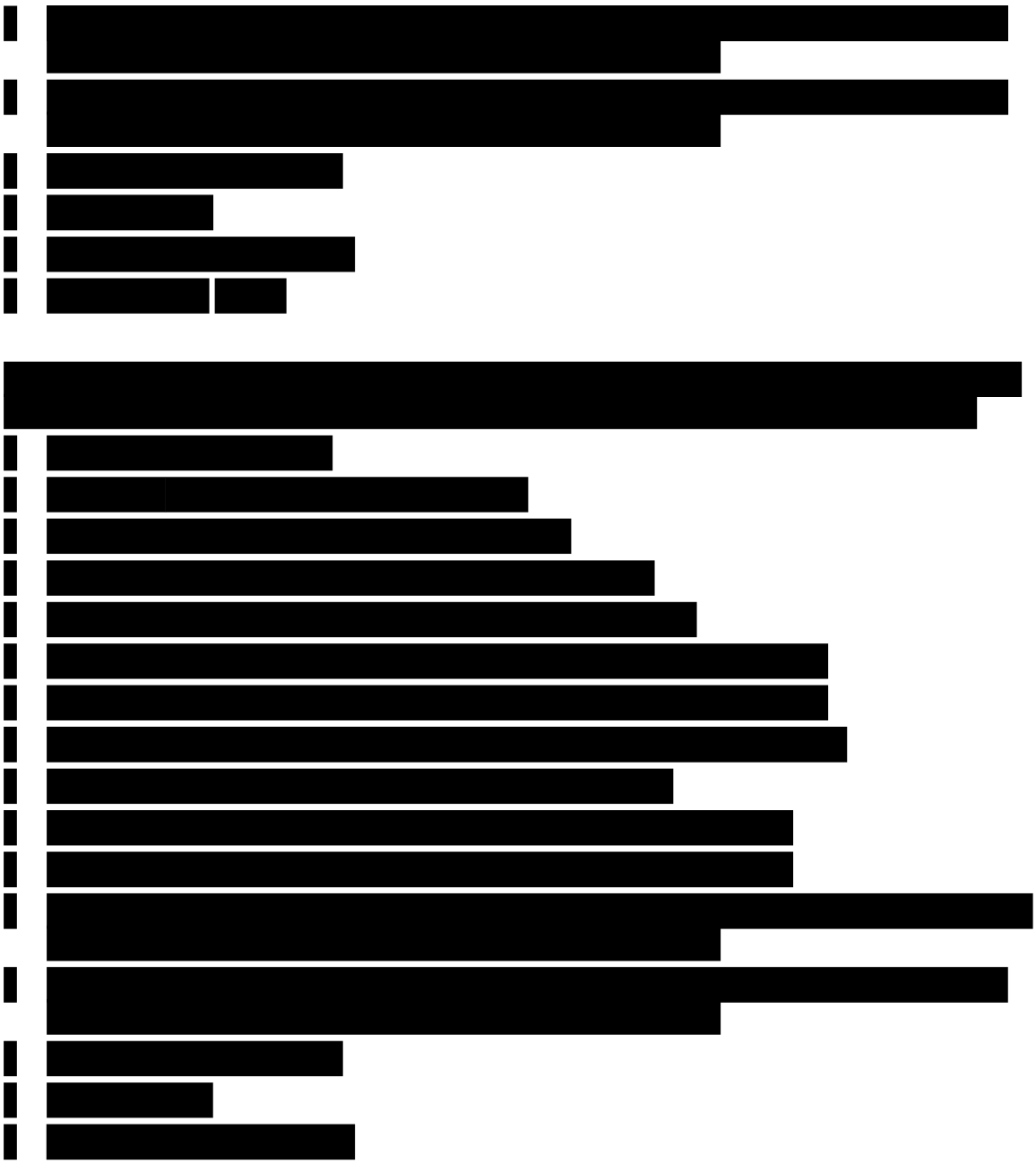
- Mean HbA1c at the end of the 12-week continuation phase period 2, simple superiority test.
- % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]) during continuation phase period 2, non-inferiority test with an absolute margin of 7.5% time in range.
- % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]) during continuation phase period 2, simple superiority test.

4.3 Safety Endpoints

The following safety endpoints will be assessed for each treatment during each 12-week period in both the study phase and continuation phase:

- Number of severe hypoglycemic events
- Number of Diabetic Ketoacidosis events (DKA)
- Number of Serious Adverse Events (SAEs)
- Number of Serious Adverse Device Events (SADEs)
- Number of Unanticipated Serious Adverse Device Events (USADEs)
- Number of Device Deficiencies for each treatment during each 12-week period in the Study Phase

[redacted]



5. Investigation Plan

This study is a pre-market, prospective, open-label, multi-center, randomized crossover trial in paediatric subjects (2-6 years old) with type 1 diabetes. The study consists of a run-in phase, a study phase, and a continuation phase (**Figure 1**).

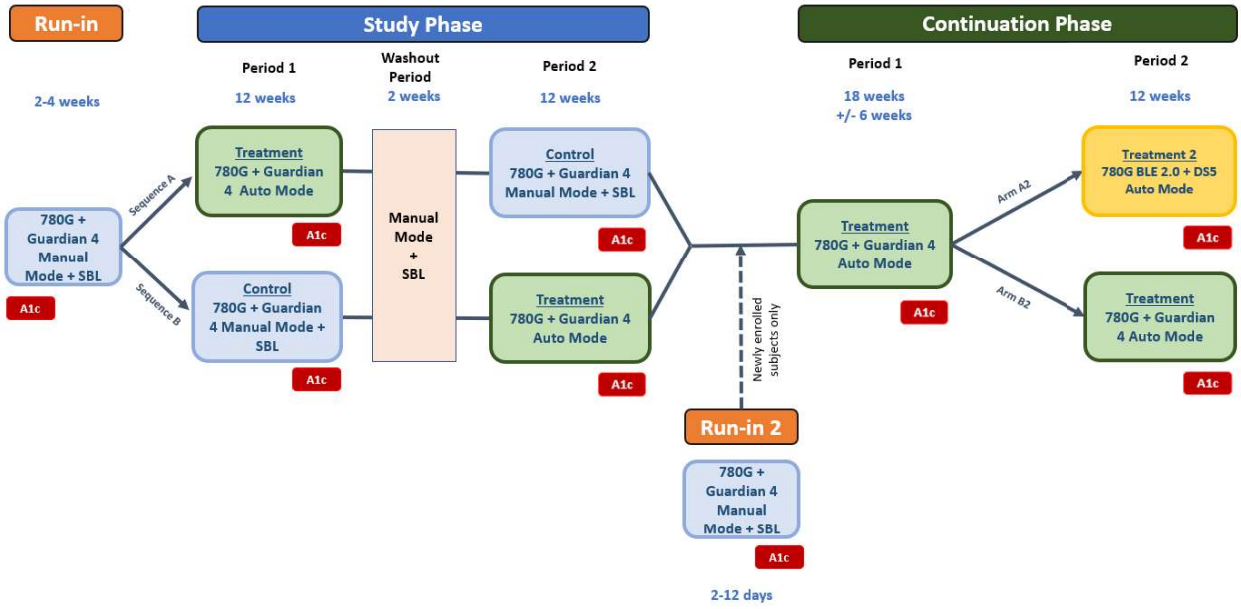


Figure 1 - Study Design - CIP version E

Study Phase - Run-in Phase:
The purpose of the run-in phase (2 to 4 weeks) is to train the subject's parent(s)/legal guardian(s) on the MiniMed 780G system in Manual Mode with Suspend before low activated and to collect 2 weeks of baseline data.
At the end of Run-in Phase, subjects will be randomized into 2 sequences (A and B).
Successful completion of run-in phase requires sensor usage ≥70% over the previous 2 weeks during the run-in phase. If this is not achieved (e.g. sensor felt off) the run-in phase can be extended for another 7 to 14 days to achieve sensor usage ≥70%.

Study Phase:
During the study phase, each sequence consists of 2 phases of 12 weeks each separated by a 2-week washout phase for a total of 26 weeks.

- Sequence A: subjects will start using the MiniMed 780G system in Auto Mode for 12 weeks (Treatment). The washout phase of 2 weeks will be followed by a 12-week phase where subjects will use 780G system in Manual Mode with SBL activated (Control).
- Sequence B: subjects will continue to use MiniMed 780G system in Manual Mode with SBL activated for 12 weeks (Control). After a washout phase of 2 weeks, subjects will start to use the MiniMed 780G system in Auto Mode for a 12-week phase (Treatment).

During the washout period all the subjects will use MiniMed 780G system in Manual Mode with SBL activated.

Continuation Phase (Visit 12-15):
For the duration of the continuation phase, enrolled subjects will enter the continuation phase period 1 and will use MiniMed 780G system in Auto Mode.
At the end of the continuation phase period 1, subjects will be randomized into 2 arms (A2 and B2) and enter period 2 for 12 weeks.

- Arm A2: Subjects will start using the MiniMed™ 780G BLE 2.0 system with the DS5 sensor for 12 weeks
- Arm B2: Subjects will continue to use MiniMed™ 780G system in Auto Mode for 12 weeks

Based on interim analysis results, enrollment may be re-opened only for the Continuation phase, and the newly enrolled patients will have a dedicated run-in 2.

Continuation Phase - Run-in 2 Phase:
The purpose of the run-in 2 phase (3 to 10 days) is to train the newly enrolled subject's parent(s)/legal guardian(s) on the MiniMed 780G system in Manual Mode with Suspend before low activated. At the end on the continuation phase run-in 2 period, subjects will start using the 780G system in Auto Mode.

[redacted]

[redacted]

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

A subject is enrolled in the study when he/she signs and dates the Patient Informed Consent.
For study phase a summary of number of subjects enrolled, entered the run-in phase, randomized, and completed (by study sequence and study period), screen failures and drop-outs will be reported.
For continuation phase a summary of number of subjects enrolled, entered the continuation phase period 1, randomized, and completed the continuation phase period 2 (by study arm), and drop-outs will be reported.
For both study and continuation phases, a listing of subjects that failed to meet randomization criteria, screen failures and drop-out with the corresponding reasons will also be reported, separately.

Two consort flow diagrams similar to figure 2 and figure 3 will be created to describe patient disposition in study and continuation phase, respectively.

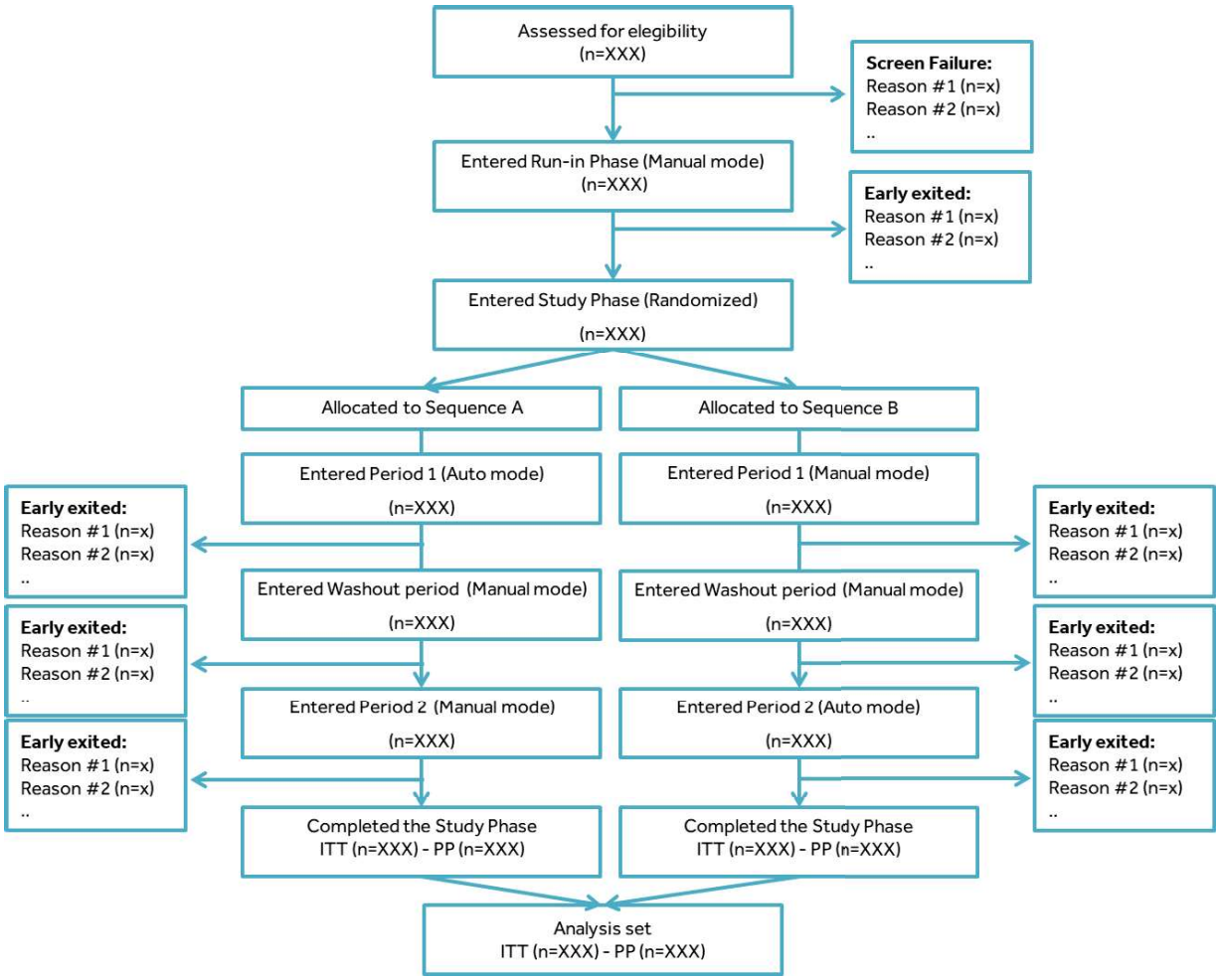


Figure 2 – Patients disposition flowchart -study phase

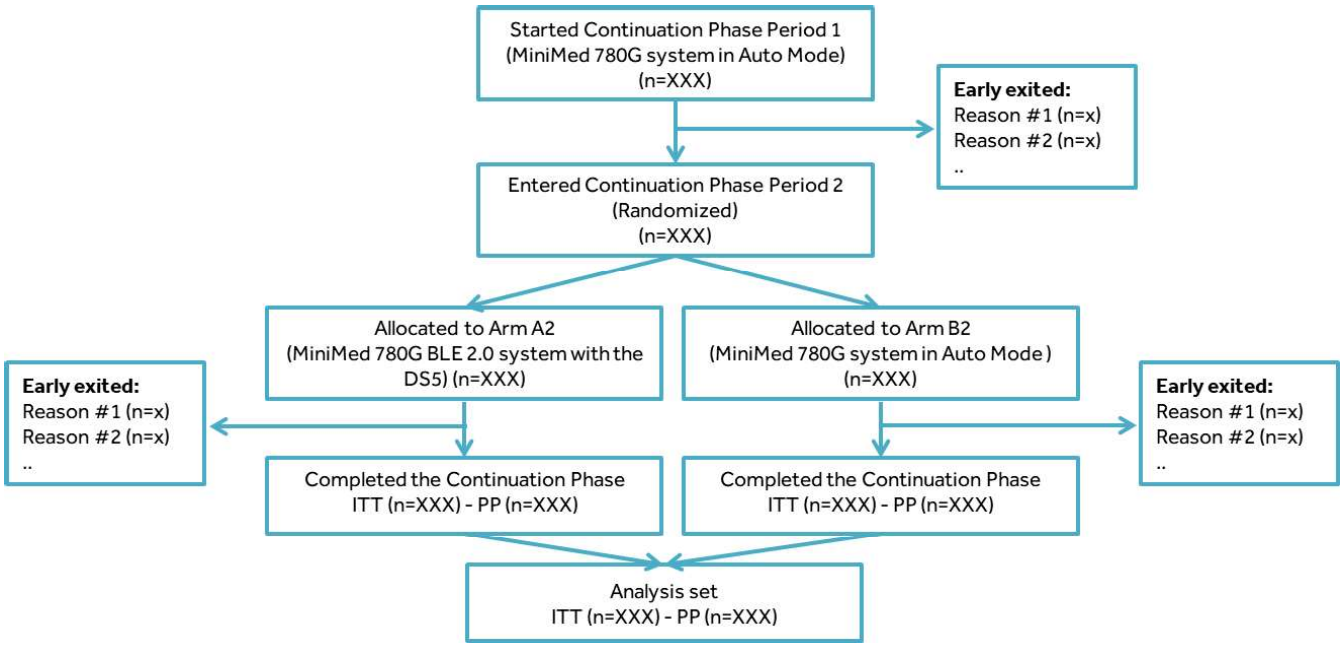


Figure 3 – Patients disposition flowchart -continuation phase

7.1.2 Clinical Investigation Plan (CIP) Deviations

Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation eCRF. Deviations will be summarized in the final report in a table by category. The number of deviations per category, the number, and percentage of subjects with a deviation in each category will be reported. Listing of deviations, including reason for deviation, will be reported.

7.1.3 Analysis Sets

The following subject sets will be used for the analysis:

- **Intention to Treat (ITT) Population:**

For the study phase, the ITT population will include all randomized subjects for that phase, and for the continuation phase, the ITT population will include all randomized subjects for that phase. These subjects will be assessed and analyzed as members of the intended period/treatment, irrespective of their compliance to the planned course of treatment or deviations from protocol. For the primary, secondary, and exploratory endpoints, efficacy analyses will be performed in the Intent to Treat (ITT) basis.

- **Per Protocol (PP) Population:**

For both, study phase and continuation phase, the PP population will include all randomized subjects in the respective phase, and excluding any subject with at least one of the following deviations (to be assessed independently in each phase):

  - Auto Mode use during is less than 75%
  - Sensor use is less than 70%
  - Subject did not complete the specific phase, respectively
  - Subject did not meet screening criteria for the specific phase but continued the phase
  - Subject did not meet randomization criteria for the specific phase but continued the phase
  - Subject not compliant with the assigned randomization treatment

For sensitivity purposes, efficacy analysis of the primary and secondary endpoints will also be performed in the Per Protocol set.

The criteria listed above will be assessed separately for study and continuation phase, respectively, and separate ITT and PP population sets will be defined accordingly.

- **As Treated (AT) Population:**

For the continuation phase, the AT population will include all randomized subjects for that phase. These subjects will be assessed and analyzed as members of the actual treatment. For sensitivity purposes, efficacy analysis of the primary and secondary endpoints will also be performed in the As Treated set.

- **Safety Population**

The Safety Population will include all subjects with signed inform consent.

7.2 General Methodology

Summary statistics for Continuous variables will be represented by number of subjects(n), mean, median, standard deviation, minimum and maximum and categorical variables will be represented by counts and percentages. P-values for hypothesis testing will be evaluated based on two-sided testing using significance level of 0.05. Confidence intervals will be reported as two-sided 95% confidence intervals. Normality will be verified by appropriate statistical methodology.

Time windows for device data metrics will be defined as follow:

- Run-in period: from Visit 2 (excluded) to Visit 3 (excluded);
- Study phase period 1: from Visit 3 (excluded) to Visit 7 (excluded);
- Washout period: from Visit 7 (excluded) to Visit 8 (excluded);
- Study phase period 2: from Visit 8 (excluded) to Visit 11 (excluded);
- (in case of newly enrolled subjects) Run-in 2 period: from Visit 2A (excluded) to Visit 3A (excluded);
- Continuation phase period 1: from Visit 11 (excluded) to Visit 13 (excluded);
- Continuation phase period 2: from Visit 13 (excluded) on.

CGM data from the day of the visits will not be included in the device data metrics calculation to avoid any possible bias due to the change in the treatment and settings.

Time windows for safety events will be defined as follow:

- Pre-Run-in period: from ICF signature date (included) to Visit 2 (excluded)
- Run-in period: from Visit 2 (included) to Visit 3 (excluded);
- Study phase period 1: from Visit 3 (included) to Visit 7 (included);
- Washout period: from Visit 7 (excluded) to Visit 8 (excluded);
- Study phase period 2: from Visit 8 (included) to Visit 11 (excluded);
- (in case of newly enrolled subjects) Pre-Run-in 2 period: from ICF signature date/Visit 1A (included) to Visit 2A (excluded)
- (in case of newly enrolled subjects) Run-in 2 period: from Visit 2A (included) to Visit 3A (excluded);
- Continuation phase period 1: from Visit 11 (included) to Visit 13 (excluded);
- Continuation phase period 2: from Visit 13 (included) on.

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

It is anticipated that SAS 9.4 or later (SAS Institute Inc., Cary, NC, USA) will be used to perform all statistical analyses.
Additional exploratory analyses will be conducted as deemed appropriate and described as ad-hoc analysis in the study report.

7.3 Center Pooling

The study is expected to be conducted in four countries. The same clinical investigational plan and training is followed, and standardized data collection methodology and electronic case report forms (eCRF) are used in all sites.

A descriptive summary of both study phase and continuation phase primary endpoints will be reported by country.

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

The Primary endpoints analyses are based on ITT using a random effect model that uses available data and accounts for missing at random. In addition, sensitivity analyses will be performed on PP set.

For per protocol analysis, if A1c is collected out of window (± 14 days from target visit date) A1c will be considered missing for that particular period/visit.

For the Run-in period, glycemic variability metrics from device data will be derived if a minimum number of 2880 of SG values (288 SG values/day × 10 days out of 14 days) is available, otherwise that data will be considered as missing.

In the case of dates collected at baseline with missing day and/or month the next procedure will be applied. A missing day and month will be imputed using the month 'July 1' and a missing day will be imputed with the day '15'. This applies only to dates related to medical history and baseline information with missing month and/or day.

For tables and listings of safety data a conservative/worst case scenario approach will be taken in case of partially missing dates. For the date of discharge with missing day, the day will be set to last day of that month. For the date of admission with missing day, the day will be set to first day of that month. If that is before the start of the study phase (within the same month), then the day will be set equal to today of the start of the study phase. Otherwise, if it is before the day of the start of the run-in (within the same month), then it will be set today of the start of the run-in. Thus, the duration is set to be as long as possible.

Outliers and influential observations will be identified via graphical plots. Once outliers or influential observations are identified, the study team will be informed and according to their decision the analysis for primary endpoint may be repeated using a statistical method robust against outliers. Additional exploratory analyses will be conducted as deemed appropriate.

7.5 Adjustments for Multiple Comparisons

Study endpoints will be tested with the use of a hierarchical gatekeeping procedure to control the type I error. The primary endpoints will be tested first and, if passing the significance testing, other endpoints will be tested in order.

If a non-significant result (hypothesis not rejected) is encountered, formal statistical hypothesis testing will be terminated, and analysis of any subsequent endpoints (lower in hierarchy) will be considered as exploratory.

7.5.1 Sequential testing for Study Phase

Fixed sequential testing of primary and selected secondary endpoints:

Study Phase Primary endpoint:

1. Between-treatment difference in percentage of time spent within range 70 - 180 mg/dL.

   It will be tested for non-inferiority with a margin of 7.5%, as described in section 7.9.1 and a p-value < 0.05 will be considered statistically significant. If p-value < 0.05, continue to next test, else stop.

Study Phase Secondary endpoints:

2. Between-treatment difference in Mean HbA1c at the end of each 12-week period.

   It will be tested for non-inferiority with a margin of 0.4%, if p-value < 0.05 reject null hypothesis and continue, else stop

3. Between-treatment difference in percentage of time spent within range 70 - 180 mg/dL.

   It will be tested for superiority, if p-value<0.05 reject null hypothesis and continue, else stop

4. Between-treatment difference in Mean HbA1c at the end of each 12-week period.

   It will be tested for superiority, if p-value<0.05 reject null hypothesis and continue, else stop

7.5.2 Sequential testing for Continuation Phase

Continuation Phase Primary endpoint:

1. Between-treatment difference in Mean HbA1c at the end of the continuation phase period 2.

   It will be tested for non-inferiority with a margin of 0.4%, as described in section 7.9.2 and a p-value < 0.05 will be considered statistically significant. If p-value < 0.05, continue to next test, else stop.

Continuation Phase Secondary endpoints:

2. Between-treatment difference in Mean HbA1c at the end of the continuation phase period 2.

   It will be tested for superiority, if p-value<0.05 reject null hypothesis and continue, else stop

3. Between-treatment difference in percentage of time spent within range 70 - 180 mg/dL during the continuation phase period 2.

   It will be tested for non-inferiority with a margin of 7.5%, if p-value < 0.05 reject null hypothesis and continue, else stop

4. Between-treatment difference in percentage of time spent within range 70 - 180 mg/dL during the continuation phase period 2.

   It will be tested for superiority, if p-value<0.05 reject null hypothesis and continue, else stop

Exploratory endpoints:

Analyses on secondary exploratory endpoints may be performed, and p-values could be reported but may not be claimed.

Safety endpoints:

No statistical test will be performed on safety endpoints.

7.6 Demographic and Other Baseline Characteristics

Baseline variables to be summarized include, but are not limited to age, sex, weight, BMI, country of enrollment, HbA1c, Diabetes history, therapy history, creatinine clearance value and total insulin dose per day.

7.6.1 Study Phase

For study phase a summary of subject demographics, current diabetes therapy at baseline, medical history and other baseline characteristics will be reported using appropriate summary statistics.

7.6.2 Continuation Phase

For continuation phase a summary by randomization arm of subject demographics, current diabetes therapy at baseline, medical history and other baseline characteristics will be reported using appropriate summary statistics.

7.7 Treatment Characteristics

Duration of Study Exposure will be measured in days starting from the time of enrollment (informed consent signed and inclusion/exclusion criteria confirmed) through and including the time of study exit.

7.7.1 Study exposure for Study Phase

For study phase, the Run-In phase starts at Visit 2, and it ends at the time of randomization. It is expected that the Run-In phase will last 2 to 4 weeks.

The Study phase starts at the time of Randomization (end of Run-In phase), and it ends at Visit 11.

The study phases exposures are calculated as:

- Study phase exposure (days) = (Visit 11 date (or study exit date, if early exited) – date of Randomization +1).
- Run-In phase exposure (days) = (date of Randomization (or study exit date, if early exited) – Visit date) +1).
- Pre-Run-In phase exposure (days) = (Visit 2 – date of Enrollment (Consent) +1).

7.7.2 Study exposure for Continuation Phase

For continuation phase, the Run-In, in case of newly enrolled patients, starts at Visit 2A, and it ends at Visit 3A. It is expected that the Run-In phase will last around 10 days.

The Continuation phase starts at Visit 11, and it ends at Visit 15.

The continuation phases exposures are calculated as:

- Continuation phase exposure (days) = Visit 15 date (or study exit date, if early exited) – Visit 11 date (or Visit 3A for newly enrolled patients, if any) +1).
- Run-In phase exposure (days) = Visit 12 date – Visit 2A date +1.
- Pre-Run-In phase exposure (days) = Visit 2A – Visit 1A +1.
- Continuation phase period 1 exposure (days) = Visit 13 date (or study exit date, if early exited) – Visit 11 date (or Visit 3A for newly enrolled patients, if any) +1.
- Continuation phase period 2 exposure (days) = Visit 15 date (or study exit date, if early exited) – Visit 13 date +1.

Extent of study exposures will be presented in a summary table.

7.8 Interim Analyses

7.8.1 Study Phase

No Interim analysis is planned to be conducted during the LENNY study phase.

7.8.2 Continuation Phase

An interim analysis will be performed during continuation phase, when approximately 50% of subjects complete the continuation phase period 1, to evaluate sample size justification assumption on HbA1c standard deviation and re-assess sample size, if needed.

7.9 Evaluation of Objectives

In this section detailed information about each objective is included together with calculations and derivations of outcome parameters, analysis methods, datasets analyzed (ITT and PP). For each endpoint will be reported at least summary statistics table.

7.9.1 Analysis of primary endpoint – study phase - between-treatment difference in TIR (70-180 mg/dL) – non inferiority test

The goal is to assess the non-inferiority in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L), during each 12-week period in the Treatment 780G in Auto Mode compared to Control MiniMed 780G in Manual Mode + SBL.
The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta TIR \leq -7.5\%$$
$$H_\alpha: \Delta TIR > -7.5\%.$$

Where ΔTIR is the average of the cross-over differences in time in range in Treatment 780G in Auto Mode vs Control MiniMed 780G System + SBL ($TIR_{AHCL} - TIR_{SBL}$), and the test will be at the 0.025 (one-sided) significance level.

The carryover effect will be tested using repeated measures mixed model with period, randomization sequence, and treatment as fixed effects, and subject as the random effect.

The 97.5% lower confidence limit of between-treatment difference will be calculated. If it is greater than -7.5%, the non-inferiority will be concluded.

If the p value of the coefficient for randomization sequence is ≤0.1 (there is a carryover effect), data from period 1 will be used for analysis only. The 97.5% lower confidence limit of between-treatment difference at period 1 will be calculated. If it is greater than -7.5%, the non-inferiority will be concluded.

Descriptive summary statistics of the primary endpoint will be presented stratified by treatment.
In addition, descriptive summary statistics of the primary endpoint will be presented stratified by country.

Pass/Fail Criteria:
The study pass/fail criteria are based on statistical hypothesis of the primary endpoint. The study will be considered as success when the evaluation criteria meet the predefined threshold on the ITT set.

7.9.2 Analysis of primary endpoint – continuation phase - between-treatment difference in HbA1C – non inferiority test

The goal is to assess the non-inferiority in the mean Hba1c during the 12-week continuation phase period 2 in the Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode compared to Control MiniMed 780G System in Auto Mode. The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta HbA1c \geq 0.4\%$$
$$H_\alpha: \Delta HbA1c < 0.4\%.$$

Where $\Delta HbA1c$ is the difference of the average of HbA1c for Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode at the end of the 12-week continuation phase period 2, will be assessed by using of mixed model adjusting by baseline value. It will be tested at the 0.025 (one-sided) significance level.

The 97.5% upper confidence limit of between-treatment difference will be calculated. If it is lower than 0.4%, the non-inferiority will be concluded.

7.9.3 Analysis of study phase secondary endpoints

Descriptive summary statistics of the secondary endpoints will be presented stratified by treatment.

7.9.3.1 Between treatment difference in HbA1c – non inferiority test endpoints

The between-treatment difference in mean HbA1c at the end of each 12-week period will be assessed similarly to primary endpoint analysis, using repeated measures mixed model with period, randomization sequence, and treatment as fixed effects, and subject as the random effect.

The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta HbA1C \geq 0.4\%$$
$$H_\alpha: \Delta HbA1C < 0.4\%.$$

Where $\Delta HbA1c$ is the average of the cross-over differences in HbA1c at the end of 12-week period in Treatment 780G in Auto Mode vs HbA1c at the end of 12-week period Control MiniMed 780G System + SBL ($HbA1C_{AHCL} - HbA1C_{SBL}$), and the test will be against at the 0.025 (one-sided) significance level.

The 97.5% upper confidence limit of between-treatment difference will be calculated. If it is lower than 0.4%, the non-inferiority will be concluded.

7.9.3.2 Between treatment difference in TIR (70-180 mg/dL) – superiority test

The between-treatment difference in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L), during each 12-week period in the Treatment 780G in Auto Mode compared to Control MiniMed 780G in Manual Mode + SBL will be assessed for superiority using repeated measures mixed model with period, randomization sequence, and treatment as fixed effects, and subject as the random effect.
The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta TIR \leq 0\%$$
$$H_\alpha: \Delta TIR > 0\%.$$

the test will be against at the 0.025 (one-sided) significance level.

The 97.5% lower confidence limit of between-treatment difference will be calculated. If it is greater than 0%, the superiority will be concluded.

7.9.3.3 Between treatment difference in HbA1c – superiority test

The between-treatment difference in mean HbA1c at the end of each 12-week period will be assessed for superiority using repeated measures mixed model with period, randomization sequence, and treatment as fixed effects, and subject as the random effect.
The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta HbA1C \geq 0\%$$
$$H_\alpha: \Delta HbA1C < 0\%.$$

the test will be against at the 0.025 (one-sided) significance level.

The 97.5% upper confidence limit of between-treatment difference will be calculated. If it is lower than 0%, the superiority will be concluded.

7.9.4 Analysis of continuation phase secondary endpoints

Descriptive summary statistics of the secondary endpoints will be presented stratified by treatment.

7.9.4.1 Between treatment difference in HbA1c – superiority test endpoints

The between-treatment difference in mean HbA1c of the 12-week continuation phase period 2 will be assessed similarly to primary endpoint analysis, using mixed model adjusting by baseline value.
The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta HbA1C \geq 0\%$$
$$H_\alpha: \Delta HbA1C < 0\%.$$

Where $\Delta HbA1c$ is the difference of the average of HbA1c for Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode at the end of the 12-week continuation phase period 2, and the test will be against at the 0.025 (one-sided) significance level.

The 97.5% upper confidence limit of between-treatment difference will be calculated. If it is lower than 0%, the superiority will be concluded.

7.9.4.2 Between treatment difference in TIR (70-180 mg/dL) – non inferiority-test

The between-treatment difference in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L), during the 12-week continuation phase period 2 in the Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode will be assessed for non-inferiority using mixed model adjusting by baseline value.

The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta TIR \leq -7.5\%$$
$$H_\alpha: \Delta TIR > -7.5\%.$$

Where ΔTIR is the difference in time in range in Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode , and the test will be against at the 0.025 (one-sided) significance level.

The 97.5% lower confidence limit of between-treatment difference will be calculated. If it is greater than -7.5%, the non-inferiority will be concluded.

7.9.4.3 Between treatment difference in TIR (70-180 mg/dL) – superiority test

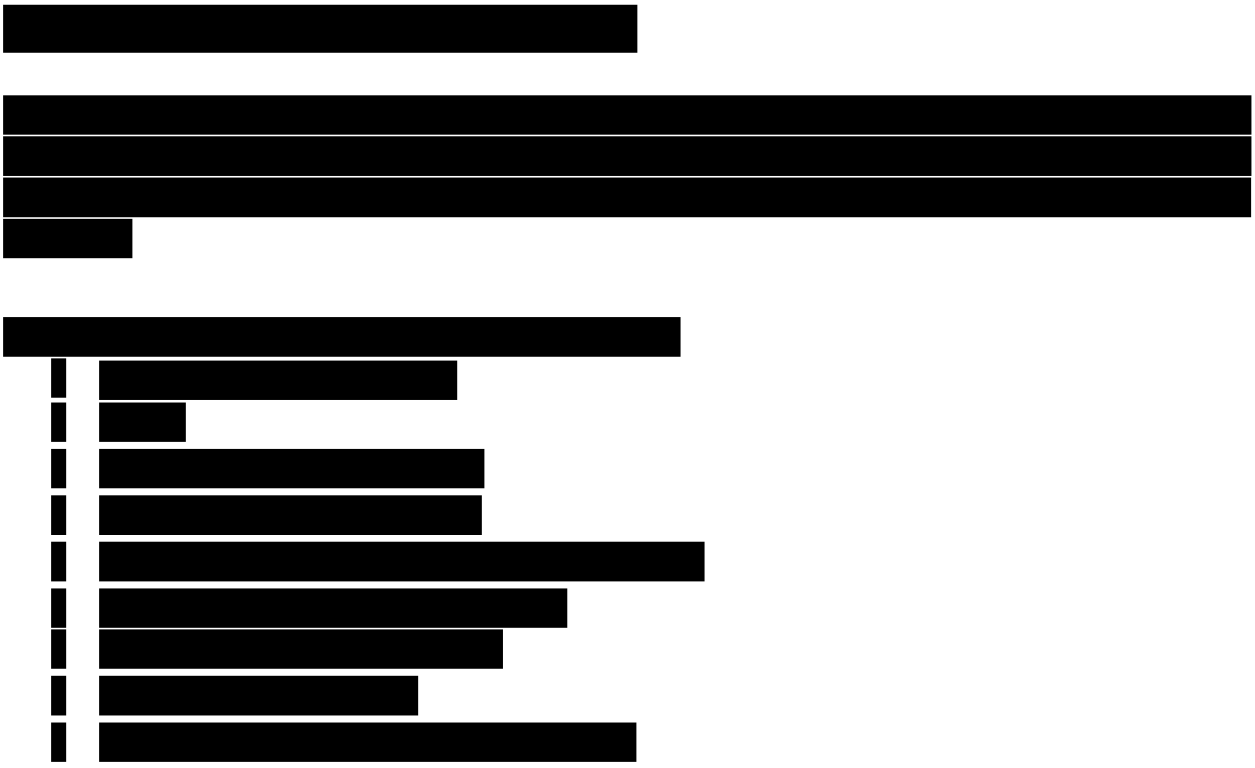
The between-treatment difference in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L), during the 12-week continuation phase period 2 in the Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode will be assessed for superiority using mixed model adjusting by baseline value.

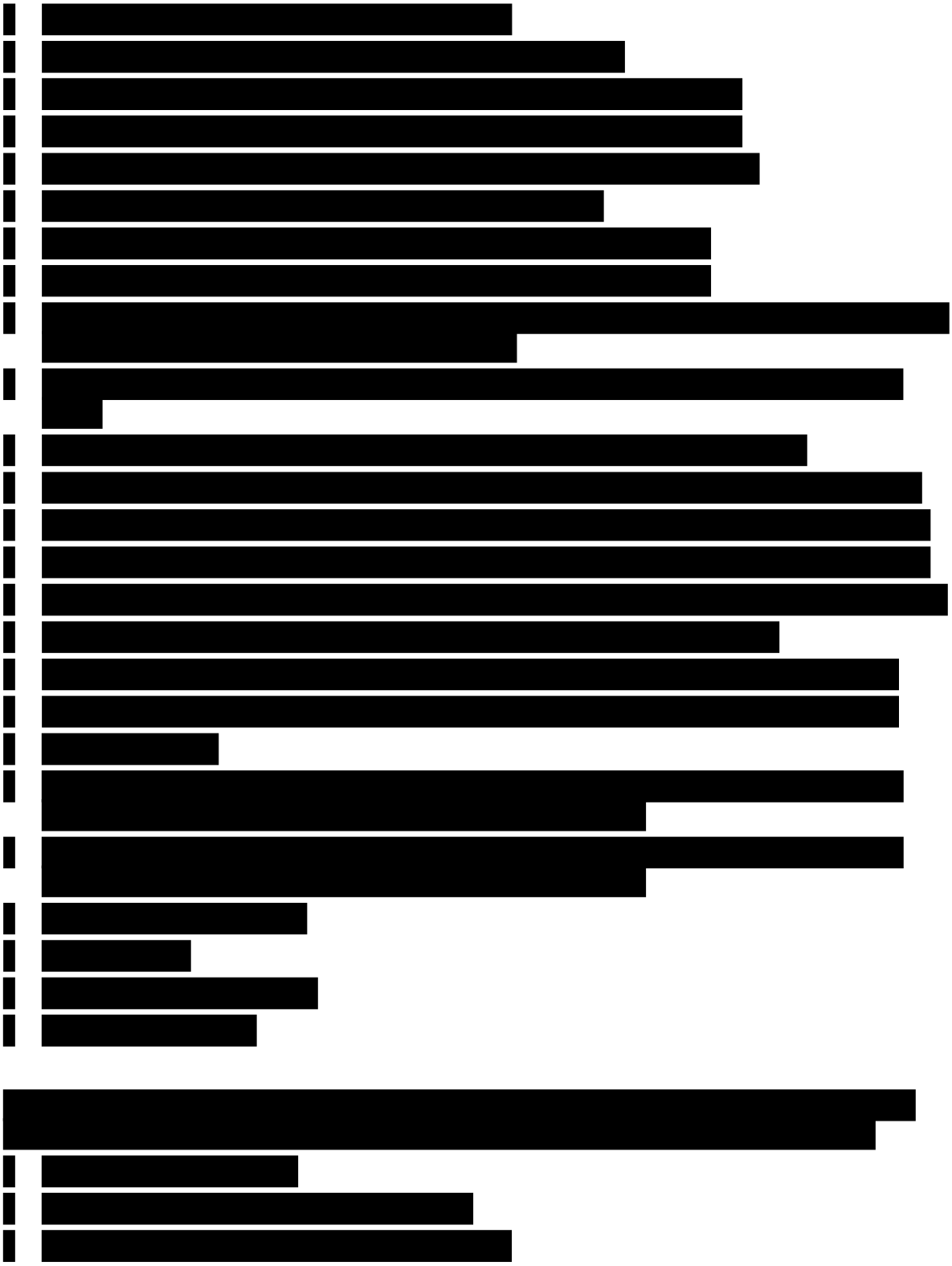
The between-treatment difference will be compared using the following hypotheses:

$$H_0: \Delta TIR \leq 0\%$$
$$H_\alpha: \Delta TIR > 0\%.$$

Where ΔTIR is the difference in time in range in Treatment MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode vs Control MiniMed 780G in Auto Mode , and the test will be against at the 0.025 (one-sided) significance level.

The 97.5% lower confidence limit of between-treatment difference will be calculated. If it is greater than 0%, the non-inferiority will be concluded.





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7.10 Safety Evaluation

The safety endpoints will be assessed separately for the study phase and continuation phase of the study. For study phase the events will be reported for each period (Run-In, Study phase period 1, washout period, study period 2). For the continuation phase the events will be reported for each period (Run-in 2, continuation phase period 1 and continuation phase period 2). For study and continuation phases events will be reported by both randomization arm and actual treatment received and will be presented for the Safety population.

Any safety related event will be classified by study period according to the rule defined in paragraph 7.2.

The listing of these events will also be reported.

7.10.1 Number of severe hypoglycemic events

Severe Hypoglycemia is an event requiring assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat him or herself, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
Total number of severe hypoglycemic events will be reported by treatment.
The number of severe hypoglycemic events per year will be computed for each subject based on the entire study phase duration. If a subject i is followed up for xi years and the number of observed severe hypoglycemic events during that follow up is mi, the number of severe hypoglycemic events per year (SHEyear) for patient i will be estimated as:

$$\frac{m_i}{x_i}$$

Annualized crude incidence rates will be expressed as number of severe hypoglycemic events per 100 patients' year and will be calculated as:

$$\frac{\sum_{i=1}^{n} m_i}{\sum_{i=1}^{n} x_i} \times 100$$

where i=1, 2, …, n and n total number of subjects.

The number of severe hypoglycemic events per 100 patients' year during the study phase will be reported by treatment.

7.10.2 Number of diabetic ketoacidosis events

A diabetic ketoacidosis event is defined as an event of blood glucose greater than 250 mg/dL (13.9 mmol/L) arterial pH less than 7.3, bicarbonate less than 15mEq/l, moderate ketonuria or ketonemia, and requiring treatment within a health care facility.

Total number of diabetic ketoacidosis events will be reported by treatment. The number of diabetic ketoacidosis events per 100 patients' year during the study phase will be calculated in a similar way as in section 7.10.1 and will be reported by treatment.

7.10.3 Number of Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs), Unanticipated Serious Adverse Device Effects (USADEs) and Device Deficiencies (DD)

Serious Adverse Event (SAE) is an adverse event that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function including chronic diseases, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment.

Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

Device deficiency (DD) is inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. It includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator.

The number of SAE, SADE, USADE and DD will be reported by study period and treatment.

The listing of these events will also be reported.

7.11 Changes to Planned Analysis

The analysis described in the CIP could differ from that presented in this SAP due to data availability. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate.

8. Validation Requirements

All collected data will be reviewed for completeness, correctness, and consistency. In case of issues, queries will be sent to the investigator to complete, correct, or comment the data. To ensure the quality of the results provided for the study in the form of tables, listings and figures, and the derived datasets the following processes are used:

- Statistical programming and analysis will be done by qualified programmer(s) and statistician(s) following applicable procedures and best practices.
- The derived datasets and tables will be validated by a second programmer or statistician.
- Statistical results will be reviewed and confirmed by a second statistician.

The complete set of Tables, Listings, and Figures (TLF) will be 100% checked for accuracy, completeness, and consistency prior to inclusion in the final clinical study report.

According to Medtronic SOPs the level I validation (double programming) will be implemented for all the outputs.

9. References

1. Federation ID. IDF Diabetes Atlas, 9th edn. International Diabetes Federation. http://www.diabetesatlas.org. Published 2019. Accessed.
2. Carlson AL, Sherr JL, Shulman DI, et al. Safety and Glycemic Outcomes During the MiniMed Advanced Hybrid Closed-Loop System Pivotal Trial in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2022;24(3):178-189.
3. Arrieta A, Battelino T, Scaramuzza AE, et al. Comparison of MiniMed 780G system performance in users aged below and above 15 years: Evidence from 12,870 real-world users. Diabetes Obes Metab. 2022.
4. Tuomaala AK. Glycemic outcomes and safety with MiniMed 780G system in children with type 1 diabetes aged 2 - 6 years. Diabetes Technology & Therapeutics. 2022;24(S1):A-1-A-237.