Medtronic

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	ADAPT **AD**vanced Hybrid Closed Loop study in **A**dult **P**opulation with **T**ype 1 Diabetes: A Prospective, Open-label, Multi-center, Adaptive, Confirmatory and Randomized Controlled Study
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1. Version History

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

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADAPT	**AD**vanced Hybrid Closed Loop study in **A**dult **P**opulation with **T**ype 1 Diabetes
ADE	Adverse Device Effect
AHCL	Advanced Hybrid Closed Loop
ASIC	Application Specific Integrated Circuit
AUC	Area Under Curve
BG	Blood Glucose
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CIP	Clinical Investigation Plan
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DQoL	Diabetes Quality of Life questionnaire
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Change Version of DTSQs
DTSQs	Status Version of DTSQs
EC	Ethics Committee
eCRF	Electronic Case Report Form
EIS	Electrochemical Impedance Spectroscopy
EMEA	Europe Middle East Africa
EOS	End of Study
ER	Emergency Room
FDA	United States Food and Drug Administration
FGM	Flash Glucose Monitoring

Abbreviation	Definition
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HFS	Hypoglycemia Fear Survey
HL	HelpLine
ICHOM	International Consortium for Health Outcomes Measurement
ICU	Intensive Care Unit
IFU	Instructions for Use
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
MAGE	Mean Amplitude of Glycemic Excursions
MDI	Multiple Daily Injections
MDRD	Modification of Diet in Renal Disease (equation)
NGSP	National Glycohemoglobin Standardization Program
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
PIC	Patient Information and Informed Consent Form
QC	Quality Control
RA	Regulatory Authority
RF	Radio Frequency
RT	Real-Time
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
TDD	Total Daily Dose
TIR	Time in Range
TLS	Transport Layer Security
USADE	Unanticipated Serious Adverse Device Effect

3. Introduction

3.1 Background

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

Patients who are using continuous glucose monitoring, including sensor-augmented pump therapy, experience improvements in glycemic control (Bergenstal, 2010; Battelino, 2012). 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 (suspend on low) or is predicted to be reached (suspend before low). 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 (Bergenstal, 2013; Bosi, 2019).

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 administered subcutaneously. 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 no longer be required.

One arm of the study will assess the MiniMed™ 670G running in advanced hybrid closed loop (AHCL) mode. The MiniMed™ 670G hybrid closed loop system is currently in commercial distribution in the United States and in an increasing number of European countries. Real world data from the MiniMed™ 670G in the United States has documented safety and efficacy in adults and children (Stone, 2018). There have, however, been further advancements to the hybrid close loop proportional integrative derivative (PID) algorithm model that seek to improve functionality and efficacy based on retrospective analysis of data from the MiniMed™ 670G insulin pump, using a modified proportional integrative derivative model, with insulin feedback and additional safety features. These enhancements intended to maximize time spent in hybrid closed-loop operation, in order to further improve glucose control and overall user satisfaction. Advancement have been implemented in the new system with the algorithm version 4.0, such as automatic correction bolusing, sensor glucose based meal bolusing, automatic calibrations of Blood Glucose (BG) measurements transmitted to the pump and a variable target for automatic basal deliveries, all of which are intended to contribute to a reduction of unnecessary Auto Mode exits, which will consequently increase time in euglycemic range and overall user satisfaction.

The advanced algorithm receives continuous glucose monitoring (CGM) data every 5 minutes, and a "basal rate" insulin delivery is computed and adjusted every five minutes. Therefore, standard "basal" insulin that is pre-programmed in regular insulin pump therapy is replaced by the algorithm derived insulin delivery (given as a micro-bolus every 5 minutes).

Meals will be announced, and sensor glucose based insulin bolus for a meal will be delivered according to the individualised patient carbohydrate ratio and insulin sensitivity factor.

In 2018, Dr. O'Neil conducted a feasibility study exploring the function of an updated iteration of the MiniMed™ 670G in Australian adults. Overall, the study showed a high percentage of time in Auto Mode with reduced Auto Mode exits per week. Overall, the subjects spent 83.8% of time in range (70 mg/dL to 180 mg/dL) with a mean sensor glucose of 125.2 mg/dL.

In 2018, Prof. Phillip conducted another feasibility study to further assess the safety and efficacy of the AHCL algorithm in adolescents and young adults in Israel, in order to refine the algorithm and assure the safety of the system, prior to entering into the planned pivotal studies to obtain market access of the AHCL algorithm in the MiniMed™ 670G System.

Following these feasibility studies, several studies are currently ongoing on AHCL MiniMed™ 670G System to demonstrate the safety and effectiveness on the AHCL MiniMed™ 670G System version 4.0 (**Table 1: AHCL**). Nevertheless, additional clinical evidence is required to support the available efficacy and safety data with additional long-term data of the AHCL system in comparison with the current standard of care for Type 1 Diabetes.

Across the world, the majority of Type 1 Diabetes patients requiring insulin are treated with Multiple Daily Injection (MDI) therapy. While a growing population have access to diabetes technology through Flash Glucose Monitoring (FGM) or Continuous Glucose Monitoring (CGM) in the EMEA region, a large proportion of insulin requiring patients with Type 1 Diabetes on MDI therapy with FGM or CGM still have sub-optimally controlled diabetes management with a HbA1c > 8.0 % (64 mmol/mol). Additional long-term efficacy and cost-effective data will be needed to further support market access and adoption of AHCL therapy for those patients who are not well controlled with the current standard of care for Type 1 diabetes patients requiring insulin.

Table 1: AHCL clinical studies

Study	Design	Primary Endpoints	Status
Dr. O'Neil	7days hotel/clinic + 3 weeks at home, single arm, with 12 subjects >18 years old with Type 1 Diabetes in Australia	Feasibility	Completed
Prof. M. Phillip	1 week, single arm with 12 subjects >14-40 years old with Type 1 Diabetes in Israel	Feasibility	Completed
Dr. De Bock	4 weeks, randomized vs PLGM, two-sequence cross-over with 60 subjects >7 – 70 years old with Type 1 Diabetes in New Zealand	Safety and Efficacy, Time in Range 3.9-10 mmol/L and Time in Hyperglycemia >10 mmol/L	Completed
Medtronic Pivotal study	12 weeks, single arm in 250 subjects > 7 years old with Type 1 in United States	Safety, HbA1c	Expected completion 2020
FLAIR Study	12 weeks, randomized vs 670G, two-sequence crossover multi-center study in 112 subjects 14-30 years old with Type 1 Diabetes in United States, Germany, Slovenia and Israel	Efficacy and Safety, Time in Hyperglycemia >10 mmol/L and Time in Hypoglycemia 3.0 mmol/L	Completed 2020
Medtronic ADAPT study	2 weeks run-in + 6-month randomized phase AHCL vs MDI, single crossover + 6-month continuation AHCL with 124 subjects > 18 years old with Type 1 Diabetes in France, UK and Germany	Efficacy and Safety, HbA1c	Expected completion 2021

This Statistical Analysis Plan (SAP) will be used to support analysis of the continuation phase of the ADAPT study. The Statistical Analysis Plan has been designed to document, before data is analyzed, the planned analyses for the final report. 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 final report. Analyses not planned in the SAP and incorporated into the final report will be referred to as "not-prespecified". Further, in case any analyses will be done differently than planned in the CIP or SAP, an explanation will be provided in the final report.

4. Continuation Phase Objectives

All analysis in this document is exploratory. Cohort A and Cohort B will be analysed independently.

4.1.1 Objective for Control Group

The primary objective for control group is to evaluate the superiority on glycemic control of the AHCL system in continuation phase versus MDI therapy in study period.

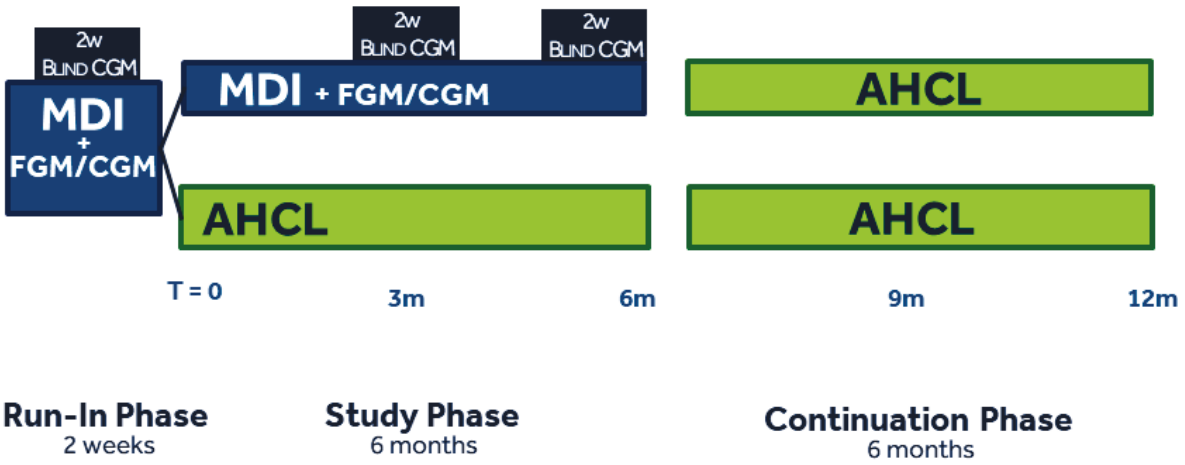
4.1.2 Objective for Treatment Group

The primary objective is to confirm the long-term benefits of AHCL therapy. The non-inferiority on glycemic control of the AHCL system in continuation phase versus in study period will be tested.

5. Investigation Plan

This study is a pre-market, multi-center, prospective, open label, adaptative, confirmatory, randomized controlled trial in insulin-requiring adult subjects with type 1 diabetes on MDI therapy. The study period for each subject will be approximately 13 months.

Figure 1: Study Design



The study consists of two separate cohorts, Cohort A with subjects on MDI + FGM (confirmatory part of the study) and Cohort B with Subjects on MDI + Real-Time CGM (exploratory part of the study). Each cohort will have a separate randomization.

5.1 Duration

Overall study duration from first subject enrollment until the last subject exit is expected to last approximatively 25 months, including an estimated 6-month site activation period, 6-month enrollment period, and a 13-month follow-up period for each subject.

Each subject will enter a run-in phase of approximately 2 weeks, followed by a study phase of 6 months, then a 6-month continuation phase.

5.2 Randomization

If subjects meet the inclusion and exclusion criteria, as well as all the following criteria assessed at the end of the run-in period, they may continue to participate in the study phase:

1. Subject has worn the sensor with blinded transmitter during the run-in period adequately, per investigator judgment.
2. Subject has shown acceptable tolerance to sensor wear, per investigator judgment.
3. CareLink data shows subject performed ≥ 2 finger stick blood glucose measurements daily, as determined by CareLink data upload as the mean number of SMBG/day over the past 14 days.
4. Subject has shown compliance with study procedures, per investigator judgment.

Subjects in each cohort will be randomized into 2 arms at the end of the run-in phase:

Cohort A (confirmatory): Subjects on **MDI + FGM** will be randomized into:

- Treatment Arm: Start AHCL (and stop FGM at visit 6A)
- Control Arm: Continue MDI + FGM

Cohort B (exploratory): Subjects on **MDI + Real-Time CGM** will be randomized into:

- Treatment Arm: Start AHCL (and stop CGM at visit 6A)
- Control Arm: Continue MDI + CGM

Each cohort will have a separate randomization.

6. Determination of Sample Size

Subjects entered the continuation phase after completed the study period. All subjects with data in the continuation phase will be included in the analysis. No power analysis has been done for this exploratory phase of the study. All analysis in this document is exploratory.

6.1 Sample Size for Study period

Subjects will be enrolled in the study at up to 20 investigational centers in EMEA (see Clinical Investigation Plan section 6.2).

In Cohort A, approximately 84 MDI + FGM subjects will be enrolled to achieve approximately 70 subjects randomized and 64 subjects completing the 6-month study phase.

In addition, in Cohort B approximately 40 MDI + RT-CGM subjects will be enrolled to achieve 34 subjects randomized and 30 subjects completing the 6-month study phase.

6.2 Sample Size Considerations for Study Period

For Cohort A (MDI+FGM), the sample size calculation was performed based on the following assumptions: alpha=0.05, power=80%, 0.7 standard deviation and 0.5 reduction in mean change of HbA1c in the treatment arm, as compared to the control arm, which is the minimum clinically meaning difference. The standard deviation was based on the *Eurythmics study* (Hermanides, 2011) comparing SAP therapy (Treatment arm) vs MDI (control arm) with a pooled standard deviation of 0.83.

Based on these assumptions, the minimum sample size required is 64 subjects (32 in each arm) in Cohort A comparing AHCL with MDI + FGM subjects.

The following drop-out assumptions have been taken into account, based on experience with previous studies: At screening: 10%; After run-in: 5%; During 6-month follow-up: 7.5%.

Incorporating these drop-out rates, a total of 84 subjects need to be screened in Cohort A (AHCL vs MDI+FGM) in order to have 74 subjects starting the run-in phase, 70 subjects randomized to start the treatment phase and 64 subjects to complete the study phase (6 months). To minimize imbalance in the number of subjects across sites, a minimum of 4 and a maximum of 20 subjects of the cohort should be randomized at each site, with the current sample size.

For the exploratory analysis in Cohort B, comparing MDI + CGM versus AHCL, 30 subjects will be required for analysis. Incorporating the expected dropout rates, a total of 40 subjects need to be screened, in order to have 36 subjects starting the run-in phase, 34 subjects randomized to start the treatment phase and 30 subjects to complete the study. Subjects will be randomized in a 1:1 ratio to the 2 arms.

7. Statistical Methods

The methods in this section are applicable to cohort A and cohort B in continuation phase. The analysis is focused on comparing the therapy outcomes of control group between the study period and continuation phase in cohort A. Similar analysis for treatment group will be conducted as well. These methods are also applicable to cohort B.

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects entered, completed, and early terminated in the continuation phase for each group and both cohorts 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

7.1.3.1 Efficacy analysis set

For the primary, secondary and ancillary endpoints efficacy analyses will be performed in the Intent to Treat (ITT) basis. The ITT set will be composed of all subjects who entered the continuation phase.

7.1.3.3 Safety set

Safety analysis will include all subjects entered continuation phase and safety data will be presented. Any AE and SAE occurring after the date of visit 9 to the date of Visit 13 will be reported as happening in the continuation phase and will be reported according to the randomization arm that the subject was assigned. For comparison of safety in the two periods, the safety set is compos
ed of all subjects in study period and continuation phase and assessed and analyzed as members of each period.

7.2 General Methodology

The data from control group and treatment group will be evaluated independently for all endpoints. Also, Cohort A and Cohort B will be analysed independently.

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. For comparison of primary, secondary, and ancillary endpoints, normality will be verified for appropriate statistical methodology. Comparisons between the study phase and the continuation phase will be performed using a paired T-test for testing the statistical significance of the difference in continuous variables if normality assumption is met or Wilcoxon signed rank test in continuous variables if normality assumption is not met.

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

7.3 Center Pooling

Data will be pooled for exploratory analysis.

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

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

7.5 Adjustments for Multiple Comparisons

7.5.1 Exploratory Analysis for Control group

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity.

Fixed sequential testing of primary and selected secondary endpoints
For the following endpoints, the procedure test hierarchically the ordered hypotheses in sequence at level α=0.05 until a first hypothesis is non-rejected.

Primary endpoint
1. Change in HbA1c
Change in HbA1c will be tested for superiority as described in section 7.9.1.1 and a p-value < 0.05 will be considered statistically significant. If p-value < 0.05, continue to next test, else stop.

Secondary endpoints
2. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL
Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop
3. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL
Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop
4. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL
Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop
5. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL
Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop
6. Percentage of time spent within range 70 - 180 mg/dL
Non-inferiority test with non-inferiority margin of 6%, if p-value<0.05 reject null hypothesis and continue, else stop
7. Percentage of time spent within range 70 - 180 mg/dL
Superiority test, if p-value<0.05 reject null hypothesis and continue, else stop
8. Percentage of time spent in hypoglycemic range with SG < 54 mg/dL
Non-inferiority test with non-inferiority margin of 2 %, if p-value < 0.05 reject null hypothesis and continue, else stop
9. Percentage of time spent in hypoglycemic range with SG < 70 mg/dL
Non-inferiority test with non-inferiority margin of 5 %, if p-value < 0.05 reject null hypothesis and continue, else stop

Additional analysis
Superiority test for percentage of time spent in hypoglycemic range with SG < 54 mg/dL, < 70 mg/dL and

analyses on ancillary endpoints and safety endpoints may be performed, and p-values will be reported but may not be claimed.

7.5.2 Exploratory Analysis for Treatment Group

The following hierarchical test procedure reflects the relative importance of the endpoints and controls for multiplicity.

Fixed sequential testing of primary and selected secondary endpoints

For the following endpoints, the procedure test hierarchically the ordered hypotheses in sequence at level α=0.05 until a first hypothesis is non-rejected.

Primary endpoint

1. Change in HbA1c

Change in HbA1c will be tested using a non-inferiority test with margin of 0.3%, 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.

Secondary endpoints

2. Percentage of time spent in hyperglycemic range with SG > 250 mg/dL

Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

3. Percentage of time spent in hyperglycemic range with SG > 180 mg/dL

Non-inferiority test with non-inferiority margin of 6%, if p-value < 0.05 reject null hypothesis and continue, else stop

4. Percentage of time spent within range 70 - 180 mg/dL

Non-inferiority test with non-inferiority margin of 6%, if p-value<0.05 reject null hypothesis and continue, else stop

5. Percentage of time spent in hypoglycemic range with SG < 54 mg/dL

Non-inferiority test with non-inferiority margin of 2 %, if p-value < 0.05 reject null hypothesis and continue, else stop

6. Percentage of time spent in hypoglycemic range with SG < 70 mg/dL

Non-inferiority test with non-inferiority margin of 5 %, if p-value < 0.05 reject null hypothesis and continue, else stop

Additional analysis

Analyses on ancillary endpoints and safety endpoints may be performed, and p-values will be reported but may not be claimed.

7.6 Demographic and Other Baseline Characteristics

A summary of basic subject demographics, medical history and other baseline characteristics will be reported using appropriate summary statistics (number of subjects (n), mean, standard deviation, median, minimum and maximum for continuous variables; frequency and percentages for categorical variables). Baseline summary for all subjects and by treatment group will be presented. Demographics, medical history and other baseline characteristics will be obtained from eCRF and baseline sensor data. Baseline variables to be summarized include, but are not limited to: age, sex, weight, BMI, country of enrollment, HbA1c, Diabetes history, Creatinine Clearance value and total insulin dose per day.

7.7 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

Not applicable for continuation phase.

7.9 Evaluation of Objectives

7.9.1 Exploratory Analysis for Control group

7.9.1.1 Primary Endpoints: Mean HbA1c

As the control group switched to AHCL therapy during the continuation phase, the goal is to compare the mean HbA1c from the end of study phase (6 months) to the end of continuation phase (12 months) within control group (MDI+FGM). The within group difference in the mean HbA1c is of primary interest and will be compared using the following hypotheses:

Null-hypothesis: H_0: $HbA1c_{\text{study period}} = HbA1c_{\text{continuation phase}}$

Alternative hypothesis: H_a: $HbA1c_{\text{study period}} \neq HbA1c_{\text{continuation phase}}$

Where $HbA1c_{\text{study period}}$ is the mean HbA1c (6 months [Visit 8]) of the control group, and $HbA1c_{\text{continuation phase}}$ is the mean HbA1c (12 months [Visit 13]) of the control group. The null hypothesis will be tested against the alternative hypothesis using paired t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected. Superiority of AHCL will be concluded if $HbA1c_{\text{study period}} > HbA1c_{\text{continuation phase}}$.

7.9.1.2 Secondary Endpoints

The blinded (for study period) or unblinded (for continuation phase) sensor data collected during the 2 periods of 2 weeks (at 3 months and 6 months for the study phase, and at 9 month and 12 month in the continuation phase) will be combined and then used to perform all statistical test mentioned below. Descriptive summaries of all outcomes mentioned below generated with all 6 month SG data in continuation phase will be provided as well.

7.9.1.2.1 Percentage of Time in Range (70-180 mg/dL), in Hyperglycemia (> 180 mg/dL, > 250 mg/dL) and Hypoglycemia (< 54 mg/dL, < 70 mg/dL)

Percentage of time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L), in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L), > 250 mg/dL (13.9 mmol/L) and in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) will be computed using the sensor data collected during each of the 2 periods of 2 weeks. The last 8064 sensor readings (4 weeks) from each period will be used for analysis.
The percentage of time spent within range (70-180 mg/dL) for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG between } 70-180 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

The percentage of time spent in hyperglycemic range > 180 mg/dL or > 250 mg/dL for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG} > 180 \text{ or} > 250 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

Similarly, the percentage of time spent in hypoglycemic range < 54 mg/dL or < 70 mg/dL for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG} < 54 \text{ or} < 70 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

The within group difference of Time in specific range (70-180, <54, <70, >180, >250 mg/dL) between study period and continuation phase will be compared using paired t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected.

7.9.1.3 Ancillary Endpoints

The blinded (for study period) or unblinded (for continuation phase) sensor data collected during the 2 periods of 2 weeks (at 3 months and 6 months for the study phase, and at 9 month and 12 month in the continuation phase) will be combined and then used to perform all statistical test mentioned below. Descriptive summaries of all outcomes mentioned below generated with all 6 month SG data in continuation phase will be provided as well.

Superiority test will be applied to ancillary endpoints if needed.

7.9.1.3.1 Number of Biochemical Hypoglycemic events

A biochemical hypoglycemic event with SG < 54 mg/dL is defined as sensor glucose values less than 54 mg/dL (3.0 mmol/L) for 15 or more consecutive minutes. A biochemical hypoglycemic event with SG < 70 mg/dL is defined as sensor glucose values less than 70 mg/dL (3.9 mmol/L) for more than 20 consecutive minutes. When the time between two successive events is less than 30 minutes, they will be combined and counted as one event. The mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) per subject per week based on 15 and 20 consecutive minutes will be computed using the sensor data collected during each of the 2 periods of 2 weeks. The last 4032 sensor readings (2 weeks) from each period will be used for analysis. The mean number of hypoglycemic events (MNHE) per week at each period for each subject will be calculated as:

$$\frac{\text{number of biochemical hypoglycemic event for subject i at period j}}{\text{duration of sensor wear for subject i at period j in weeks}}$$

Where the duration of sensor wear for subject i at period j is the number of sensor readings (capped at 4032) for subject i at period j divided by 2016. Mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L) based on 20 minutes definition and < 70 mg/dL (3.9 mmol/L) per week based on 15 minutes definition will be analyzed and reported as additional analyses. Analysis on mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L) (based on 15 minutes) will be using non-inferiority test with non-inferiority margin of 35% of the observed mean in the control group.

7.9.1.3.2 Mean of Sensor glucose Values and GMI

Mean number of sensor glucose (SG) in mg/dL and GMI will be analyzed and reported. The mean SG and GMI for a subject at period j will be calculated as the overall mean of the SG and GMI values (maximum of 8064 readings closer to the visit during the period.

7.9.1.3.3 Standard Deviation (SD) and Coefficient of Variation of Sensor Glucose Values (CV)

The standard deviation (SD) and coefficient of variation of sensor glucose values (CV) will be analyzed and reported. The CV for subject i at period j will be calculated as:

$$\frac{\text{standard deviation of sensor glucose values for subject i at period j}}{\text{mean of sensor glucose values for subject i at period j}}$$

The mean of sensor glucose values for subject i at period j will be calculated as described in section 7.9.1.2.3 The standard deviation of sensor glucose values for subject i at period j will be the standard deviation of all sensor readings (with maximum of 4032 recent readings) during period j.

7.9.1.3.4 Amplitude of Glycemic Excursions (MAGE)

The excursion amplitudes of the glucose values measured by mean amplitude of glycemic excursions (MAGE) will be calculated for two periods using the blinded 4 weeks sensor glucose data from study phase and unblinded 4 weeks sensor glucose data from continuation phase. Analysis will be performed and reported.

7.9.1.3.5 Percentage of Time Spent in Auto Mode and in Manual Mode

The percentage of time spent in auto mode and manual mode for subjects in the continuation phase will be calculated as:

$$\frac{\text{time spent in auto/manual mode}}{\text{total time in AHCL therapy}} \times 100\%$$

Descriptive statistics for the percentage of time in auto mode and manual mode.

7.9.1.3.6 Percentage of Sensor Use for Continuation Phase

Descriptive statistics for the percentage of sensor use during the 6 months (After visit 9 to visit 13) continuation phase will be reported.

7.9.1.3.7 Change in Weight and BMI

The change in weight and BMI from 6 month (Visit 8) to end of 12 months continuation phase (Visit 13) will be calculated, analyzed and reported.

7.9.1.3.8 Change in Total Daily Insulin Dose

The change in total daily insulin dose from end of study phase to end of continuation phase will be computed, analyzed and reported. The total daily insulin dose will be based on self-reported data (from CRF) when in study period and will be based on pump data uploaded in CareLink Clinical in continuation phase. No comparison but only descriptive of TDD will be performed in the control phase.

7.9.1.3.9 Mean number of SMBG

The mean number of self-monitored blood glucose (SMBG) readings and mean of SMBG values will be calculated in study period and continuation phase from the pump data uploaded in CareLink Clinical and will be reported using summary statistics for quantitative variables.

7.9.1.3.10 Lost days from school or work

Summary number of lost days from school or work will be reported during study phase and continuation phase.

7.9.1.3.11 Questionnaires' scores

The Hypoglycemia Fear Survey (HFS) score, Diabetes Treatment Satisfaction Questionnaire (status version, DTSQs and change version DTSQc) scores and Diabetes Quality of Life Questionnaire (DQoL) will be calculated in each study arm and reported using descriptive statistics for quantitative variables.

Hypoglycemia Fear Survey (HFS)

Hypoglycemia can lead to various aversive symptomatic, affective, cognitive, physiological, and social consequences, which in turn can lead to the development of possible phobic avoidance behaviors associated with hypoglycemia. The hypoglycemia fear survey (HFS) is a psychometric instrument designed to quantify this fear. The instrument has internal consistency and test-retest stability and varies with elevated glycosylated hemoglobin. The HFS has in most translations two subscales, the behavior subscale and the worry subscale and has a recollection period of 6 months. The two subscales of the HFS are scored as: behavior subscale (first 15 items) items are added together,
the 18 Worry subscale items are added together. Additionally, a total score, adding all 33 items, will be computed. Descriptive statistics for the HFS score (behavior, worry and total) will be reported for Visit 2 (baseline), visit 8 (end of 6 months) and visit 13 (end of 12 months).

DTSQs and DTSQc

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) has been specifically designed to measure satisfaction with diabetes treatment regimens in people with diabetes. The DTSQ [status version (DTSQs)] is an eight-item questionnaire, in which six questions (items 1, 4, 5, 6, 7 and 8) assess treatment satisfaction and the other two assess perceived frequency of hyper- and hypoglycemia. Each item is scored from 6 (very satisfied) to 0 (very dissatisfied) such that the Treatment Satisfaction score can range from 36 (very satisfied) to 0 (very dissatisfied) and the perceived frequency of hyper- and hypoglycemia scores range from 6 (most of the time) to 0 (none of the time).
Although the DTSQs has proved highly sensitive to change, in many studies where patients are very satisfied with treatment used at baseline, the DTSQs cannot show improvements when they switch to a new treatment, even though they might be even more satisfied with the new treatment. To overcome the limitation of the DTSQs, a change version (DTSQc) has also been developed, which asks participants to rate how their current treatment compared with their previous treatment.

The DTSQc instrument contains the same 8 items as the DTSQs version. The difference lies in the wording of the response options and instructions, which, in the DTSQc, direct the respondent to compare their experience of treatment before the study began. All items are rated from +3 to -3.
The DTSQc instructions and response options differ from those of the DTSQs to produce measures of relative change in satisfaction rather than measures of absolute satisfaction:
Treatment satisfaction (change): items 1, 4, 5, 6, 7 and 8 are summed to produce a Treatment Satisfaction (change) score (range: +18 to -18). The higher the score, the greater the improvement in

satisfaction with treatment; the lower the score, the greater the deterioration in satisfaction with treatment. A score of 0 represents no change.
A major advantage of the DTSQs and DTSQc is that they have been developed to be suitable for people with type 1 or type 2 diabetes using a wide range of treatments, including various methods of insulin delivery, oral medications and diet alone, and is, therefore, appropriate for use before and after patients switch between very different treatment regimens.
Descriptive statistics for DTSQs will be reported for Visit 2 (baseline), visit 8 (end of 6 months) and visit 13 (end of 12 months).

Diabetes Quality of Life Questionnaire (DQoL)
DQoL has been widely used to measure quality of life among diabetes patients. The instrument has four scales: satisfaction with treatment, impact of treatment, worries about future effects of diabetes, and worries about social and vocational issues. The instrument also includes a generic health item that does not contribute to the scales. A score will be obtained for each dimension. A higher score represents higher quality of life. Descriptive statistics for the DQoL score will be reported for Visit 2 (baseline), visit 8 (end of 6 months) and visit 13 (end of 12 months).

7.9.2 Exploratory Analysis for Treatment group

7.9.2.1 Primary Endpoint: Mean HbA1c

As the treatment group were still using AHCL therapy during the continuation phase, the goal is to check the equivalence of the mean HbA1c from the end of study phase (6 month) to the end of continuation phase (12 month) within control group (MDI+FGM). The within group difference in the mean HbA1c will be compared using the following hypotheses:

Null-hypothesis: H_0: $HbA1c_{\text{continuation phase}} \geq HbA1c_{\text{study period}} + 0.3\%$

Alternative hypothesis: H_a: $HbA1c_{\text{continuation phase}} < HbA1c_{\text{study period}} + 0.3\%$

Where $HbA1c_{\text{study period}}$ is the mean HbA1c (6 months [Visit 8]) of the control group, and $HbA1c_{\text{continuation phase}}$ is the mean HbA1c (12 months [Visit 13]) of the control group. The null hypothesis will be tested against the alternative hypothesis using paired t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected.

7.9.2.2 Secondary Endpoints

All sensor data collected during the 6 month study period and 6 month continuation phase will be used to perform all statistical test mentioned below. Descriptive summaries of all outcomes mentioned below generated with all 6 month SG data in continuation phase will be provided as well.

7.9.2.2.1 Percentage of Time in Range (70-180 mg/dL), in Hyperglycemia (> 180 mg/dL, > 250 mg/dL) and Hypoglycemia (< 54 mg/dL, < 70 mg/dL)

Percentage of time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L), in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L), > 250 mg/dL (13.9 mmol/L) and in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) will be computed using the sensor data collected during 6 months from each period will be used for analysis.
The percentage of time spent within range (70-180 mg/dL) for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG between } 70-180 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

The percentage of time spent in hyperglycemic range > 180 mg/dL or > 250 mg/dL for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG} > 180 \text{ or} > 250 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

Similarly, the percentage of time spent in hypoglycemic range < 54 mg/dL or < 70 mg/dL for subject i at period j will be calculated as:

$$\frac{\text{Total number of sensor reading with SG} < 54 \text{ or} < 70 \text{ mg/dL for subject i at period j}}{\text{Total number of sensor readings for subject i at period j}}$$

The within group difference of Time in specific range (70-180, <54, <70, >180, >250 mg/dL) between study period and continuation phase will be compared using paired t test if normality assumption is met, Wilcoxon signed rank test if normality assumption is rejected.

7.9.2.3 Ancillary Endpoints

Non-inferiority test will be applied to ancillary endpoints if needed.

7.9.2.3.1 Number of Biochemical Hypoglycemic events

A biochemical hypoglycemic event with SG < 54 mg/dL is defined as sensor glucose values less than 54 mg/dL (3.0 mmol/L) for 15 or more consecutive minutes. A biochemical hypoglycemic event with SG < 70 mg/dL is defined as sensor glucose values less than 70 mg/dL (3.9 mmol/L) for more than 20 consecutive minutes. When the time between two successive events is less than 30 minutes, they will be combined and counted as one event. The mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) per subject per week based on 15 and 20 consecutive minutes will be computed using the sensor data collected during each of the 2 periods of 6 months. The mean number of hypoglycemic events (MNHE) per week at each period for each subject will be calculated as:

$$\frac{\text{number of biochemical hypoglycemic event for subject i at period j}}{\text{duration of sensor wear for subject i at period j in weeks}}$$

Where the duration of sensor wear for subject i at period j is the number of sensor readings (capped at 4032) for subject i at period j divided by 2016. Mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L) based on 20 minutes definition and < 70 mg/dL (3.9 mmol/L) per week based on 15 minutes definition will be analyzed and reported as additional analyses. Analysis on mean number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L) (based on 15 minutes) will be using non-inferiority test with non-inferiority margin of 35% of the observed mean in the control group.

7.9.2.3.2 Mean of Sensor glucose Values and GMI

Mean number of sensor glucose (SG) in mg/dL and GMI will be analyzed and reported. The mean SG and GMI for a subject at period j will be calculated as the overall mean of the SG and GMI values.

7.9.2.3.3 Standard Deviation (SD) and Coefficient of Variation of Sensor Glucose Values (CV)

The standard deviation (SD) and coefficient of variation of sensor glucose values (CV) will be analyzed and reported. The CV for subject i at period j will be calculated as:

$$\frac{\text{standard deviation of sensor glucose values for subject i at period j}}{\text{mean of sensor glucose values for subject i at period j}}$$

The mean of sensor glucose values for subject i at period j will be calculated as described in section 7.9.1.2.3 The standard deviation of sensor glucose values for subject i at period j will be the standard deviation of all sensor readings during period j.

7.9.2.3.4 Amplitude of Glycemic Excursions (MAGE)

The excursion amplitudes of the glucose values measured by mean amplitude of glycemic excursions (MAGE) will be calculated for two periods using the 6 months sensor glucose data. Analysis will be performed and reported.

7.9.2.3.5 Percentage of Time Spent in Auto Mode and in Manual Mode

The percentage of time spent in auto mode and manual mode for subjects in the continuation phase will be calculated as:

$$\frac{\text{time spent in auto/manual mode}}{\text{total time in AHCL therapy}} \times 100\%$$

Descriptive statistics for the percentage of time in auto mode and manual mode.

7.9.2.3.6 Percentage of Sensor Use for Continuation Phase

Descriptive statistics for the percentage of sensor use during the 6 months (After visit 9 to visit 13) continuation phase will be reported.

7.9.2.3.7 Change in Weight and BMI

The change in weight and BMI from 6 month (Visit 8) to end of 12 months continuation phase (Visit 13) will be calculated, analyzed and reported.

7.9.2.3.8 Change in Total Daily Insulin Dose

The change in total daily insulin dose from end of study phase to end of continuation phase will be computed, analyzed and reported. The total daily insulin dose will be based onpump data uploaded in CareLink Clinical in both study and continuation phase.

7.9.2.3.9 Mean number of SMBG

The mean number of self-monitored blood glucose (SMBG) readings and mean of SMBG values will be calculated in study period and continuation phase from the pump data uploaded in CareLink Clinical and will be reported using summary statistics for quantitative variables.

7.9.2.3.10 Lost days from school or work

Summary number of lost days from school or work will be reported during study phase and continuation phase.

7.9.2.3.11 Questionnaires' scores

The Hypoglycemia Fear Survey (HFS) score, Diabetes Treatment Satisfaction Questionnaire (status version, DTSQs and change version DTSQc) scores and Diabetes Quality of Life Questionnaire (DQoL) will be calculated in each study arm and reported using descriptive statistics for quantitative variables.

Hypoglycemia Fear Survey (HFS)

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the 18 Worry subscale items are added together. Additionally, a total score, adding all 33 items, will be computed.
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Descriptive statistics for DTSQs will be reported for Visit 2(baseline), visit 8 (end of 6 months) and visit 13 (end of 12 months).

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7.10 Safety Evaluation

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 her self, 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 reported in the eCRF, during Continuation Phase will be reported. Total number of severe hypoglycemic events during the Continuation Phase (from date of Visit 9 to date of Visit 13) will be reported by treatment arm. The number of severe hypoglycemic events per year will be computed for each subject based on the entire continuation phase duration (happening after Visit 10 to and including Visit 13). If a subject i is followed up for x_i years and the number of observed severe hypoglycemic events during that follow up is m_i, 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 study arm.

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 continuation phase categorized bystudy arm. 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 periods.

7.10.3 Number of Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects and Device Deficiencies

Serious Adverse Event (SAE) is 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 disease, 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

For the purpose of this study, the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Device Effect (SADE) is adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Unanticipated Serious Adverse Device Effect (USADE) is serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current e risk assessment.

Device deficiency 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 labeling. This definition includes device deficiencies related to the investigational medical device or the comparator.

The number of serious adverse events, serious adverse device effects, unanticipated serious adverse device effects, device deficiencies (DD), DD with SADE potential will be reported for run-in and study phase categorized by study arm. The listing of these events will also be reported.

7.11 Health Outcomes Analyses

Not applicable.

7.12 Changes to Planned Analysis

This SAP will be executed in full but does not limit the analysis in reports, and additional analysis of the study data beyond this plan is expected. Analyses beyond the SAP will be identified as such and referred

to as not pre-specified. Any deviation from the analyses described in this statistical analysis plan and a justification for making the change, will be described in the clinical study report.

8. Validation Requirements

Level I validation is required for Statistical and SAS programming of primary and secondary endpoints. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

For the other endpoints, baseline characteristics and other summary outputs, minimally a Level II validation will be used. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

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