Medtronic

Study Title	ADvanced Hybrid Closed Loop study in Adult Population with Type 1 Diabetes (ADAPT)
NCT Number	NCT04235504
Document Description	Clinical Investigational Plan (Version H)
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Medtronic

Clinical Investigation Plan (CIP)

Clinical Investigation Plan/Study 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*
Clinical Investigation Plan Identifier	327 *EUDAMED number will be provided under a separate cover, when applicable.*
Study Product Name	MiniMed™ 670G system version 4.0 AHCL
Sponsor/Local Sponsor	Medtronic International Trading Sàrl. ("Medtronic") Route du Molliau 31 1131 Tolochenaz, Switzerland
EU-based Legal representative of the Sponsor	Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	H
Version Date	17 SEP 2020
Document Reference Number	10933285DOC

1. Investigator Statement

Study product Name	MiniMed™ 670G system version 4.0 AHCL
Sponsor	Medtronic International Trading Sàrl
Clinical Investigation Plan Identifier	327
Document Reference Number	10933285DOC
Version Number/Date	Version G / Date 17 SEP 2020
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. *I agree to comply with International Standard ISO 14155:2020 (International Conference on Harmonization Guidelines on Good Clinical Practice), the protocol, and the applicable regulatory requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.* *I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.*	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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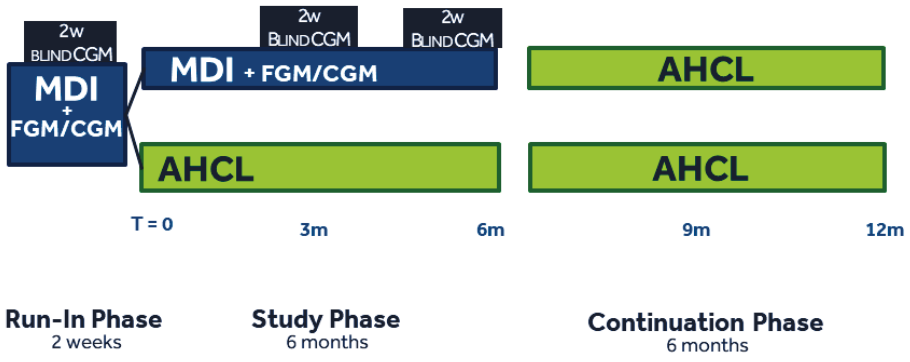
2. Glossary

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
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HFS	Hypoglycemia Fear Survey
HL	HelpLine
ICHOM	International Consortium for Health Outcomes Measurement
ICU	Intensive Care Unit

Abbreviation	Definition
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

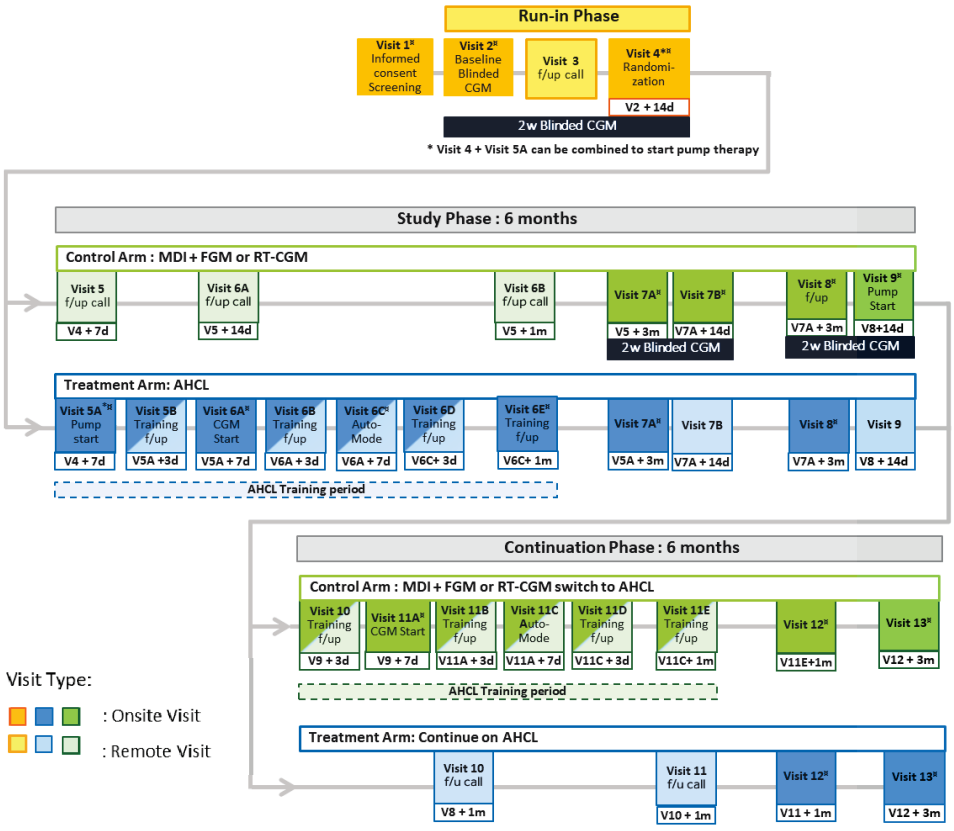
3. Synopsis

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*
Clinical Study Type	Premarket, interventional prospective, open-label, multi-center, adaptive, confirmatory and randomized controlled study
Product Name	Advance Hybrid Close Loop (AHCL) MiniMed™ 670G system version 4.0
Sponsor	Medtronic International Trading Sàrl ("Medtronic") Route du Molliau 31 1131 Tolochenaz, Switzerland *(Sponsor is the funding source)*
Indication under investigation	Type 1 diabetes (T1D)
Investigation Purpose	The purpose of the study is to evaluate the safety and efficacy of the Advanced Hybrid Closed Loop (AHCL) system in sub-optimally controlled patients with T1D, in comparison with Multiple Daily Injection (MDI) therapy with Flash Glucose Monitoring (FGM) or Continuous Glucose Monitoring (CGM).
Product Status	The following investigational products will be provided during the study: ▪ AHCL MiniMed™ 670G Insulin Pump, version 4.0 (referred to as "MiniMed™ 670G AHCL pump" or "AHCL pump" throughout the document) (MMT-1741 or MMT-1742) The following CE-marked products will be provided during the study: ▪ Guardian™ Sensor 3 (MMT-7020) ▪ Guardian™ Link 3 Transmitter accessories: – Guardian™ Link 3 Transmitter (MMT-7810) – Charger (MMT-7715) – Tester (MMT-7736L) ▪ CONTOUR® NEXT LINK 2.4 blood glucose meter by Ascensia (MMT-1151 or 1152) with CONTOUR® NEXT Test Strips ▪ One-press Serter (MMT-7512) ▪ CareLink™ Personal for Clinical Research Therapy Management Software (MMT-7333) or subsequent versions In addition, the Dock (T8381) and Download Utility Software (9029393) are study tools that will be used only by the center staff for sensor glucose data collection. Consumables and accessories will be provided during the study (detailed list in appendix 17.6).

Study Design	This is a pre-market, prospective, open-label, multi-center, adaptive, confirmatory and randomized controlled trial in patients with Type 1 diabetes. The study consists of a run-in phase, a study phase and a continuation phase. The purpose of the run-in phase is to collect CGM baseline data while subjects are on their current therapy. During the 6-month study phase, subjects will be randomized to continue with their current therapy or to start using the AHCL system. For the duration of the 6-month continuation phase, all enrolled subjects will be using the AHCL system. **Figure 1:** Study Design 
Randomization	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.
Sample Size and Investigational Sites	Subjects will be enrolled in the study at up to 20 investigational centers in EMEA (see section 13.3). 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.
Duration	The study is anticipated to last no longer than 19 months from center initiation to completion of all data entry and monitoring procedures. The study will target 6 months to complete enrollment. Subjects can expect to participate for approximately 13 months from the run-in period to end of study participation.
Inclusion Criteria	Subjects will be considered included in the study, if they meet all the following criteria and none of the exclusion criteria: 1. Subject is age ≥ 18 years old at time of screening 2. Subject has a clinical diagnosis of Type 1 diabetes for ≥ 2 years prior to screening as determined via source documentation 3. On MDI therapy (defined as ≥ 3 insulin injections per day and/or a basal/bolus regimen) ≥ 2 years prior to screening 4. Subject has been followed and treated by the investigator at this investigational site for at least 3 months prior to screening and subject has already undergone local educational therapeutic programs. 5. Subject is using: - Flash Glucose Monitoring (FGM) for ≥ 3 months with a daily average number of scans ≥ 5 over and with sensor readings > 70% of time over the previous month prior to screening (based on sensor usage from the download summary report of the FGM system over 30 days prior to screening) Or - Continuous Glucose Monitoring (CGM) for ≥ 3 months with a frequency of sensor use ≥ 70% of the time over the previous month prior to screening (based on download summary report from the CGM system over 30 days prior to screening). 6. Subject has a glycosylated hemoglobin (HbA1c) ≥ 8.0% (64 mmol/mol) at time of screening visit (as processed by a Central Lab). 7. Subject is willing to take or switch to one of the following insulins: a. Humalog™* (insulin lispro injection) b. NovoLog™* (insulin aspart) 8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 8 units and a maximum of 250 units. 9. Subject is willing to upload data from the study pump and meter, must have Internet access and a compatible computer system that meets the requirements for uploading the study pump data at home. 10. Subject is willing and able to sign and date informed consent, comply with all study procedures and wear all study devices, as required during the study.

Exclusion criteria	A subject who meets any of the following criteria will be excluded from participation in this study. 1. Subject has untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis, per investigator judgment. 2. Subject is using pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at time of screening. 3. Subject has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ 12 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations. 4. Subject is planning to switch from FGM to CGM therapy during the 6 months study phase. *Note: Subject randomized to Control Arm should remain on their current FGM or CGM therapy during the study phase and will be switched to AHCL during the continuation phase.* 5. Subject has a history of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices, per investigator judgment. 6. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study. 7. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study, per investigator judgment. 8. Subject has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 9. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, as per investigator judgment. 10. Subject is currently abusing illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine), per investigator judgment. 11. Subject has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment. 12. Subject is legally incompetent, illiterate or vulnerable person. 13. Research staff involved with the study.
Randomization criteria	If subjects meet the above 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.
Study Procedures and Assessments	**Figure 2: Visit schedule overview** *Under pandemic situation, all the visits can be conducted remotely and organized accordingly, per Investigator decision.*  *¤ Visits allowed to be conducted remotely in pandemic period.* *For study procedures details, refer to Section 9. and Appendix 17.8.*

Safety Assessments	All adverse events and device deficiencies will be collected and reported, as required. A Clinical Events Committee (CEC) will be responsible for assessing all Serious Adverse Events (SAEs), Serious Adverse Device Events (SADEs), Unanticipated Serious Adverse Device Events (USADEs), Severe Hypoglycemia, Diabetic Ketoacidosis (DKA) and Deaths. An independent Data Monitoring Committee (DMC) will advice regarding the continued safety of subjects.
Objective	The primary objective of the study is to evaluate the superiority on glycemic control of the AHCL system versus MDI + FGM in patients with Type 1 Diabetes.
Primary Endpoint	Confirmatory test for the difference in the mean HbA1c change (baseline versus 6 months) between the AHCL and the MDI + FGM arm will be performed. Measurements will be done from venous blood and analyzed as per National Glycohemoglobin Standardization Program (NGSP) standards in a central laboratory.
Secondary Endpoints	The following secondary endpoints will be assessed in AHCL vs MDI + FGM (Cohort A)): ▪ % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) ▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) ▪ % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L) ***Safety***: Number of severe hypoglycemic events, DKA events, SAEs, SADEs, USADEs and device deficiencies. The above endpoints will also be assessed in Cohort B in an exploratory manner, as well as the difference in the mean HbA1c change (6 months - baseline) between the AHCL and the MDI + RT-CGM arm.

Ancillary endpoints	▪ % Time spent in 70 - 140 mg/dL (3.9 -7.8 mmol/L) range ▪ Area Under the Curve (AUC) in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L) ▪ % Time spent and AUC in hyperglycemic range with SG > 140 mg/dL (7.8 mmol/L), >350 mg/dL (19,4 mmol/L) and AUC in hyperglycemic range with SG >180 (10 mmol/L)) , >250 mg/dL (13,9 mmol/L) ▪ Number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) (defined as sensor values below the threshold per 15 and 20 consecutive minutes). ▪ Mean of SG values (mg/dL) ▪ % Time spent in Auto Mode and in Manual Mode All the above endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00) and overall (24h). ▪ % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) ▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) ▪ % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L) The above five endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00). ▪ Number of scans and % of sensor readings for MDI + FGM control arm ▪ Number of SMBGs in the AHCL arm ▪ Percentage of sensor use ▪ Excursion amplitudes of the glucose values measured by mean amplitude of glycemic excursions (MAGE). ▪ Coefficient of variation of SG values ▪ Change in Total Daily Dose (TDD) of insulin from baseline to end of study (EOS) ▪ Change in weight from baseline to EOS ▪ Change in BMI from baseline to EOS ▪ Mean HbA1c change (from baseline to 12 months) ▪ Mean HbA1c change (baseline to 6 month) by age groups and duration of diabetes ▪ Diabetes-related number and mean duration of hospitalizations, number and mean duration intensive care unit (ICU) care, number of

	emergency room admissions, number of events requiring ambulance assistance, categorized by reason of diagnosis ▪ Number of lost days from school or work ▪ Hypoglycemia Fear Survey (HFS) score ▪ Diabetes Treatment Satisfaction Questionnaire score ▪ Diabetes Quality of Life (DQoL) questionnaire score These ancillary endpoints will also be assessed in Cohort B in an exploratory manner.
Statistical Analysis for Endpoints and Hypothesis	The primary analysis will be conducted in the Cohort A, comparing the AHCL vs MDI + FGM arms. **Primary Endpoint Analysis** The primary objective is to compare the mean HbA1c change from baseline to end of study (6 month) between control arm ($\Delta_{HbA1c\ MDI\ therapy + FGM}$) and treatment arm ($\Delta_{HbA1c\ AHCL}$). The null hypothesis H_O: $\Delta_{HbA1c\ MDI\ therapy + FGM} = \Delta_{HbA1c\ AHCL}$ will be tested against the alternative hypothesis H_A: $\Delta_{HbA1c\ MDI\ therapy + FGM} \neq \Delta_{HbA1c\ AHCL}$ using a linear mixed model (random effect model) that uses all available data and account for possible missing at random data. Analysis will be performed on the Intent to Treat (ITT) basis An exploratory analysis will be conducted in the Cohort B, comparing the AHCL vs MDI + RT-CGM arms (refer to section 13 for more details).

4. Introduction

4.1. 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

4.2. Purpose

The purpose of the study is to evaluate the safety and efficacy of the Advanced Hybrid Closed Loop (AHCL) in comparison with sub-optimally controlled patients on Multiple Daily Injection (MDI) therapy with Flash Glucose Monitoring (FGM) or Real-Time Continuous Glucose Monitoring (CGM) over 6 months duration.

5. Objective and Endpoints

5.1. Primary Objective

The primary objective of the study is to evaluate the superiority on glycemic control of the AHCL system versus MDI + FGM with patients with Type 1 Diabetes.

5.2. Exploratory Objective

A second objective of the study is to conduct an exploratory analysis on the efficacy of the AHCL system versus MDI + RT-CGM with patients with Type 1 Diabetes.

5.3. Endpoints

5.3.1. Primary Endpoint

HbA1c remains the reference marker for assessing glycemic control and predicting the risk of development of long-term complications (Danne, 2017; ICHOM, 2019).

Confirmatory test for the difference in the mean HbA1c change (baseline versus 6 months) between the AHCL and the MDI + FGM arm will be performed.

Measurements will be done from venous blood and analyzed as per National Glycohemoglobin Standardization Program (NGSP) standards in a central laboratory.

5.3.2. Secondary Endpoints

Secondary endpoints include diabetes control parameters to be evaluated in clinical studies following the recommendations from the International Consensus on CGM (Danne, 2017) and the International Consortium for Health Outcomes Measurement (ICHOM) standards for Diabetes (ICHOM, 2019).

Glycemic variability such as Time in Range(s) is now accepted as a clinically valuable marker of glycemic control beyond HbA1c alone (Danne, 2017).

Below secondary endpoints will be assessed in AHCL vs MDI + FGM (Cohort A)

- % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L)
- % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L)
- % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L)
- % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L)
- % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L)

5.3.2.1. Safety Endpoint

- Number of severe hypoglycemic events
- Number of DKA events
- Number of Serious Adverse Events (SAE)
- Number of Serious Adverse Device Effects (SADE)
- Number of Unanticipated Serious Adverse Device Effects (USADE)
- Number of Device deficiencies

The above endpoints will also be assessed in Cohort B in an exploratory manner, as well as the difference in the mean HbA1c change (6 months - baseline) between the AHCL and the MDI + RT-CGM arms.

5.3.3. Ancillary endpoints

- % Time spent in 70 - 140 mg/dL (3.9 -7.8 mmol/L) range
- Area Under the Curve (AUC) in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L), <70 mg/dL (3.9 mmol/L)
- % Time spent and AUC in hyperglycemic range with SG > 140 mg/dL (7.8 mmol/L), >350 mg/dL (19,4 mmol/L) and AUC in hyperglycemic range with SG >180 (10 mmol/L)), >250 mg/dL (13,9 mmol/L)
- Number of biochemical hypoglycemic events with SG < 54 mg/dL (3.0 mmol/L), < 70 mg/dL (3.9 mmol/L) (defined as sensor values below the threshold per 15 and 20 consecutive minutes).
- Mean of SG values (mg/dL)
- % Time spent in Auto Mode and in Manual Mode

All the above endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00) and overall (24h).

- % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L)
- % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L)
- % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L)
- % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L)
- % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L)

The above five endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00).

- Number of scans and % of sensor readings for MDI + FGM control arm
- % of sensor readings for MDI + RT-CGM control arm only.
- Number of SMBGs in the AHCL arm
- Percentage of sensor use
- Excursion amplitudes of the glucose values measured by mean amplitude of glycemic excursions (MAGE).
- Coefficient of variation of SG values
- Change in Total Daily Dose (TDD) of insulin from baseline to end of study (EOS)
- Change in weight from baseline to EOS
- Change in BMI from baseline to EOS
- Mean HbA1c change (from baseline to 12 months)
- Mean HbA1c change (baseline to 6 month) by age groups and duration of diabetes
- Diabetes-related number and mean duration of hospitalizations, number and mean duration intensive care unit (ICU) care, number of emergency room admissions, number of events requiring ambulance assistance, categorized by reason of diagnosis
- Number of lost days from school or work.
- Hypoglycemia Fear Survey (HFS) score

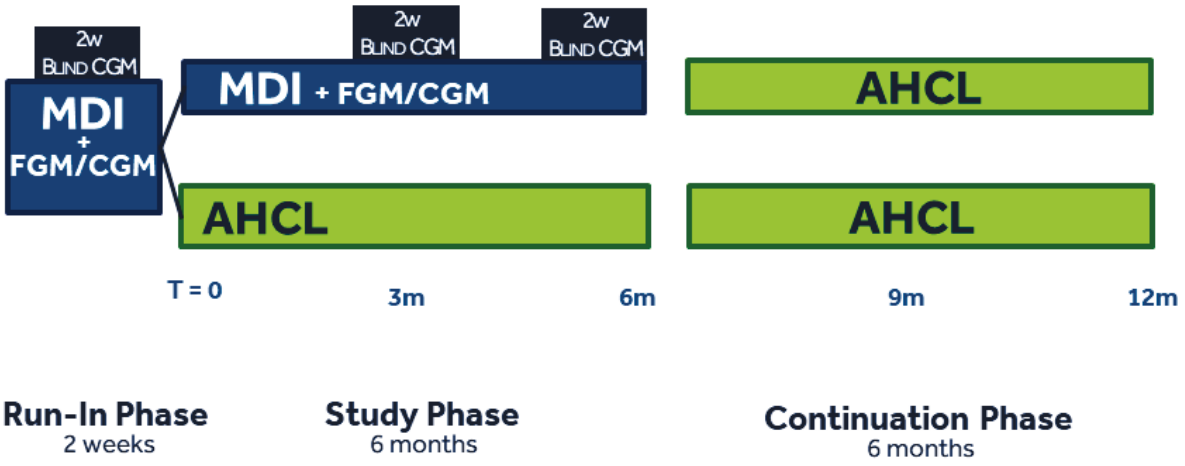
- Diabetes Treatment Satisfaction Questionnaire score
- Diabetes Quality of Life (DQoL) questionnaire score

These ancillary endpoints will also be assessed in Cohort B in an exploratory manner.

6. Study Design

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 3: 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.

6.1. 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.

6.2. Rationale

Several studies on the AHCL are being conducted to demonstrate the safety and the efficacy of the investigational configuration of this system (**Table 1**), however additional clinical evidence is required to evaluate its efficacy and safety over a longer duration in a home setting in comparison with MDI therapy with Flash or Continuous Glucose Monitoring, as the current standard of care (refer to section 4.1). This study is intended to show the benefit of Sensor Augmented Pump therapy (SAP) with AHCL in patients uncontrolled with MDI + FGM (or RT-CGM) which is expected to improve glycemic control in terms of HbA1c and time in target, versus the MDI + FGM (or RT-CGM) therapy.

7. Product Description

7.1. General Overview of the AHCL system

The Medtronic AHCL MiniMed™ 670G system version 4.0 evaluated in this study includes investigational insulin pump and CE-marked components, which will all be used within their intended use according to the labelling and instructions for use.

The AHCL MiniMed™ 670G system, version 4.0 system is indicated for management of type 1 diabetes.

Figure 4: AHCL MiniMed™ 670G system version 4.0

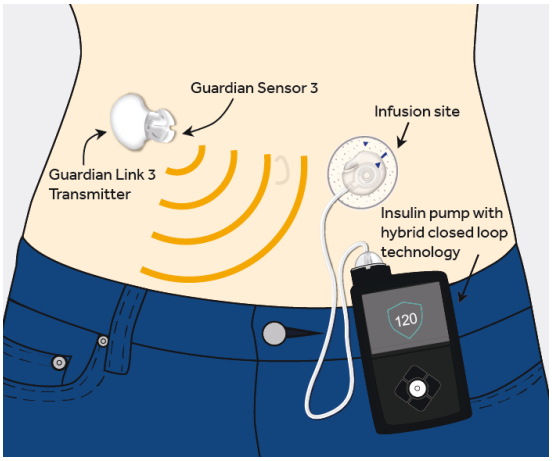


Table 2. Status of the AHCL System components and consumables

Device name	MDT Model number	Device Status
AHCL MiniMed™ 670G Insulin Pump, version 4.0	MMT-1741 or MMT-1742	Investigational ǂ
Guardian™ Sensor 3	MMT-7020	Non-Investigational / CE-marked
Guardian™ Link 3 Transmitter *	MMT 7810	Non-Investigational / CE-marked
Charger *	MMT-7715	Non-Investigational / CE-marked
Tester *	MMT-7736L	Non-Investigational / CE-marked
One-Press Serter*	MMT-7512	Non-Investigational / CE-marked
CareLink™ Personal For Clinical Research Software	MMT-7333	Non-Investigational / CE-marked
CONTOUR® NEXT LINK 2.4 blood glucose meter and CONTOUR® NEXT Test Strips by Ascensia	MMT-1151 or MMT-1152	Non-Investigational / CE-marked
Consumables and accessories	See appendix 17.6	Non-Investigational / CE-marked

ǂ *The insulin pump may receive CE-mark and become commercially available during the course of the study.*

**Devices may be combined and distributed in kits.*

Note: The Dock (T8381) and Download Utility Software (9029393) are study tools that will be used by the site staff only for sensor data collection with the Guardian Link 3 Transmitter used in a blinded mode. These tools are not evaluated during the study.

Table 3. Indicative numbers of devices per subject during the entire study

Item	Units per Subject (Treatment Arm)	Units per Subject (Control Arm)
AHCL MiniMed™ 670G Insulin Pump, version 4.0	1	1
Guardian™ Link 3 Transmitter	3	7
Guardian™ Sensor 3	84	52
One-press Serter	1	1
Reservoirs	130	70
Infusion Sets	130	70
Infusion Set Serter (if applicable)	1	1
AA Alkaline Battery	56	32
CONTOUR NEXT LINK 2.4 meter	1	1
CONTOUR NEXT Strips	3330	1990

7.2. AHCL MiniMed™ 670G Insulin Pump, version 4.0

The Medtronic AHCL MiniMed™ 670G Insulin Pump, version 4.0 system is intended for continuous insulin delivery of basal insulin, at user selectable and variable rates and administration of insulin boluses (in user selectable amounts), for the management of Type 1 diabetes mellitus (T1DM) in persons requiring insulin. When used with the CGM components (Guardian™ Sensor 3 and Guardian™ Link 3 transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels via a sensor that is inserted in the interstitial fluid under the skin, including the detection of possible low or high blood glucose episodes. The pump also displays glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled systems (e.g. MiniMed™ 530G, 670G systems in the US, MiniMed™ 640G and Veo systems outside the US).

The AHCL pump also includes the hybrid closed loop algorithm as part of the SmartGuard™ collection of features that may be enabled by the user. SmartGuard™ is comprised of Manual Mode Low Management, which includes the Suspend on low feature (suspends insulin delivery when a pre-set low SG threshold is reached), the Suspend before low feature (enables insulin to suspend 30 minutes before a pre-set low SG threshold is reached) and the Auto Mode (hybrid closed loop) feature. The Auto Mode and Manual Mode Low Management features will not be active at the same time.

The pump may also be used as a simple pump without CGM or as SAP without use of the SmartGuard™ features.

When Auto Mode is enabled on the AHCL pump, the SG values received from the Guardian™ Link 3 transmitter by the insulin pump will be used to automatically calculate a basal (background) insulin dose. It will then deliver insulin to the patient, at five-minute intervals, to achieve glycemic control.

When Auto Mode is not enabled, the user may use the Smart Guard™ Low Management features. Here, basal rate delivery will be suspended either when the SG has reached a programmed low threshold (Suspend on Low) or before the SG value has reached the programmed low threshold (Suspend before Low). If the Low Management features were programmed at the time Auto Mode was enabled, they will be automatically available in the event of an exit from Auto Mode.

With the AHCL system, subjects must still deliver bolus insulin for meals as calculated by the insulin to carbohydrate ratio. This ratio is determined by the Health Care Professional and patient. In addition, the setting for active insulin must be programmed in order for Auto Mode to function. Basal rates must be programmed by the health care provider/user for periods when patients are in Manual Mode.

Compared to the current commercialized MiniMed 670G system, the AHCL MiniMed 670G system version 4.0 includes the following advanced features:

- **Automatic Correction Bolus:** Automatic correction boluses that can be based on SG values and a lowered correction target from 150 to 120 mg/dL (8.3 to 6.7 mmol/L) to increase Time in Range (TIR).

- **Safe Meal Bolus algorithm:** Reduction of the amount of a meal bolus, if it is predicted to increase the risk of post-prandial hypoglycemia to increase TIR.
- **SG Based meal bolus:** Patients have the option to use a sensor glucose value to bolus for meals
- **Auto-Basal Control:** Optional lower basal rate target in Auto Mode, either 120mg/dL (6.7 mmol/L) or 100 mg/dL (5.6 mmol/L)
- **Confirmed Calibrations:** Each Blood Glucose Measurement is used as a calibration resulting in less unnecessary Auto Mode exits and missed calibrations, and consequently in less alarms to increase TIR and user satisfaction.

Figure 5. AHCL MiniMed™ 670G Insulin Pump, version 4.0

7.3. Other Non-Investigational Devices

The following non-investigational devices designated for use in the study are described in this section. These devices are all CE-marked and will be used within their intended use according to the labelling and instructions for use.

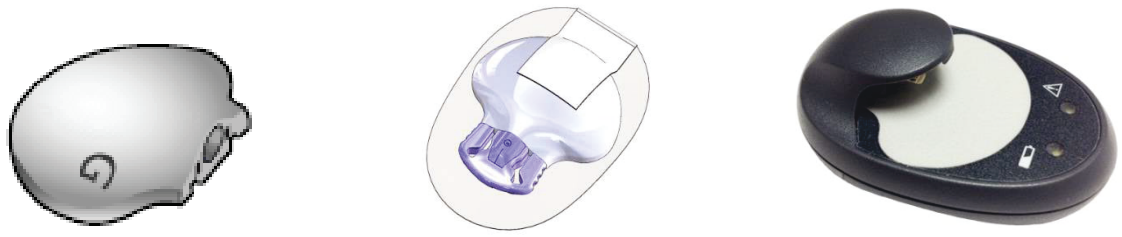
7.3.1. Guardian™ Sensor 3

The Guardian™ Sensor 3 glucose sensor, referred to as "sensor" in this protocol, is a subcutaneous sensor that contains one micro-electrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. It is intended to penetrate the skin at a 90-degree angle. The sensor is tubeless and as a result has a smaller volume than previous Medtronic MiniMed™ sensors (e.g. Enhanced Enlite). An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

7.3.2. Guardian™ Link 3 Transmitter

The Guardian™ Link 3 transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables the electrochemical impedance spectroscopy (EIS). The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic. In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration blood glucose (BG) values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D communication protocol). Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as "Smart Cal," instead of strictly scheduled time-based calibration.

Figure 6. Guardian™ Link 3 Transmitter



Transmitter | Transmitter + Sensor | Charger

7.3.3. One-Press Serter

The One-Press Serter, referred to as the Serter (Figure 7. One-Press Serter) in this protocol, is an insertion device that is used to ensure correct placement of the Guardian™ Sensor 3 into the user's subcutaneous tissue. Insertion is triggered when the two spring loaded buttons on the sides of the Serter are pressed simultaneously. The Serter is intended as a single patient, non-sterile, multi-use device.

Figure 7. One-Press Serter

7.3.4. Charger

The Charger is used to recharge the Guardian™ Link 3 Transmitter as needed. A fully charged battery provides up to 7 days of Guardian™ Link 3 Transmitter use. The system includes a battery charger that will recharge the device according to the user guide.

7.3.5. Tester

The Tester operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation.

7.3.6. CareLink™ Personal For Clinical Research Software

Medtronic CareLink™ Personal Therapy Management Software for Diabetes is an internet-based software system, which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A Personal Computer (PC) is used to access the Medtronic CareLink™ system via the Internet, which then allows subjects and site staff to upload data from Medtronic MiniMed™ insulin pumps and a range of system-supported, third-party BG meters.

The clinical support version of CareLink™ Personal Therapy Management Software for Diabetes used in this study was developed for use by site staff and subjects who are participating in clinical trials. For the purposes of this study, all references to CareLink™ Personal For Clinical Research software in this document relate to the clinical support version of Medtronic CareLink™ Personal Therapy Management Software for Diabetes (also referred to as “CareLink”). The data uploaded in CareLink is accessible to the subject and study site personnel only in a secured manner, using a standard browser (i.e., Microsoft Internet Explorer on an Internet enabled personal computer) and a unique study username (i.e., 327-XXX-XXX) and password created for each subject.

The CareLink™ Personal For Clinical Research system uses standard Transport Layer Security (TLS) technology. TLS transmission protocol invokes encryption on both ends of the transmissions and is the standard for all security-based systems. The encryption remains in effect whether the data is moving to and from the client and server in the United States, or to and from a client in another country to the United States. The data is secure behind a three-tier industry standard architecture, which places the database behind three different firewalls, where each firewall separates a tier:

- The internet to the web server;
- Web server to the application server;
- Application server to the database server.

7.3.7. CONTOUR® NEXT LINK 2.4 Study Meter

A Contour® NEXT LINK 2.4 BG meter, referred to as "study meter" in this protocol, will be provided to all subjects. The RF-enabled study meter measures a subject's capillary blood glucose level using the CONTOUR® NEXT Strips, which is then used to calibrate the glucose sensor. The result of the fingerstick (capillary SMBG) reading is sent into the AHCL pump and can be stored in its memory as a glucose data point.

7.3.8. Consumable devices and accessories

Infusion sets, reservoirs, infusion set serter devices, glucose meter accessories and other consumables and accessories will be provided to subjects for use in the study (refer to Appendix 17.617.6).

7.4. Study tools for Blinded CGM

The Guardian™ Link 3 attached to the Guardian™ Sensor 3 will be used as a blinded continuous glucose recording system at baseline and for the control arm recording and storing SG data. The Guardian™ Link 3 transmitter will not be linked to a MiniMed™ pump, and therefore sensor data will not be transmitted to the pump. The sensor data the transmitter contains will be downloaded with the Download Utility software to a computer. The recorded and transferred sensor data are blinded and not available to subjects and healthcare professionals. Therefore, this data cannot be used for therapy adjustment during the study and will only be used to collect data at baseline and for comparison with the treatment arm during study data analysis.

7.4.1.1. Dock for Guardian™ Link 3 Transmitters (T8381) – Investigational tool

The investigational Dock for the Transmitter (T8381), referred to as Dock in this protocol, is similar to the dock of the commercial iPro2 device which was slightly modified to be compatible with the Guardian Link 3 Transmitter when used as a blinded CGM recorder. It is being used in this study as tool serving two functions:

- It creates a communication link between the Guardian Link 3 Transmitter and a computer to be used for uploading the data stored on the transmitter and clearing the stored data. In this function, a USB cable connects the Dock to a USB port on the computer.

- It charges the internal battery of the Guardian Link 3 Transmitter, while it is docked in the Charger, that is either connected to a computer (while the computer is on) or to a wall-powered adapter. The wall-powered adaptor configuration will only charge the recorder and will not provide the upload functionality.

7.4.1.2. Download Utility Software (9029393) – Investigational software

The Download Utility for use with the Guardian™ Link 3 Transmitter in a blinded mode is an investigational computer-based program used to set time, upload data and clear data from the Transmitter. Communication between the Guardian™ Link 3 Transmitter and the computer is done via the Dock and USB cable.

The data contained in the Download Utility is transferred to a secured database by site personnel, using a standard browser, i.e., Microsoft Internet Explorer on an Internet enabled computer and a unique username and password for each site. The Download Utility provides encrypted data that can't be used during the study for therapy adjustments.

7.4.2. Packaging

The labelling of the Investigational devices and CE marked devices will be provided in accordance with local language requirements.
The outer packaging of the Investigational devices will be labelled "Exclusively for clinical investigations" and as required by national regulations, in local language(s) of the participating countries.

7.5. Insulin

Subjects will use their own rapid-acting analogue insulin (Novolog™ [aspart insulin] or Humalog™ [lispro insulin]) during this study.

7.6. Anticipated Devices Change

There are no changes anticipated for any of the devices during the course of the study.

7.7. Product Training Requirements

Device training for the Investigational center staff will organized prior to a clinical site's first subject enrollment. Training will be provided by Medtronic educators and/or clinical team.

7.8. Device Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational device used in a research trial. It is expected that all investigational devices will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions, and that they will be used only by subjects who have consented to participate in the research study.
Any investigational serialized device being used in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, Ethics Committee (EC)/ Institutional Review Board (IRB) have been received. This includes keeping records of:

1. Center receipt and inventory management
2. Subject Disbursement
3. Return (by Subjects and Center) and/or disposal

During the conduct of the study the investigational center staff will account for and document the following:

Table 4 Device Accountability Requirements

Device	Site Receipt: Device Acknowledgement of Receipt (AoR) at Investigational Site level (Site to sign packing slip)	Record Disbursement to Subject on Subject Device Disposition eCRF	Record Subject Return Device to Investigational Center (Subject Device Disposition eCRF)	Site Returns Device to Sponsor at Conclusion of Study	Destruction onsite
AHCL MiniMed™ 670G Insulin Pump, version 4.0	Yes	Yes	Yes	Yes	No
Guardian™ Link 3 Transmitter*	Yes-	Yes	Yes	Yes	No
CONTOUR®NEXT LINK 2.4 Study Meter	Yes	Yes	Yes	Return unused	If applicable, dispose used
One-Press Serter*	Yes	No	No	No	If applicable
Charger*	Yes	No	No	No	If applicable
Tester*	Yes	No	No	No	If applicable
Consumables (sensors, Infusion sets, reservoirs, strips, tape…)	Yes	No	No	No	If applicable
Dock (T8381)	Yes	N/A	N/A	Yes	No
Download Utility Software (9029393)	Software Installation certificate signed by Site	N/A	N/A	Software Uninstallation Certificate signed by Site	N/A

*Devices may be combined and distributed in kits.

Note: The Dock and Download Utility Software are study tools that will be used by the Investigational Site staff only for data collection with the Guardian Link 3 Transmitter used in a blinded mode. These tools are not evaluated during the study.

The investigational center will promptly notify the sponsor of any device handling violation that might impact either the safety or welfare of subjects or data integrity.

7.8.1. Receipt and Inventory of Investigational Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff must check the inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:
    - Ship to Address
    - Reference Number
    - Device Type
    - Quantity
    - Quantity per package
    - Lot number (where applicable)
    - Serial number (where applicable)
- Ensure that devices and supplies received have not reached or exceeded their expiration date
- Sign and date the packing slip/invoice, noting any discrepancies, send a copy to the Medtronic Study Team as an Acknowledgement of Receipt and file in appropriate study binder.
- Notify the Medtronic Study Team of any discrepancies.

7.9. Storage of Study Devices at Investigational Center

Study devices are to be stored in a secure environment with access limited to authorized research personnel. Study devices are stored in the appropriate environmental conditions as identified in the IFU/labelling.

7.10. Disbursement of Study Devices

Each time a serialized study device is disbursed to a subject by the investigator or authorized member of the research team, all required eCRF and source documentation will be completed (see Table 4). Documentation may include:

- Date of disbursement
- Subject ID
- Serial Number
- Amount dispensed

7.11. Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in **Table 4 Device Accountability Requirements** and store them in a secure environment. If

containers/units/devices are missing, the reasons should be documented. If discrepancies between the amounts used by subjects and the amounts expected to be returned exist, the reasons should be documented.

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in Table 4. The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at study closure or upon sponsor request.

Other unused consumable devices (i.e., infusion sets, alcohol wipes, study meter supplies, tape, etc.), will be disposed of appropriately by investigational center staff.

Disposable devices and supplies that have been used by a subject will be disposed of appropriately by the subject or the investigational center staff during the conduct of the study.

Disposal of devices and supplies will be documented in a destruction form.

All study devices that are required to be entered into the study database must be accounted for as described above before they are returned to the sponsor.

7.12. Comparator

Subject enrolled in the study are treated with any Multiple Daily Injection device and Flash or Continuous Glucose Monitoring systems. Subject can use any model, as prescribed per standard of care prior to screening, through the commercial pathway. There is no device accountability requirement for the comparator for the purpose of this study. Subjects will continue to use it as needed throughout the study, as per randomization assignment.
Examples of Flash Glucose Monitoring Systems: Abbott Freestyle Libre 1 or 2.
Examples of Continuous Glucose Monitoring systems: Dexcom G4, G5, G6; Medtronic Guardian Connect; Sugarbeat.
Any other model that may be/become available for prescription during the study can also be used.

8. Selection of Subjects

8.1. Study Population

Subjects (aged ≥ 18 years old) will be enrolled at up to 20 investigational centers in EMEA.

The study will include subjects in two different cohorts, as follow:
Cohort A with subjects on **MDI + FGM**

Cohort B with Subjects on **MDI + Real-Time CGM**

Approximately 84 MDI + FGM subjects will be enrolled in cohort A to achieve approximately 70 subjects randomized and 64 subjects completing the 6-month study phase. The primary and confirmatory analysis will be conducted on cohort A.
In addition, approximately 40 MDI + RT-CGM subjects will be enrolled in cohort B to achieve approximately 34 subjects randomized and 30 subjects completing the 6-month study phase. An exploratory analysis will be conducted on cohort B.

8.2. Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Patient Informed Consent Form (PIC).

A subject will be assigned a unique study subject identification (SID) via the eCRF, which is a 9-digit code (327-XXX-XXX). The first three digits refer to the CIP number (327), the next three digits refer to the investigational center number, and the last 3 digits refer to the subject number assigned during Visit 1 (e.g., 327002001 is subject 001 from site 002).

The investigator will maintain a log of all subjects enrolled in the clinical study, assigning a SID linked to their names, alternative subject identification and contact information.

A site-specific recruitment plan will be provided to all investigational sites at enrollment start to ensure enough subjects are enrolled with a balanced enrollment in both cohorts (e.g. MDI+FGM and MDI+CGM) and according to HbA1c (with a target of 50 % of subjects with HbA1c ≥ 8.5% (69 mmol/mol)) across the whole study population.

8.3. Inclusion Criteria

Subjects will be considered included in the study, if they meet all the following criteria and none of the exclusion criteria:

1. Subject is age ≥ 18 years old at time of screening
2. Subject has a clinical diagnosis of Type 1 diabetes for ≥ 2 years prior to screening as determined via source documentation
3. On MDI therapy (defined as ≥ 3 insulin injections per day and/or a basal/bolus regimen) ≥ 2 years prior to screening
4. Subject has been followed and treated by the investigator at this investigational site for at least 3 months prior to screening and subject has already undergone local educational therapeutic programs.
5. Subject is using:
   - Flash Glucose Monitoring (FGM) for ≥ 3 months with a daily average number of scans ≥ 5 over and with sensor readings > 70% of time over the previous month prior to screening (based on sensor usage from the download summary report of the FGM system over 30 days prior to screening)
   Or

- Continuous Glucose Monitoring (CGM) for ≥ 3 months with a frequency of sensor use ≥ 70% of the time over the previous month prior to screening (based on download summary report from the CGM system over 30 days prior to screening).

6. Subject has a glycosylated hemoglobin (HbA1c) ≥ 8.0% (64 mmol/mol) at time of screening visit (as processed by a Central Lab).
7. Subject is willing to take or switch to one of the following insulins:
    a. Humalog™* (insulin lispro injection)
    b. NovoLog™* (insulin aspart)
8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 8 units and a maximum of 250 units.
9. Subject is willing to upload data from the study pump and meter, must have Internet access and a compatible computer system that meets the requirements for uploading the study pump data at home.
10. Subject is willing and able to sign and date informed consent, comply with all study procedures and wear all study devices, as required during the study.

8.4. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from participation in this study.

1. Subject has untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis, per investigator judgment.
2. Subject is using pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at time of screening.
3. Subject has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ 12 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations.
4. Subject is planning to switch from FGM to CGM therapy during the 6 months study phase. *Note: Subject randomized to Control Arm should remain on their current FGM or CGM therapy during the study phase and will be switched to AHCL during the continuation phase.*
5. Subject has a history of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices, per investigator judgment.
6. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study.
7. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study, per investigator judgment.
8. Subject has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).
9. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, as per investigator judgment.
10. Subject is currently abusing illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine), per investigator judgment.

11. Subject has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment.
12. Subject is legally incompetent, illiterate or vulnerable person.
13. Research staff involved with the study.

8.5. Randomization Criteria

If subjects meet the above 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.

9. Study Procedures

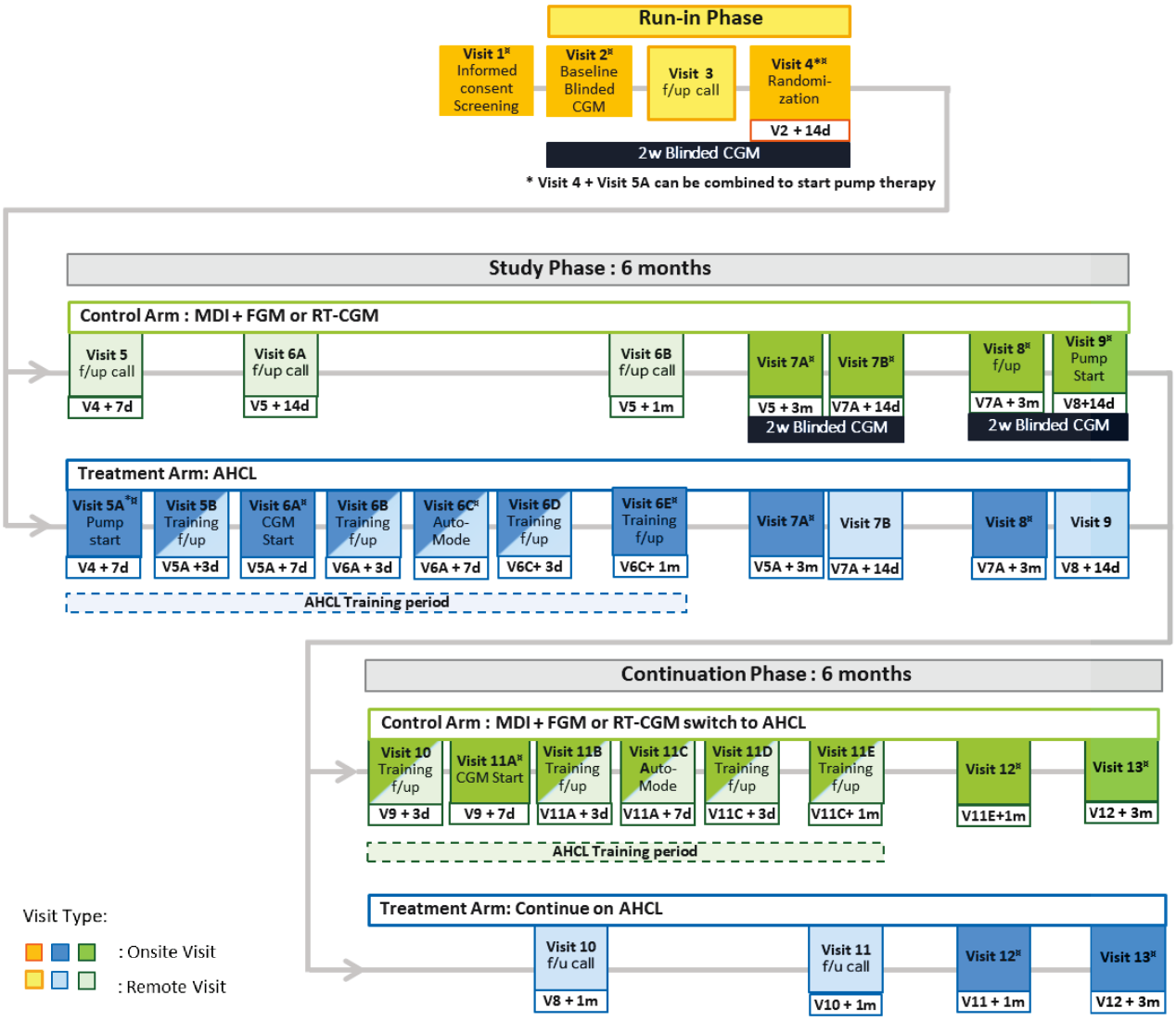
The below section and appendix 17.8: CIP327 Study Visit Procedures Table describe the study procedures that the subject will undergo during the clinical study.

9.1. Schedule of Events

Under pandemic situation, all the visits can be conducted remotely (via phone or video call) and organized accordingly (see details below), per Investigator decision. Investigator may decide to conduct a remote visit during pandemic to maintain safety and when onsite visit is not possible as it would expose subject and staff to increased risks. Rationale will be documented in the source files.

Figure 8: Visit schedule overview

¤ *Visits allowed to be conducted remotely in pandemic period.*



The ADAPT study is comprised of a run-in phase of approximately 2 weeks, a study phase of 6 months and a continuation phase of 6 months.

Prior to study start, Investigator or authorized designee must obtain written informed consent from the patient before any clinical study related activity (including screening) takes place and document informed consent process in the medical chart of the patient (refer to section 9.9 Subject Consent).

Eligible subjects must successfully complete the run-in phase by demonstrating tolerance to sensor wear and compliance with blinded Continuous Glucose Monitoring (CGM) prior to being randomized for the study phase, in which subjects will either be using the AHCL (Treatment Arm = T) or will continue under their MDI therapy + FGM/CGM (Control Arm = C) for another 6 months. After the end of the study phase of 6 months, subjects randomized to the Control Arm will crossover to AHCL pump therapy for another 6 months starting with an AHCL training program.

Successful completion of run-in phase requires blinded sensor glucose data and an average of at least 2 blood glucose (BG) measurements per day 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 repeat Blinded CGM.

Subjects that are randomized to the Treatment arm (T) will start a AHCL training program, including e.g. infusion set insertions/replacements, meal bolus procedure, what to do when exercising, when to perform calibrations, what to do with significant illness, how to react on safety/alert notifications, when to perform BG measurements and when to contact site staff and/or the HelpLine with the contact information provided.

Study Staff will conduct remote (via phone or video) or onsite visit following the Study Visit Schedule (Figure 8). The recommended minimum time on pump therapy alone before starting CGM in Manual Mode, and thereafter CGM in Auto Mode, is 7 days. Subjects will stop FGM/CGM at visit 6A, when starting on CGM in Manual Mode with AHCL system. Study staff will conduct at the minimum a subject visit (or may substitute for a phone contact) 3 days after pump, Manual Mode and Auto Mode have been started. Additional phone contacts or visits may be conducted (unscheduled visits), as needed.

Subjects will be expected to use Auto Mode at all times at home after completion of the pump training, and to perform approximately monthly uploads of the system, with a minimum upload prior to each phone or site contact for therapy review by site staff.

After the end of the study phase of 6 months, subjects randomized to the Control Arm will crossover to AHCL pump therapy for another 6 months starting with an AHCL training program.

Study staff will discuss with the participant the visit schedule and will make arrangements with the subjects for the contacts at site and the 24hr HelpLine (if applicable). Participants who are not compliant with the arranged contacts, which may impact patient's safety, may be discontinued at the discretion of the investigator.

9.2. STUDY START and RUN-IN PHASE

Visit 1: Screening

At this visit, the subject will come at the site or the visit will be conducted remotely:

The Investigational site staff will:

- Determine if subject meets eligibility criteria (see sections 8.3 and 8.4).
- Collect demographic information (age, gender)
- Review subject's Medical History: including date of Type 1 DM diagnosis, indication for Glucose Monitoring System, diabetes-related complications, length of time on MDI therapy (inclusion criteria ≥ 2 years), mean daily insulin dose, insulin molecule, type of FGM or RT-CGM therapy (model) with average number of scans and percentage of sensor readings for FGM users over the previous month (based on downloaded report) or percentage of use of CGM over the previous month (based on downloaded report) for CGM users (*Download Reports will be printed, signed and filed in the source document of the subject).*
- Measure/Collect height and weight
- Perform blood sample collection for **HbA1c** with central laboratory kit.
    - *Reminder*: HbA1c value ≥ 8.0% (64 mmol/mol) for inclusion

  Screening status will be confirmed once HbA1c result is received by the site from central lab. Repeated testing will not be permitted. Lab result will be printed, signed and filed in the source document of the subject.

  If the Visit 1 is conducted remotely, a nurse will visit the subject to collect the blood sample.
- Perform blood sample collection for **creatinine clearance** at local lab, if needed.
    - If creatinine clearance test was performed ≤ 12 months prior to screening, only confirm date of collection at local lab and creatinine clearance value in medical chart. Reminder: creatinine clearance threshold for exclusion< 30 mL/min and must be calculated with the Cockcroft or MDRD equations. The sites will follow routine practice for evaluation of the creatinine clearance. If the visit 1 is conducted remotely, a nurse visit can be organized with the subject to collect the blood sample.
- Perform **pregnancy test** at local lab (urinary or blood test), if applicable. The blood or urine sample will be collected and disposed according to the local Lab procedure.
  If the Visit 1 is conducted remotely, a nurse will visit the subject to collect the blood sample. Alternatively, a urinary pregnancy test can be shipped to the subject, if applicable. Result will be documented in medical chart.
- Report any Adverse Events, if applicable

If Visit 2 is planned to be conducted remotely, site staff can start initial training of the subject on Blinded CGM usage (sensor insertion, transmitter use) at this visit.

Visit 2: Start Run-In **[Visit 1 +7 days** (Window min + 3 d / max + 14 d)**]**

This visit can be done remotely or onsite.

- Site staff should confirm HbA1c result has been received prior to the visit and meet inclusion criteria (HbA1c ≥ 8.0%, 64 mmol/mol).

  Once eligibility has been confirmed, subject will start a 2-week run-in phase.

The objective of the 2-week run-in phase is to collect baseline data of CGM and assess subjects' compliance and ability to comprehend the study procedures and tolerance of wearing the sensor and transmitter continuously. Subjects continue their current MDI + FGM/CGM therapy during the run-in phase.

- Site staff will:
  - Train the subject on Blinded CGM usage (sensor insertion, transmitter use)
  - Advise subject to perform at least 4 fingerstick BG measurements per day with the study meter
  - Provide Blinded CGM Diary to Subject and instruct subject on diary completion
  - Instruct Subject to complete HFS questionnaire
  - Instruct Subject to complete DTSQs (status version of DTSQ) questionnaire
  - Instruct Subject to complete DQoL

If Visit 2 is conducted remotely, Questionnaires HFS, DTSQs and DQoL and Blinded CGM Diary will be sent to subject prior to the visit. Subject will ship them back to the site upon completion.

- Report any Adverse Events or Device Deficiency, if applicable
- Site staff will dispense supplies* to subject if visit is onsite, or ship the supplies to the subject prior to Visit 2 if the visit is conducted remotely.
  - 1 CONTOUR NEXT LINK 2.4 meter by Ascensia – *Subject will use this meter throughout the study*
  - 80 Strips *(indicative quantity for 3 weeks)*
  - 2 Guardian Link 3 Transmitters (1 is back-up),
  - 1 One-Press Serter
  - 1 Charger
  - 4 sensors (2 are back-up)
- Plan next call at Visit 3 with subject in 1 week and Visit 4 in 2 weeks.

** Note: All supplies quantities are indicative based on visit schedule and can be adjusted based on subject specific needs.*

Visit 3: Follow-Up Call **[Visit 2 + 7 days** (Window +3 days max)**]**

Site staff will call the subject to:

- Discuss sensor tolerance of subject since Visit 2
- Confirm that new sensor with same transmitter is started adequately with correct sensor insertion. Retrain subject if needed.
- Remind subject to perform at least 4 fingerstick blood glucose measurements per day with the study meter.
- Ask if any adverse event or device deficiency occurred.
- Confirm with subject next scheduled visit in 1 week (Visit 4).
- Remind subject to bring or ship back all devices and unused consumables upon blinded CGM completion for the next scheduled visit.

Visit 4*: End Run-In & Randomization **[Visit 2 + 14 days** (Window +7 days max)**]**
**Note: Visit 4 and Visit 5A can be combined to start pump therapy.*

This visit can be done remotely or onsite.

- If the Visit 4 is conducted remotely, subject will return the devices via post-mail/courier, using the provided shipping box prior to the visit.
- Site staff will collect /receive from the subject:
    - 1 Blinded CGM Diary
    - 1 CONTOUR NEXT LINK 2.4 meter by Ascensia
    - 2 Guardian Link 3 Transmitters
    - 1 Charger
    - One-Press Serter
    - Unused sensors, if applicable.

  And, if visit 2 was conducted remotely:
    - HFS questionnaire
    - DTSQs questionnaire
    - DQoL questionnaire

- Site staff will upload data from the Meter in CareLink™ Personal For Clinical Research using correct Subject ID (327-XXX-XXX).
- Site staff will upload data of Transmitter using the Download utility. Make sure to use correct file name (Subject ID_VISIT4_DATE). Refer to Blinded CGM Instructions for more details.
- Site staff will record average number of scans and % of sensor readings for FGM users and % of use of CGM for CGM users over the previous 2 weeks (based on downloaded and printed report). If the visit is conducted remotely, the site can contact the subject and record the data in medical chart or the subject can share the report via email.
- In case Blinded CGM data collection is less than 14 days (i.e. Sensor fell off), subject may be asked to repeat Blinded CGM and postpone Visit 4. Site can provide or ship new supplies to subject as needed to repeat the recording.
- Site staff will report any Adverse Events or Device Deficiency, if applicable
- Investigator will review randomization criteria per section 8.5.

If subject is eligible: subject will be randomized after completion of the Visit 4 eCRF to one of the 2 arms:

For the patients on MDI+FGM at baseline, a subject can be randomized into:

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

For the patients on MDI+ RT-CGM at baseline, a subject can be randomized into:

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

- **For subject randomized to the Treatment Arm:**
  Site staff will program AHCL insulin pump training.
  Visit 4 and Visit 5A can be combined to start pump therapy.

- **For All Subjects:**
  Site staff plans the visits with subject until Visit 9.
  It is strongly recommended to schedule all study visits and calls (Visit 5 to Visit 13) with the subject, following protocol visit schedule and visit windows.

If subject is not eligible: subject will be withdrawn from the study.
All devices and unused consumables will have to be returned to the site.

For patients randomized to Treatment arm for which Visit 5A is planned to be conducted remotely, site staff will ship supplies to subject:

- 1 AHCL insulin pump
- 250 Strips
- 10 Infusion sets (1 box of 10)
- 10 Reservoirs (1 box of 10)
- 8 AA batteries (2 packs of 4)

9.3. STUDY PHASE

Treatment Arm	Control Arm
Visit 5A: Pump Start **[Visit 4** + 7 days (Window ± 7 day)**]** *Note: Visit 4 and Visit 5A can be combined to start pump therapy.* This visit can be done remotely or onsite. Site staff will: ▪ Train subject on the AHCL insulin pump and subject starts using the insulin pump at this visit. ▪ Set-up subject CareLink Account. ▪ Train subject to perform weekly CareLink uploads. ▪ Dispense/Ship supplies to subject *(indicative quantity for 1 month):* ○ 1 AHCL insulin pump ○ 250 Strips ○ 10 Infusion sets (1 box of 10) ○ 10 Reservoirs (1 box of 10) ○ 8 AA batteries (2 packs of 4)	**Visit 5: Follow-up call** **[Visit 4** + 7 days (Window ± 5 days)**]** Study staff will call the subject to: ▪ Review therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any.

Treatment Arm	Control Arm
▪ Review adverse event or device deficiency, if any. If Visit 6A is planned to be conducted remotely: Site staff can start CGM training at Visit 5A and dispense/ship supplies to subject *(indicative quantity for 3 months*): ○ 1 Guardian Link 3 Transmitter kit ○ 20 sensors ○ 750 strips ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4) **Visit 5B: Pump Training Follow-Up** **[Visit 5A** + 3 days (Window ± 1 day)**]** This visit can be done by phone or onsite. Site staff will: ▪ Subject will be trained on first infusion set change and receive additional retraining on pump, as needed. ▪ Review AHCL therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload the AHCL into CareLink. Use correct Subject ID (327-XXX-XXX).	

Treatment Arm	Control Arm
Visit 6A: CGM Start **[Visit 5A** + 7 days (Window + 7 days)**]** This visit can be done remotely or onsite. Site staff will: ▪ Upload the AHCL into CareLink, if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done/Advise and (re)train subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump therapy as needed. ▪ Start CGM with AHCL (in Manual Mode) and subject stops FGM/RT-CGM. ▪ Review adverse event or device deficiency, if any. If visit is onsite: ▪ Dispense supplies to subject *(indicative quantity for 3 months*): ○ 1 Guardian Link 3 Transmitter kit ○ 20 sensors ○ 750 strips ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4)	**Visit 6A: Follow-up call** **[Visit 5** + 14 days (Window ± 5 days)**]** Study staff will call the subject: ▪ Review therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any.

Treatment Arm	Control Arm
Visit 6B **[Visit 6A** + 3 days (Window ± 1 day)**]** This visit can be done by phone or onsite. Site staff will: ▪ Ensure CareLink upload was done/Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM therapy as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX).	

Treatment Arm	Control Arm
Visit 6C: Auto Mode Start **[Visit 6A** + 7 days (Window -1 /+ 7 days)**]** This visit can be done by phone or onsite. Site staff will: ▪ Ensure CareLink upload was done/Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Site staff/Subject to start **Auto Mode** on AHCL. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX). **Visit 6D** **[Visit 6C** + 3 days (Window ± 2 days)**]** This visit can be done by phone or onsite. Site staff will: ▪ Ensure CareLink upload was done/Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX).	

Treatment Arm	Control Arm
Visit 6E **[Visit 6C** + 1 month (Window ± 14 days)**]** This visit can be done remotely or onsite. Site staff will: ▪ Upload AHCL into CareLink if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any.	**Visit 6B** **[Visit 5** + 1 month (Window ± 14 days)**]** Study staff will call the subject: ▪ Review therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any.
Visit 7A [**Visit 5A** + 3 months (Window ± 10 days)] This visit can be done remotely or onsite. Site staff will: ▪ Collect blood sample for HbA1c (central lab kit). If visit is conducted remotely, a nurse visit can be organized with the subject to collect the blood sample. ▪ Upload AHCL into CareLink, if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings ▪ Retrain subject on Pump/CGM as needed ▪ Review adverse event or device deficiency, if any. ▪ Dispense/Ship supplies to subject (indicative quantities for 3 months): ○ 750 Strips ○ 20 sensors ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4)	**Visit 7A** [**Visit 5** + 3 months (Window ± 10 days)] This visit can be done remotely or onsite. ▪ If the visit is planned remotely, site staff will ship the following supplies to the patient prior to the visit: ○ Blinded CGM Diary ○ 1 Contour Next Link 2.4 (subject uses same meter as dispensed previously) ○ 80 Strips ○ 2 Transmitters (1 is back-up) ○ 4 sensors (2 are back-up) ○ Charger ○ One-press Serter Site staff will: ▪ Collect blood sample for HbA1c (central lab kit). If visit is conducted remotely, a nurse visit can be organized with the subject to collect the blood sample. ▪ Review therapy / Adjust settings ▪ Review adverse event or device deficiency, if any ▪ Record % of use of CGM and average number of scans and % of sensor readings for FGM over the previous month (based on downloaded and printed report). If the

Treatment Arm	Control Arm
	visit is conducted remotely, the site can call the subject and record in medical chart or the subject can share the report via email. ▪ (Re)train the subject on Blinded CGM usage (sensor insertion, transmitter use) ▪ Advise subject to perform at least 4 fingerstick blood glucose measurements per day with the study meter ▪ Provide Blinded CGM Diary to Subject ▪ Dispense supplies to subject *(indicative quantity for 3 weeks):* o 1 CONTOUR NEXT LINK 2.4 meter (subject uses same meter as dispensed previously) o 80 Strips o 2 Transmitters (1 is back-up) o 4 sensors (2 are back-up) o Charger o One-press Serter ▪ If Visit 7B is planned to be conducted remotely, a shipping box with instructions for supplies return will be provided/shipped to the subject.
Visit 7B [Visit 7A + 14 days (Window + 7 days)**]** Site staff will call the subject to: ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any.	**Visit 7B [Visit 7A** + 14 days (Window + 7 days)**]** This visit can be done remotely or onsite. If the Visit 7B is conducted remotely, the subject will return the devices via post-mail/courier, using the provided shipping box. Upon receipt of the supplies at the site, site staff will conduct Visit 7B. Site staff will: ▪ Collect/Receive from the subject: o 1 Blinded CGM Diary o 2 Guardian Link 3 Transmitters1 CONTOUR NEXT LINK 2.4 meter o 1 Charger o One-press serter o Unused Sensors

Treatment Arm	Control Arm
	▪ Upload data from the Meter in CareLink using correct Subject ID (327-XXX-XXX). ▪ Upload data of Transmitter using the Download utility. Make sure to use correct file name (Subject ID_Visit7B_DATE). Refer to Blinded CGM Instructions for more details. ▪ Record % of use of CGM and average number of scans and % sensor readings for FGM over the previous 2 weeks (based on downloaded and printed report). If the visit is conducted remotely, the site can call the subject and write in medical chart or subject can share the report via email. ▪ Review therapy / Adjust settings

Treatment Arm	Control Arm
Visit 8: Follow-Up Visit **[Visit 7A** + 3 months (Window ± 10 days)**]** This visit can be done remotely or onsite. ▪ Ask subject to complete questionnaires HFS, DTSQs, DTSQc and DQoL during the visit. If the visit is planned remotely, site staff will send the questionnaires HFS, DTSQs, DTSQc and DQoL to the subject prior to the visit and subject will send them back to site upon completion. ▪ Collect blood sample for HbA1c (central lab kit). If visit is conducted remotely, a nurse visit can be organized with the subject to collect the blood sample. ▪ Upload AHCL into CareLink, if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings ▪ Retrain subject on Pump/CGM as needed ▪ Review adverse event or device deficiency, if any ▪ Measure/Collect height and weight. ▪ Dispense/Ship supplies to subject *(indicative quantity for 3 months):* ○ 20 sensors ○ 750 Strips ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4)	**Visit 8: Follow-Up Visit** **[Visit 7A** + 3 months (Window ± 10 days)**]** This visit can be done remotely or onsite. If the visit is planned remotely, site staff will send the following supplies/documents to the subject prior to the visit: ○ Blinded CGM Diary ○ 1 CONTOUR NEXT LINK 2.4 *(subject uses same meter as dispensed previously*) ○ 80 Strips ○ 2 Transmitters (1 is back-up) ○ 4 sensors (2 are back-up) ○ Charger ○ One-press Serter ○ Questionnaires HFS, DTSQs, DTSQc and DQoL ▪ Ask subject to complete questionnaires HFS, DTSQs, DTSQc and DQoL during the visit and to send them back upon completion ▪ Collect blood sample for HbA1c (central lab kit). If visit is conducted remotely a nurse visit can be organized with the subject to collect the blood sample. ▪ Review therapy / Adjust settings ▪ Review adverse event or device deficiency, if any. ▪ Measure/Collect height and weight ▪ Record % of use of CGM and average number of scans and % sensor readings for FGM over the previous month (based on downloaded report). If the visit is conducted remotely, the site can call the subject and record the data in medical chart or the subject can share the report via email. ▪ (Re)Train the subject on Blinded CGM usage (sensor insertion, transmitter use).

Treatment Arm	Control Arm
	▪ Advise subject to perform at least 4 fingerstick blood glucose measurements per day with the study meter. ▪ Provide Blinded CGM Diary to Subject ▪ Dispense supplies to subject *(indicative quantity for 3 weeks):* ○ 1 CONTOUR NEXT LINK 2.4 *(subject uses same meter as dispensed previously*) ○ 80 Strips ○ 2 Guardian Link 3 Transmitters (1 is back-up) ○ 4 sensors (2 are back-up) ○ Charger ○ One-press serter

Treatment Arm	Control Arm
Visit 9: End of Study Phase **[Visit 8** + 14 days (Window + 7 days)**]** Site staff will call the subject to: ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads ▪ Review AHCL therapy / Adjust settings ▪ Review adverse event or device deficiency, if any. ▪ Plan the next visits until Visit 13.	**Visit 9: End of Study Phase / Pump Start** **[Visit 8** + 14 days (Window + 7 days)**]** This visit can be done remotely or onsite. If the Visit 9 is conducted remotely, the subject will return the devices dispensed at Visit 8 via post-mail/courier, using the provided shipping box. Upon receipt of the supplies at the site, site staff will conduct Visit 9. ▪ Collect/Receive from the subject: ○ 1 Blinded CGM Diary ○ 2 Guardian Link 3 Transmitters ○ 1 CONTOUR NEXT LINK 2.4 meter ○ 1 Charger ○ One-press serter ○ Unused Sensors ▪ Upload data from the Meter in CareLink using correct Subject ID (327-XXX-XXX). ▪ Upload data of Transmitter using the Download utility. Make sure to use correct file name (Subject ID_Visit9_DATE). Refer to Blinded CGM Instructions for more details. ▪ Record % of use of CGM and average number of scans and % sensor readings for FGM over the previous 2 weeks (based on downloaded and printed report). If the visit is conducted remotely, the site can call the subject and document this in medical chart or subject can share the report via email. ▪ Review adverse event or device deficiency, if any. ▪ Site staff will train subject on the AHCL insulin pump and subject starts using the insulin pump. ▪ Set-up subject CareLink Account. ▪ Train subject to perform weekly CareLink uploads.

Treatment Arm	Control Arm
	▪ Dispense supplies onsite or ship supplies to subject prior to Visit 9 if visit is conducted remotely to subject *(indicative quantity for 1 month):* ○ 1 MiniMed™ 670G version 4.0 AHCL ○ 250 Strips ○ 10 Infusion sets (1 box of 10) ○ 10 Reservoirs (1 box of 10) ○ 8 AA batteries (2 packs of 4) ▪ Plan the next visits until Visit 13.

Table 5 RUN-IN and STUDY PHASE PROCEDURES

Visit Number	V1	V2	V3	V4*	V5A* T only	V5 C only	V5B T only	V6A	V6B	V6C T only	V6D T only	V6E T only	V7A	V7B	V8	V9
Visit Name	Scree-ning	Start Run-in	FU	End Run-in/ Rando	Pump Start	FU	FU	CGM Start /FU	Training FU	Auto Mode	Training FU	Training FU	3M FU	FU	6M FU	End Study Phase
Visit Type	Visit/	Visit/	call	Visit/	Visit/	call	Visit/ call	T: visit/call C: call	T: visit/call C: call	Visit/ call	Visit/ call	Visit/	Visit/	C: visit/ T: call	Visit/ I	C: visit/ T: call
Pandemic measure	Remote ¤	Remote ¤		Remote ¤	Remote ¤			Remote ¤				Remote ¤	Remote ¤	Remote ¤	Remote ¤	Remote ¤
Target date		V1 + 7d	V2 + 7d	V2 + 14d	V4 + 7d	V4 + 7d	V5A + 3d	T: V5A +7d C: V5 +14d	T: V6A +3d C: V5 +1m	V6A + 7d	V6C + 3d	V6C + 1m	T:V5A +3m C: V5 +3m	V7A+14d	V7A+3m	V8 + 14d
Window	-	+3/+14d	+3d	+7d	± 7d	± 5d	± 1d	T : +7d C : ± 5d	T : ± 1d C : ± 14d	-1 / +7d	± 2d	± 14d	± 10d	+7d	± 10d	+ 7d
Informed consent	X[1]															
Eligibility criteria	X	X														
Randomization				X												
Demographics	X															
Medical history	X															
Height and weight	X														X	
HbA1c (Central lab)	X												X		X	
Creatinine test (local lab)	O															
Pregnancy test (local lab)	O															
Blinded CGM training		X	X										C		C	
Blinded CGM placement		X	X										C		C	
Give Blinded CGM diary		X											C		C	
Collect Blinded CGM diary				X										C		C
Blinded CGM upload				X										C		C
Meter upload in CareLink				X										C		C
Review FGM/CGM usage	X			X									C	C	C	C
Pump & CareLink training					T		T	T	T	T	T	T	T		T	C
CGM training								T	T	T	T	T	T		T	
Auto-Mode Training/Start										T						
CareLink upload at site							T°	T	T°	T°	T°	T°	T		T	
CareLink upload by subject							T	T	T	T	T	T	T		T	T
Review therapy					T	C	T	X	X	T	T	T	X	X	X	X

Visit Number	V1	V2	V3	V4*	V5A* T only	V5 C only	V5B T only	V6A	V6B	V6C T only	V6D T only	V6E T only	V7A	V7B	V8	V9
Visit Name	Scree-ning	Start Run-in	FU	End Run-in/ Rando	Pump Start	FU	FU	CGM Start /FU	Training FU	Auto Mode	Training FU	Training FU	3M FU	FU	6M FU	End Study Phase
HFS questionnaire		X													X	
DTSQs questionnaire		X													X	
DTSQc questionnaire															X	
DQoL questionnaire		X													X	
AEs and DDs	Reported upon awareness															
Study deviations	Reported upon awareness															
Device Accountability		X		X	T			T	T°	T°	T°		X	C	X	C
Distribution supplies		X			T			T	T°	T°	T°		X		X	C
Return supplies				X										C		C

Notes:

X = both arms; **T** = Treatment arm; **C** = Control arm; **O / °=** Optional; **FU**= Follow Up

[1] Informed Consent must be obtained prior to any study conducted activity including screening procedures.

[2] Only for subjects who did not have recent results <12 months prior to screening (see Visit 2: Screening for details).

[3] Early Termination visit should be performed at any time if patient withdraws after randomization (Visit 4) and before the end of the study (Visit 13).

* Visit 4 and Visit 5A can be combined to start pump therapy.

¤ In pandemic situation, visit can be conducted remotely.

9.4. CONTINUATION PHASE

Treatment Arm	Control Arm
Visit 10 Follow-up call **[Visit 8** + 1 month (Window ± 7 days)**]** Site staff will call the subject to: ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any.	**Visit 10 Training Follow-Up** **[Visit 9** + 3 days (Window ± 1 day)**]** This visit can be done remotely or onsite. Subject will be trained on infusion set change and receive additional retraining on pump, as needed. Site staff will: ▪ Review AHCL therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX).
Visit 11 Follow-up call **[Visit 10** + 1 month (Window ± 7 days)**]** Site staff will call the subject to: ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Review adverse event or device deficiency, if any.	**Visit 11A CGM Start** **[Visit 9** + 7 days (Window + 7 days)**]** This visit can be done remotely or onsite. ▪ Upload AHCL into CareLink if visit is onsite. Use correct Subject ID (327-XXX-XXX) ▪ Ensure CareLink upload was done /Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump as needed. ▪ Start CGM with AHCL (Manual Mode) and subject stops FGM/RT-CGM. ▪ Review adverse event or device deficiency, if any. If Visit is planned to be conducted remotely, site staff can dispense supplies to subject at a previous visit or ship those to subject prior to the visit ▪ Dispense/ship supplies to subject *(indicative quantity for 3 months):* ○ 1 Guardian Link 3 Transmitter kit ○ 20 sensors ○ 750 strips

Treatment Arm	Control Arm
	○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4) **Visit 11B Follow-up** **[Visit 11A** + 3 days (Window ± 1 day)**]** This visit can be done remotely or onsite. ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX). **Visit 11C Auto Mode Start** **[Visit 11A** + 7 days (Window -1/+7 days)**]** This visit can be done remotely or onsite. ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Start Auto Mode on AHCL. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX)

Treatment Arm	Control Arm
	Visit 11D Follow-up **[Visit 11C** + 3 days (Window ± 2 day)**]** This visit can be done remotely or onsite. ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX). **Visit 11E Follow-up** **[Visit 11C** + 1 month (Window ± 14 days)**]** This visit can be done remotely or onsite. Site staff will: ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. If the visit is conducted onsite, site staff will additionally: ▪ Upload AHCL into CareLink. Use correct Subject ID (327-XXX-XXX).

Treatment Arm	Control Arm
Visit 12 [Visit 11 + 1 month (Window ± 10 days)**]** This visit can be done remotely or onsite. ▪ Upload AHCL into CareLink if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. ▪ Plan next visit with subject in 3 months. ▪ Dispense/ship supplies to subject *(indicative quantity for 3 month):* ○ 20 sensors ○ 750 Strips ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4)	**Visit 12 [Visit 11E** + 1 month (Window ± 10 days)**]** This visit can be done remotely or onsite. ▪ Upload AHCL into CareLink if visit is onsite. Use correct Subject ID (327-XXX-XXX). ▪ Ensure CareLink upload was done / Advise subject to perform weekly CareLink uploads. ▪ Review AHCL therapy / Adjust settings. ▪ Retrain subject on Pump/CGM as needed. ▪ Review adverse event or device deficiency, if any. ▪ Plan next visit with subject in 3 months. ▪ Dispense/ship supplies to subject *(indicative quantity for 3 months):* ○ 20 sensors ○ 750 Strips ○ 30 Infusion sets (3 boxes of 10) ○ 30 Reservoirs (3 boxes of 10) ○ 12 AA batteries (3 packs of 4)

Treatment Arm	Control Arm
Visit 13: Study Exit **[Visit 12** + 3 months (Window ± 10 days)**]** This visit can be done remotely or onsite. ▪ Collect blood sample for HbA1c (central lab kit). A nurse visit can be organized with the subject to collect the blood sample. Upload AHCL into CareLink if the visit is onsite. Use correct Subject ID (327-XXX-XXX)/Ensure CareLink upload was done. Subject to complete questionnaires HFS, DTSQs, DTSQc and DQoL. If the visit is conducted remotely, questionnaires HFS, DTSQs, DTQSc DQoL will be sent to subject prior to the visit. Subject will send them back to the site upon completion. ▪ Measure/Collect height and weight. ▪ Review adverse event or device deficiency, if any. ▪ Collect all study supplies back from subjects. Shipping box for device return can be provided to subject if visit is conducted remotely.	**Visit 13: Study Exit** **[Visit 12** + 3 months (Window ± 10 days)**]** This visit can be done remotely or onsite. ▪ Collect blood sample for HbA1c (central lab kit). A nurse visit can be organized with the subject to collect the blood sample. ▪ Upload AHCL into CareLink if the visit is onsite. Use correct Subject ID (327-XXX-XXX)/ Ensure CareLink upload was done. ▪ Subject to complete questionnaires HFS, DTSQs, DTSQc and DQoL. If the visit is conducted remotely, questionnaires will be sent to subject prior to the visit. Subject will send them back to the site upon completion. ▪ Measure/Collect height and weight. ▪ Review adverse event or device deficiency, if any. ▪ Collect all study supplies back from subjects. Shipping box for device return can be provided to subject if visit is conducted remotely.

Table 6 CONTINUATION PHASE PROCEDURES

Visit Number	V10	V11 T only	V11A C only	V11B C only	V11C C only	V11D C only	V11E C only	V12	V13	Early Termination[3]
Visit name	FU	FU	CGM Start	Training FU	Auto Mode	Training FU	Training FU	FU	Study Exit	
visit type	C: visit or call T: call	call	Visit or remote¤	visit or call	visit or call	visit or call	visit or call	Visit or remote¤	Visit or remote¤	
Pandemic measure			Remote ¤					Remote ¤	Remote ¤	Remote ¤
Target date	T: V8 + 1m C: V9 + 3d	V10 + 1m	V9 + 7d	V11A + 3d	V11A + 7d	V11C + 3d	V11C + 1m	T: V11+1m C: V11E +1m	V12 + 3m	Unscheduled
Window	T: ± 7d C: ± 1d	± 7d	+7d	± 1d	-1/+7d	± 2d	± 14d	± 10d	± 10d	-
Height and weight									X	X
HbA1c (Central lab)									X	X
Pump training	C		C	C	C	C	C			
CGM training			C	C	C	C	C			
Auto Mode Training/Start					C					
CareLink upload at site	C°		C	C°	C°	C°	C°	X	X	X
CareLink upload by subject	T	T	C	C	C	C	C	X	X	X
Review therapy / Adjust settings	X	T	C	C	C	C	C	X		
HFS questionnaire									X	X
DTSQs questionnaire									X	X
DTSQc questionnaire									X	X
DQoL questionnaire									X	X
AEs and Deficiencies	Reported upon awareness									
Study deviations	Reported upon awareness									
Device Accountability	X		C						X	
Distribution supplies	X		C	C°	C°	C°		X		
Return supplies									X	X

X = both arms; **T** = Treatment arm**; C** = Control arm ; **O** / **°** = Optional **FU** = Follow Up

[3] Early Termination visit should be performed at any time if patient withdraws after randomization (Visit 4) and before the end of the study (Visit 13).

¤ In pandemic situation, visit can be conducted remotely.

9.5. Unscheduled visit

In case an additional visit is performed for study purposes or in case of an early termination visit outside of a normal protocol visit, an unscheduled visit can be used to report data. This visit can be conducted onsite or remotely.

Unscheduled visit procedures could include, but are not limited to:

- Insulin pump and/or CGM training
- Upload AHCL pump into CareLink. Use correct Subject ID (327-XXX-XXX).
- Upload data from the Meter in CareLink™ Personal for Clinical Research using correct Subject ID (327-XXX-XXX).
- Upload data of Transmitter using the Download utility, if used in previous weeks. Make sure to use correct file name (Subject ID_UNSCHEDULED_DATE). Refer to Blinded CGM Instructions for more details.
- Review adverse event or device deficiency, if any.

9.6. Early Termination Visit

Whenever possible, the study staff will perform an Early Termination visit when a subject decides to withdraw from the study early or if the subject is withdrawn early upon decision of investigator (during a normal study visit or an unscheduled visit). This visit can be conducted onsite or remotely.

Early Termination procedures:

- Upload AHCL pump into CareLink. Use correct Subject ID (327-XXX-XXX).
- Subject to complete questionnaires HFS, DTSQs, DTSQc and DQoL, if possible.
- Collect blood sample for HbA1c (central lab kit), if possible.
- Review adverse event or device deficiency, if any.
- Collect all study supplies back from subjects.

9.7. Study Exit

After the study has been completed (at Visit 13 or in case of early termination), the subjects will be exited from the study. The subjects will continue to be treated following the routine practice of each center.

9.8. Study procedures

9.8.1. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG levels, SG levels, and HbA1c will be assessed using the methods outlined in this section.

9.8.1.1. HbA1c at central laboratory

A Central laboratory will be used for HbA1c testing. Refer to Lab manual for details.

All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow NGSP standards. The blood sample will be destroyed according to the Central laboratory procedure after analysis.
Collected at baseline (Visit 1), the first HbA1c value, will be used as screening criteria. HbA1c is also collected at 3 months (Visit 7A), 6 months (Visit 8) and 12 months (Visit 13).

9.8.1.2. Daily Blood Glucose

Values will be assessed during the study by all subjects using the CONTOUR®NEXT LINK 2.4 study meter. The control solution test will be performed following the manufacturer's user guide. Subjects will be trained on the use of the CONTOUR®NEXT LINK 2.4 study meter per the manufacturer's instructions.

9.8.1.3. Sensor Glucose Values

At baseline during the run-in phase and in the control arm during the study phase, SG data will be collected using the blinded CGM. Refer to Blinded CGM instructions and section 7.4 for more details.

In the treatment arm, SG data will be collected by subject's study pump and calibrated by subject's CONTOUR®NEXT LINK 2.4 study meter.

9.8.2. AHCL use

Subjects will be trained to wear the pump and CGM continuously by site staff and they need to stay as much as possible in Auto Mode (with target of ≥ 85 % of the time) to maximize time in range.

The recommended settings for the Auto Mode during the study are the following:
Auto Basal Target: 100 mg/dL (5.6 mmol/L)
Active Insulin Time: 2h

9.8.3. CareLink uploads

CareLink uploads of the pump will be performed at each site visit by the site staff.

Subjects will be trained to perform weekly CareLink uploads from home, following CareLink instructions.

9.8.4. Subject Blinded CGM diary

A diary will be provided to subjects with instructions on appropriate completion at the beginning of each Blinded CGM period at Visit 2, 7A and 8. The site staff will review the diary for completeness upon return by the subjects at Visits 4, 7B and 9 and report data in eCRF as needed. Refer to Blinded CGM diary for more details.

9.8.5. Creatinine Clearance

To assess renal failure as part of the exclusion criteria at screening, the creatinine clearance will be calculated based on lab test results either performed ≤ 12 months before screening or performed at screening by the local lab, following local lab procedures for blood sample collection and disposition. Creatinine clearance threshold for exclusion < 30 mL/min must be calculated with the Cockcroft or MDRD equations. The sites will follow routine practice for evaluation of the creatinine clearance.

9.8.6. Patient Questionnaires

The following validated Patient Reported Outcome (PRO) questionnaires are included in this study:

- Hypoglycemia Fear Survey (HFS)
- Diabetes Treatment Satisfaction Questionnaire (DTSQ status (s) and change (c) versions)
- Diabetes Quality of Life (DQoL)

9.8.6.1. 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 behaviours associated with hypoglycemia. The hypoglycemia fear survey (HFS) is a psychometric instrument designed to quantify this fear (Cox, 1987). The instrument has internal consistency and test-retest stability and varies with elevated HbA1c. The HFS has in most translations two subscales, the behaviour subscale and the worry subscale and has a recollection period of 6 months.

All subjects will be asked to complete the HFS at Visit 2 (Baseline); Visit 8 (at 24 weeks of follow-up), and at Visit 13 (at 12-month follow-up) which is also the end of study. In case the subject withdraws from the study early, it is important to ensure that he/she is asked to complete the HFS at the time of study exit. Data collected from the paper questionnaire will be copied by the site staff into the electronic database.

9.8.6.2. Diabetes Treatment Satisfaction Questionnaire (Status Version and Change Version)

The DTSQ has been specifically designed to measure satisfaction with diabetes treatment regimen in people with diabetes (Bradley, 1994). The DTSQ [status version (DTSQs)] is an eight-item questionnaire, in which six questions assess treatment satisfaction and the other two assess perceived frequency of hyper- and hypoglycemia (Bradley, 1994; Bradley, 1999; Bradley, 1990).

Each item is scored from 6 (very satisfied) to 0 (very dissatisfied) such that the Treatment Satisfaction scale 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 this 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 (Howorka, 2000; Bradley, 1999).

This 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.

The DTSQc, used in conjunction with the DTSQs, overcomes the problem of ceiling effects that are often encountered when the status measure is used alone. The DTSQc has been shown to exhibit greater sensitivity to changes in treatment than the DTSQs and is particularly valuable when ceiling effects occur (Bradley, 2007). A major advantage of the DTSQs and DTSQc is that it has 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.

All subjects will be asked to complete the DTSQs questionnaire at: Baseline (Visit 2), at Visit 8 (24 weeks of follow-up), which is before the last blinded CGM period in the Control Arm and at 12 months (Visit 13), at study end.

All subjects will be asked to complete the DTSQc questionnaire at: Visit 8 (24-week follow-up) and Visit 13 (12-month follow-up).

In case the subject withdraws from the study before Visit 13, it is important to ensure that he/she is asked to complete: the DTSQs and DTSQc questionnaire at the time of study exit.

Data collected from the paper questionnaire will be entered by the investigation site into the electronic database.

9.8.6.3. Diabetes Quality of Life Questionnaire (DQoL)

In addition to the previous two questionnaires, a specific assessment of the quality of life will be done with the Diabetes Quality of Life Questionnaire (DQoL). DQoL has been widely used to measure quality of life among diabetes patients (DCCT, 1988; DCCT, 1996). 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 and a total score will be calculated as the average score across the four dimensions. A higher score represents higher quality of life.

All subjects will be asked to complete questionnaire at: Visit 2 (baseline), Visit 8 (24-week follow-up) and Visit 13 (12-month follow-up).
In case the subject withdraws from the study before Visit 13, it is important to ensure that he/she is asked to complete the questionnaire at the time of study exit.
Data collected from the paper questionnaire will be entered by the investigation site into the electronic database.

9.9. Subject Consent

Informed Consent will be obtained in accordance to ISO 14155:2020.

The investigator or authorized designee must obtain written informed consent from the patient before any clinical study related activity takes place.

In advance of the consent discussion, the patient should receive the EC/IRB approved Patient Information and Informed Consent Form (PIC). Documentation can be sent by mail to the subject (two copies of the PIC will be sent for signature). If the visit is conducted remotely in pandemic context, the investigator or his/her authorized designee will conduct the discussion via phone or video call. During the consent discussion the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. Illiterate patients will not be enrolled in this study. All items addressed in the PIC must be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the PIC to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Patient Informed Consent must be signed and personally dated by the patient and investigator or authorized designee. If applicable (ie. during pandemic), the patient can send the signed consent back by regular mail to the site. Site will wait for the signed copy before proceeding with any study related procedure. Once received, the investigator or authorized designee will date and sign.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the patient with a copy of the Patient Information and the signed and dated Informed Consent Form. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

A patient contact card will be provided to the patient.

9.9.1. Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. Study sponsor will send the revised information to the EC and RA (Regulatory Authority), if applicable, for approval. After approval by the EC/IRB and RA, if applicable, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

9.10. Randomization and Treatment Assignment

Each cohort will have a separate randomization.

Subjects in the Cohort A, with MDI+FGM before study start, will be randomized into:

- Treatment arm: AHCL (and stop FGM at Visit 6A)
- Control arm: MDI + FGM

The randomization will follow a block randomization with blocks of different sizes. At country level, the order of the block sizes will be selected randomly and a random 1:1 treatment allocation will be performed within each block.

Investigators will be blinded to the number and size of the blocks.

Subjects in the Cohort B, with MDI + RT-CGM standalone before study start, will be randomized into:

- Treatment arm: AHCL (and stop RT-CGM at Visit 6A)
- Control arm: MDI + RT-CGM

The randomization will follow a block randomization with blocks of different sizes. At each country recruiting subjects for the exploratory study, the order of the block sizes will be selected randomly and a random 1:1 treatment allocation will be performed within each block.
Investigators will be blinded to the number and size of the blocks.

Randomization will be performed via the electronic CRF.

Block randomization was chosen in order to preserve a 1:1 randomization ratio as much as possible, while minimising the likelihood of predicting treatment allocation to the next participant.

Confounding is addressed by the random allocation, with the aim that any confounding variable should be equally distributed in the two groups to give balanced groups.

9.11. Assessment of Safety

AE information is collected in this study. See Section 11 for further information regarding the collection of AEs and safety information.

9.12. Recording Data

Data will be captured on eCRFs using Oracle Clinical Remote Data Capture (OC- RDC) module. Original eCRFs will not be considered as source data and supporting documentation will be required, except for the Lab eCRFs which will be considered as source data (results directly transferred from the central lab into eCRF.

Electronic device data will be collected from the study pump using CareLink™ Personal For Clinical Research software. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11

compliant). Certain data points stored in the downloaded information may also be captured on the appropriate eCRF.

The investigator will ensure that all eCRFs are completed promptly, completely, and accurately. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the OC-RDC system; otherwise, irresolvable data-related issues will be routed to the sponsor for review and final disposition. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. System backups for data stored in the Oracle Clinical system will be consistent with Medtronic Standard Operating Procedures (SOPs).

Medtronic will only consider eCRFs to be complete when all discrepancies between source data and eCRF have been resolved. eCRF content will be reviewed by a study monitor, as described in the Monitoring Plan. In addition, specific eCRFs must also be reviewed and electronically signed by the investigator, indicating his/her agreement with the accuracy of all recorded data. It is expected that the investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

9.13. Deviation Handling

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. It is expected that the investigator will conduct this clinical trial in compliance with the CIP and all applicable regulations governing the conduct of clinical research involving human subjects.

Deviations will not be issued for the following situations:

- If subjects do not follow the fingerstick recommendations or upload devices, unless the site staff did not train the subject on SMBG study procedures or upload procedures.
- If subjects miss or delay protocol visits, unless the site staff did not plan the visit according to the protocol schedule.
- If subject did not (fully or partly) complete the Blinded CGM Diary

It is otherwise prohibited to use waivers from the CIP.

9.13.1. Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the Clinical Investigation Plan (CIP). In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and regulatory authority must also be obtained before implementation. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the CIP do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform EC/IRB and/or RA, if required.

9.13.2. Reporting requirements for study deviations

All study deviations must be recorded on the eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency. The date, description and reason for each deviation will be documented.

Investigator must report deviations to Medtronic as soon as possible upon the center becoming aware of the deviation, especially in the following examples of deviations that could impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study:

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the EC/IRB and RA

For medically justifiable conditions that pre-empt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation that will apply to all visits going forward. This may also apply to other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval from sponsor is required for such situations.

Reporting of deviations by investigator and Medtronic must comply with EC/IRB policies, local laws, and/or regulatory authorities' requirements, as applicable.

9.13.3. Analyzing deviations

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying if any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation) are needed. Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the Investigator and investigational site, and in some cases necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.14. Subject Withdrawal or Discontinuation

Subjects may choose to withdraw from the study at any time by notifying investigational center staff of their intent. Whenever possible, the investigational site staff will perform an Early Termination visit when a subject decides to withdraw from the study early or if the subject is withdrawn early upon decision of investigator (during a normal study visit or an unscheduled visit) (described in section 9.5).

Subjects may also be withdrawn from the study at the discretion of the investigator.

If a subject chooses to end his or her study participation or if the subject is removed from the study at the investigator's discretion or for failure to meet the study requirements, the reason for withdrawal must be documented both in source documents and on the Exit eCRF. All study devices and supplies must be returned (as applicable) and documented in the appropriate eCRF.

After subject ends his participation, he will continue to be treated according to routine practice.

9.14.1. Lost to Follow-Up

If a subject does not return to the site for required follow-up visit(s) and cannot be reached, the investigation site personnel should make 3 documented attempts to contact the subject by phone to verify if the subject should be considered "lost-to follow up". In the event the subject is not able to perform follow-up visits at the investigation site, subject will be considered "lost to follow up" and this needs to be documented in the Study Exit eCRF. All efforts will be made by investigation site personnel to collect all study devices and supplies back from subject, if applicable.

10. Risks and Benefits

10.1. Potential Risks

The clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the clinical investigation plan and constantly monitored.

Subjects participating in this study have a medical diagnosis of Type 1 diabetes requiring the daily use of insulin infusion or injections. There are risks inherent to Type 1 diabetes that are independent from their participation in the study:

- (Severe) Hypoglycemia
- (Severe) Hyperglycemia

- Diabetic Ketoacidosis

Standard risks associated with the medical device used in this clinical study and analyses of Adverse Device Effects are listed in the User Guides / Instructions for Use or Investigator Brochure.

Possible interactions of the devices used in the study with concomitant medical treatments other than acetaminophen are not known.

10.1.1. Potential risks associated with the use of the investigational device AHCL MiniMed 670G version 4.0

Risks with Hybrid Closed Loop Therapy	Prevention and Mitigation

Risks with Hybrid Closed Loop may include:
• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• Diabetic ketoacidosis
• User Entry Error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypoglycemia or hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia
• Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Patient takes insulin via injection while in Hybrid Closed Loop (Auto Mode)
• Hypoglycemia or hyperglycemia related to entering or exiting Hybrid Closed Loop (Auto Mode)
• Insulin over-delivery due to potential interference from acetaminophen
	Prevention and mitigation include:
	• Follow the provided user guides for insulin pump management.
	• Training prior to study on device use and diabetes management principles and instructed to call with problems.
	• Subjects are instructed to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.
	• Subjects are instructed to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.
	• Subjects are instructed if there are no sensor values, no treatments decision should be made until a BG is confirmed.
	• Subjects are instructed to have glucose on hand for hypoglycemia
	• Subjects will be instructed to consider avoiding the use of products containing acetaminophen.
	• If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels.
	• If acetaminophen is taken, subjects should turn off Auto Correction and consider exiting Auto Mode.

The following risks that apply to the AHCL system are the same as for other commercialized insulin pump models.

Risks with Insulin Pump Infusion	Prevention and Mitigation
General risks related to insulin pump infusion set may include: • Localized infection • Skin irritation or redness • Bruising • Discomfort or pain • Bleeding • Irritation • Rash • Occlusions that can interrupt insulin delivery and lead to hyperglycemia or diabetic ketoacidosis	Prevention and mitigation include: • Patients should be instructed to follow the provided user guides for insertions and care of infusion sets. • If an infusion site becomes irritated or inflamed, the infusion set should be removed and another placed in a new location. • Patients will receive training prior to study on device use and diabetes management principles and will be instructed to call with problems. • Subjects are instructed to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions. • Subjects are instructed to check their meter glucose if there are any concerns that the sensor glucose value is not accurate. • Subjects are instructed to have glucose on hand for hypoglycemia. • Change infusion set if suspected catheter occlusion or administer insulin with pen/syringe for persistent hyperglycemia especially if ketones develop.

Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Patients will receive training prior to study on device use and diabetes management principles. • Subjects are instructed to check their meter glucose if their low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions. • Subjects are instructed to check their meter glucose if there are any concerns that the sensor glucose value is not accurate. • Subjects are instructed if there are no sensor values, no treatment decisions should be made until a BG is confirmed. • Subjects are instructed to have glucose on hand for hypoglycemia.
Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Patients will receive training prior to study device use and diabetes management principles. • Subjects are instructed to check their meter glucose if their high symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions. • Subjects are instructed to check their meter glucose if there are any concerns that the sensor glucose value is not accurate. • Subjects are instructed if there are no sensor values, no treatments decision should be made until a BG is confirmed. • Alternative method of managing glucose levels should be available (insulin and syringe for example).

Note: The Dock (T8381) and the Download Utility (9029393) are study tools, used by the Investigational Site staff only for data collection at baseline for all subjects and to allow data comparison between AHCL and control arm during the study phase. These tools are not used by subjects and the data being collected with those are blinded to the study team and subjects and will not be used to make therapy adjustment, therefore, no risks are associated to their use.

10.1.2. Potential risks associated with the use of commercialized devices and consumables

The potential side effects related to the use of sensors, transmitter, insulin pump infusion sets, study meter and fingerstick are anticipated to be the same as when used per standard of care and are described in the IFUs of each component.

10.1.3. Potential risk associated with study procedures

10.1.3.1. Calibration of CGM Risk

When an erroneous glucose value is used to calibrate a CGM, the bias is carried through until the next opportunity to calibrate the CGM. This can result in an incorrect bias. Subjects will be trained on appropriate calibration.

10.1.3.2. Reuse Risk

All study devices will be single patient use.

10.1.3.3. Misuse Risk

Comprehensive training will take place at the initiation visit for investigational center staff regarding the operation of the AHCL, to include all of its functional components and all other study devices to be used during the study at the investigational center. Subjects will be trained by the Investigational center staff to ensure adequate use of the AHCL study device, its functional components and all other study devices. During the patient onboarding, there are several calls and visit scheduled to ensure correct usage of the AHCL system, and if the subject and/or center staff feels additional training is needed, additional unscheduled can be added. Furthermore, the subject can upload the AHCL pump in CareLink, which also provide the center staff remote access to patients' data, which provides the center staff useful insights and to mitigate potential misuse by the patient.

10.1.3.4. Remote follow-up

In response to pandemic situation, to continue study execution, visits can be conducted remotely (via phone or video call) as site staff have built up experience with virtual clinics to train and can follow-up their patients on insulin pump therapy, using virtual tools and videos. The same standard of care process can be followed in this study, with no additional risk for the patients.

Investigators may decide to conduct a remote visit during pandemic to maintain safety and when onsite visit is not possible as it would expose subject and staff to increased risks. Rationale will be documented in the source files.

10.2. Potential Benefits

The goal of the study is to evaluate the safety and efficacy of the new AHCL MiniMed™ 670G system version 4.0. It will help increasing knowledge about using an automated closed-loop to control the glucose level. It is anticipated that this new system will allow improving glycemic control in the selected population of patients failing on their current MDI therapy with glucose monitoring system. Previous studies on the MiniMed 670G™ have shown a significant improvement in HbA1c and an increase in time in glycemic range (Garg, 2017; Bergenstal, 2016).

The study will give the opportunity to all subjects to have access to this new system (12 months for the Treatment arm and 6 months for the Control arm during continuation phase).

The information gathered in this study may help the patients and physicians determine the best treatment options in the future. The experience of participating in this study may also help other patients benefit from improved diabetes management experienced by patients and investigational staff using the AHCL MiniMed™ 670G system, version 4.0. Furthermore, results from this study may address potential device and clinical issues not identified in previous studies, support the development of advanced devices and therapies, and may facilitate reimbursement of the device components (and subsequent systems) in countries where they are not currently reimbursed.

10.3. Risk-Benefit Rationale

Access to automated insulin devices during the trial may offer improved glycemic control for participants, and may increase understanding of the disorder, due to the fact that the participants will be followed with higher frequency of visits, which will allow a closer medical follow-up when compared to standard of care.

Previous studies have demonstrated safety and efficacy of the MiniMed 670G system in the pivotal study (Garg, 2017) and in real-life settings (Agrawal, 2018). It is anticipated that with the newer iterations of the investigated AHCL algorithm maximize time spent in hybrid closed-loop operation, relative to the current commercialized MiniMed™ 670G system, which will further improve glucose control, time in glycemic range and overall user satisfaction.

The current commercialized MiniMed™ 670G system and advanced algorithm involve periodic automated insulin dosing, that may increase the likelihood of hypoglycemia, and periodic automated attenuation of

insulin delivery, that may increase the likelihood of hyperglycemia. However, the number of Serious Adverse Events that occurred in past studies involving the commercialized MiniMed™ 670G system (Bergenstal, 2016) were relatively rare, and none occurred during the feasibility studies with new AHCL MiniMed™ 670G, version 4.0.

Furthermore, with any externally worn device there are small risks of insulin infusion site reactions, infection, and skin reactions to tapes – however it should be noted that this is no different to standard of care insulin pump therapy and utilizing continuous glucose monitoring. Also, one goal of the run-in phase is to identify patients who do not tolerate sensor wear and therefore, they would not be eligible to be randomized into the study.

In addition, any potential risks with this study are minimized by selecting qualified investigators experienced with insulin pump therapy, careful assessment of each subject during the study conduct to effectively monitor and rapidly remedy the problem. Furthermore, subjects can call the local support line to obtain technical support, if needed.
Medtronic has further minimized the possibility of risks by completing product testing prior to the use of the system in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labelling according to local requirements.

All above these risks are contained within the patient information sheet, and indications and contraindications are provided in the Instructions for Use given to all patients.

Finally, in the context of pandemic, the risk of visiting the site for the subject has been mitigated via the setup of remote visits.

11. Adverse Events and Device Deficiencies

11.1. Adverse Events

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events (AEs) or untoward findings. All adverse events identified from the point of enrollment until the subject's exit from the study will be reported to the sponsor and documented on the Adverse Event eCRF and in the subject's medical records. The study personnel will elicit reports of adverse events (AEs) from the subject at each visit (including phone calls) documenting the medical diagnosis, date of event start and end, causality (relationship to device or procedure), treatment, outcome, and description that includes the details of the event.

11.2. Definitions and Classification

Medtronic uses the definitions provided in ISO 14155:2020 for AE definitions.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. Medtronic follows MEDDEV 2.7/3 revision 3 (or subsequent versions) guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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 his 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. *(Adapted from American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005)*

Severe Hyperglycemia is defined as hyperglycemia (blood glucose greater than (>)300 mg/dL (16.7 mmol/L) with blood glucose ketones greater than (>) 0.6mmol/L or accompanied by symptoms of nausea, vomiting or abdominal pain.

Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than (>) 250 mg/dL (or greater than (>) 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. *(American Diabetes Association-Diabetes Care, Volume 27, Supplement 1, January 2004; S94-S102)*

Hyperglycemic events will be recorded as DKA if the event includes the presence of all of the following:

- Arterial blood pH less than (<)7.30 or serum bicarbonate less than (<) 15mEq/l
- Blood glucose greater than (>) 250 mg/dL (or greater than (>) 13.9 mmol/L)
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

Adverse Event (AE): *(ISO 14155:2020, 3.2)*

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.

Adverse Device Effect (ADE): *(ISO 14155:2020, 3.1)*

Adverse event related to the use of an investigational medical device

NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.

NOTE 3: this includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE): *(ISO 14155:2020, 3.45)*

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. (ICH Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. EMEA 2006)

Definition for Germany only: **Serious Adverse Event (SAE):** *(MPSV § 2 Definition Abs 5)*

A serious adverse event is an event that occurs in a clinical investigation subject to approval or occurring in a performance evaluation which led, might have led or could lead directly or indirectly to death or serious deterioration of health of the subject, the user or a third party, without consideration if the event has been caused by the medical device itself; this applies accordingly to serious adverse events occurring in a clinical investigation or performance evaluation for which an exemption of the approval authorization as per MPG § 20 paragraph 1 sentence 2 has been granted.

Serious Adverse Device Effect (SADE): *(ISO 14155:2020, 3.44)*

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2020, 3.51)*

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

NOTE 1: ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Serious Health Threat *(ISO 14155:2020, 3.46)*

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Device deficiency: *(ISO 14155:2020, 3.19)*

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling.
NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Relatedness:

Device Related: An AE that results from the presence or performance (intended or otherwise) of the device.

Procedure Related: An AE that occurs due to any study procedure (ie. Blood draw).

11.3. Adverse Event and Device Deficiency Reporting Requirements

Adverse events and device deficiencies should be reported by the investigator to Medtronic as soon as possible after the event occurs, but no later than the timeframes listed in Table 7 or local requirements, whichever is more stringent.

In addition, investigators are obligated to report adverse events and device deficiencies in accordance with the requirements of their reviewing EC/IRB and local regulations.

Table 7 Adverse Event and Device Deficiencies Reporting Requirements by Investigator

Event Type to report	Timeframe for Reporting to Medtronic	Reporting To Regulatory Authority and Ethics Committee
• Serious Adverse Device Effect (SADE) • Unanticipated Serious Adverse Device Effect (USADE) • Serious Adverse Event (SAE) • Adverse Device Effect (ADE) • Device Deficiency that might have led to a SADE •	Report immediately, but no later than **72 hours** after investigational site study personnel's awareness of the event (or sooner if required by local regulation)	**All countries**: Submit per local reporting requirements
• Adverse Event (AE) • Device Deficiency (DD)	Report in a **timely manner** from the investigator's / site's first knowledge of the event	**All countries**: Submit per local reporting requirements

Medtronic is obligated to report adverse events and device deficiencies that occur during this study to the regulatory authorities and EC/IRB as per local requirements. For Germany, refer to German Local Amendment A, or subsequent versions, for more details.

Table 8 Adverse Event and Device Deficiencies Reporting Requirements by Medtronic to Regulatory Authorities & EC

Event Type to report	To Regulatory Authorities	To Ethics Committees
• Serious Adverse Device Effect (SADE) • Unanticipated Serious Adverse Device Effect (USADE) • Serious Adverse Event (SAE) • Device Deficiency that might have led to a SADE • Adverse Event (AE) • Adverse Device Effect (ADE) • Device Deficiency (DD)	**All countries**: Submit per local reporting requirements Reporting timeframe as per local requirement For Germany, refer to German Local Amendment A, or subsequent versions, for more details.	**All countries**: Submit per local reporting requirements

In addition, Medtronic shall prepare and submit complete, accurate, and timely study reports, as per local reporting requirements.

11.3.1. Reporting of Adverse Events

The investigator or designee will record all AEs while the subject is enrolled in the clinical study (including at minimum the following information: date of the adverse event, date of first awareness by investigator, action taken, outcome status and resolution, and assessment of both the seriousness and the relationship to the investigational device and procedure).

Each AE needs to be assessed for its device or procedure relatedness. A device related AE is associated with the use of the study device (e.g. infection of sensor site or infusion set occlusion resulting in DKA). A procedure related AE is associated with testing related to the study procedures specified in the CIP.

Examples of device or procedure related AEs include:

- ***Device*** related: insertion site infection
- Serious adverse ***device effect***: cellulitis at device insertion site requiring hospitalization
- ***Procedure*** related AE: bruising at IV insertion site

Adverse events that have not resolved at the time of the subject's discontinuation or completion of the study should have an "outcome" of Not Recovered/Not Resolved at study end in subject source and on an eCRF. The investigator should ensure that subject is aware of any follow-up or additional treatment that is required for any ongoing AE at end of study participation; however, there will be no eCRF entry for the ongoing follow-up.

Subjects participating in the study have diabetes and are expected to experience hypoglycemia and or hyperglycemia. These normal events are not expected to be reported to sponsor on an AE eCRF as this is not considered an untoward event, but rather an expected occurrence. Any glycemic excursion that meets the protocol definition of Severe Hypoglycemia, Severe Hyperglycemia or DKA is considered an untoward event and a worsening from the subject's baseline and would be reported to sponsor on an AE eCRF.

Medical conditions should only be reported to sponsor on an AE eCRF, if there is a worsening from the subject's baseline. For example, a subject previously diagnosed with Asthma is hospitalized for severe asthma attack would be a reportable event.

Adverse events will be documented in the subject source file and reported to sponsor on an eCRF. The investigational center is responsible for documentation of AEs including obtaining source documents related to the event, such as emergency medical technician/paramedic reports, hospital records (admission summary; lab results, test results, discharge summary) or device uploads to support the event. Source documents will be reviewed to determine if additional AEs have occurred and require reporting.

The Adverse Event (AE) information will be collected throughout the study and reported to Medtronic on an Adverse Event eCRF. One Adverse Event eCRF will be completed for *each adverse event*, including AEs that require immediate reporting. The Adverse Event eCRF must be validated and saved "complete", for submission to Medtronic. See the Adverse Event eCRF for the information to be reported for each Adverse Event.

In case the database is not functioning, the site staff will report any safety data (AE/DD) on the applicable CRF via email to rs.mc2safetyportfoliodiabetespainbrain@medtronic.com as soon as possible and/or within reporting guidelines outlined in this document (see Table 7 Adverse Event and Device Deficiencies Reporting Requirements by Investigator). In the event the internet is not functioning, the site will inform the Medtronic Study Manager via phone (see Sponsor list for contact details).

In case the Adverse Event is related to a non-Medtronic market released device (i.e. study meter) used during the study, post market surveillance applies, and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact their local clinical referent or the Study Manager. Contact details of the Study Manager are given in the Sponsor List.

11.3.2. Reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic, via the electronic CRF. Vigilance reporting will be done for CE-Marked devices, according to these CRF reported data.

All Device Deficiencies that did not lead to an Adverse Event should be reported on the Device Deficiency eCRF, one for each Device Deficiency, completing as much information as is available. This Device Deficiency eCRF must be validated / saved "complete" for submission to Medtronic.

See the Device Deficiency eCRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

Device deficiencies that did not lead to an Adverse Event, but could have led to a SADE:
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate
also defined as Device Deficiencies with SADE potential require immediate reporting to the sponsor via completion of the applicable CRF, to IRB/EC and to regulatory authority per local reporting requirements ISO14155:2020 (Refer to Table 8). For Germany, refer to German Local Amendment A, or subsequent versions, for more details.

All Device deficiencies will be reported to Investigators, Regulatory Authorities and IRB/IEC as part of the Study report(s).

In case technical issue occurs with the electronic CRF (i.e. Internet access, system maintenance…), initial reporting for Device Deficiencies that require immediate reporting (see Table 7), may be done via email: rs.mc2safetyportfoliodiabetespainbrain@medtronic.com. In the event the internet is not functioning, the site will inform Medtronic Study Manager via phone (see Sponsor list for contact details).

The site should contact their local clinical referent or the study manager in case of questions. Contact details are given in the Sponsor List.

11.4. Adverse Event and Device Deficiency review process

The potential adverse events (risks) and their mitigations associated with the use of these devices are identified in the Instructions for Use (IFU) for the CE-marked commercially available devices/consumables and in the Investigator Brochure (IB) for the pre-market devices/consumables (also see Section 10.1 of this CIP).

All Adverse Events and Device Deficiencies will be reviewed by Medtronic. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements. The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global regulatory requirements.

Medtronic will immediately report any Adverse Events/Device Deficiencies that are associated with the commercially released devices to the Medtronic Diabetes Complaint Handling Unit. The Diabetes Complaint Handling Unit will ensure prompt review, and appropriate reporting.

11.5. Causality Assessment

An AE is not automatically related to the study device or procedure simply because the subject is wearing the device and participating in the study. The event should be reviewed to determine if the device or study procedure could have possibly caused the event and therefore is related to the study device or procedure.

Causality assessment is the determination of the relationship between an AE and the device being studied. It is expected that the investigational center will review all elements surrounding the AE to properly assess the causality of the event to the study device or to a study procedure.

Investigators should classify the relationship between the AE and the study device or study procedures using one of the five possible causality categories listed below:

1) Not related: relationship to the device or procedures can be excluded when:

- The event is not a known[1] side effect of the product category the device belongs to or of similar devices and procedures;
- The event has no temporal relationship with the use of the investigational device or the procedures
- The event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;
- The event involves a body-site, or an organ not expected to be affected by the device or procedure;
- The event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- The event does not depend on a false result given by the investigational device used for diagnosis[2], when applicable;
- Harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

[1] *When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.*

[2] *If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition.*

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

5) Causal relationship: the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- The event has a temporal relationship with investigational device use/application or procedures;
- The event involves a body-site or organ that:
    - The investigational device or procedures are applied to;
    - The investigational device or procedures have an effect on;
- The event follows a known response pattern to the medical device (if the response pattern is previously known);
- The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- Harm to the subject is due to error in use;
- The event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Example: A severe hyperglycemia AE with the following event description would have the following causality assessment for device relatedness:	
Improved glucose without an infusion set/site change	**Not related**
Changed infusion set with glucose improvement	**Possible**
Infusion set fell out, bent cannula, occlusion alarm	**Causal relationship**

12. Data Review Committees

12.1. Clinical events Committee

A Clinical Event Committee (CEC) consisting of external physicians with an expertise in endocrinology and the management of diabetes, including insulin pumps and CGM will be convened. The CEC will review on periodic basis AEs as required per protocol, and may include reports of:

- Serious Adverse Event (SAE)
- Serious Adverse Device Effect (SADE)
- Unanticipated Serious Adverse Device Effect (USADE)
- Severe Hypoglycemia
- Diabetic Ketoacidosis (DKA)
- Deaths

The CEC will assess events to determine agreement or disagreement with the investigator classification of an event (e.g. seriousness, relatedness to device and procedure, unanticipated/anticipated). The CEC will only provide three causality assessments for device and procedure relatedness: Not Related, Possible, and Causal relationship.

Causality Categories for Investigational Center		**Causality Categories for CEC:**
• Not Related • Unlikely • Possible • Probable • Causal relationship		• Not Related • Possible • Causal relationship

The sponsor will notify the investigator of any disagreement in assessment of an event by the CEC.
All other events will be reviewed and classified by the Sponsor's qualified internal safety individual(s) to ensure they should not be adjudicated by the CEC and that the events are appropriately classified by the investigator.

12.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) consisting of external physicians with an expertise in Endocrinology and the management of insulin-requiring diabetes including pump and CGM therapy, along with an external statistician will be convened to review study progress and safety. Periodic meetings will be scheduled with DMC.

The DMC is established by the sponsor to oversee the following responsibilities:

- Review the interim analysis of effectiveness and safety measures after approximately 32 subjects (16 subjects in the treatment arm and 16 subjects in the control arm) have been randomized and followed up for 6 months.
- Following predefined rules in the DMC charter, implement the assessment of modifications to the trial design. The primary planned modification is a sample size re-estimation.
- Monitor baseline comparability.
- Monitoring adverse events.
- Review aggregate subject data.
- Provide recommendations to continue or terminate the trial depending upon these analyses.

13. Statistical Design and Methods

13.1. Subject Disposition

The number of subjects enrolled, randomized, completed, early terminated the study will be presented. The reasons for discontinuing prior to study completion will be summarized.

13.2. Subject Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

13.3. Sample Size Considerations

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.

13.4. Sample size reassessment - Interim Analysis in Cohort A

Due to the uncertainty about the magnitude of the treatment effect and the standard deviation, the sample size will be re-estimated by an independent DMC in an interim assessment based on conditional power after a minimum of 32 subjects in cohort A (approximately 16 subjects in the treatment arm and 16 subjects in the control arm) have been randomized and completed the study phase of 6 months. Enrolment period is expected to be 6 months and it may be adjusted based on the outcome of the interim analyses and enrolment rate. Early stopping is only considered in case of futility. No sample size decrease is considered for efficacy.

13.5. Analysis of Primary Endpoint

The primary objective is to compare the mean HbA1c change from baseline to end of study (6 month) between control arm ($\Delta_{HbA1c\ MDI\ therapy\ +\ FGM}$) and treatment arm ($\Delta_{HbA1c\ AHCL}$). The null hypothesis H_O: $\Delta_{HbA1c\ MDI\ therapy\ +\ FGM}=\Delta_{HbA1c\ AHCL}$ will be tested against the alternative hypothesis H_A: $\Delta_{HbA1c\ MDI\ therapy\ +\ FGM} \neq \Delta_{HbA1c\ AHCL}$ using a linear mixed model (random effect model) that uses all available data and account for possible missing at random data. This confirmatory analysis aims at demonstrating the superiority of AHCL and will be performed on the Intent to Treat (ITT) basis. The ITT population will be composed of all randomized subjects irrespective of their compliance to the planned course of treatment or deviations from protocol. Significant between arm difference will be concluded if P-value < 0.05.

Descriptive summary statistics of the primary endpoint will be presented stratified by study phase, treatment arm, investigational (study) site and other variables.

13.6. Analysis of Secondary Endpoints

Analysis on secondary endpoints listed in section 5.3.2 will be performed using a linear mixed model on the ITT population. This is a confirmatory trial for primary and secondary endpoints in cohort A as described in following sequential testing. If the primary endpoint analysis is significant, the procedure tests hierarchically the ordered hypotheses in sequence at level α=0.05 until one of the hypotheses is non-rejected.

- % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L)

  Non-inferiority test with non-inferiority margin of 6%

  (the margin of 6% corresponds to approximately 90 minutes per day which is considered as a clinically relevant reduction in time spent in hyperglycemia).
- % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L)

  Superiority test
- % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L)

  Non-inferiority test with non-inferiority margin of 6%
- % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L)

  Superiority test
- % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L)

  Non-inferiority test with non-inferiority margin of 6%
- % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L)

  Superiority test
- % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L)

  Non-inferiority test with non-inferiority margin of 2% (the margin of 2% corresponds to approximately 30 minutes per day increase which is considered as a clinically relevant reduction in time spent in level II hypoglycemia)
- % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L)

  Non-inferiority test with non-inferiority margin of 5% (the margin of 5% corresponds to 72 minutes per day which is considered as a clinically relevant reduction in time spent in level 1 hypoglycemia).

Superiority test for % Time spent in hypoglycemic range with SG < 54 mg/dL, < 70 mg/dL and analyses on the ancillary endpoints listed in section 5.3.3 and safety endpoints listed in section 5.3.2.1, may be performed for exploratory purpose and significance of these tests will not be claimed. Linear mixed model will be used for the endpoints with repeated measures and analysis of variance will be used for single measurements.

Descriptive summary statistics will be presented for all secondary, safety and ancillary endpoints.

13.7. Handling Missing Data

Primary endpoints and Secondary endpoints will be collected at baseline, end of 3 months and end of 6 months and primary and secondary analysis will be based on ITT (Intention to Treat).

For the primary analysis (change of A1c), if A1c at 3 months or 6 months is not available in subjects that drop-out of the study, various sensitivity analyses will be performed:

- Per Protocol Dataset
- Baseline Observation Carry Forward (BOCF)
- Data will be imputed by selected A1c data from the same arm considering baseline characteristics such as age, gender and duration of diabetes

For the secondary endpoints, as suggested by International Consensus Group (ICG), during the two weeks period of SG comparison at 3 months and 6 months between control and treatment arm, a minimum number of 2880 of SG values (288 SG values/day × 10 days out of 14 days) is required to evaluate the glycemic outcome. For those subjects with less than 2880 SG during the two weeks of sensor wear, the following sensitivity analysis will be carried out to mitigate the impact of data loss:

- CGM data gap filled within the same subject: Missing CGM data in one arm will be imputed by randomly replaced CGM data in the same subject during the same period of sensor wear.
- CGM data gap filled within the arm, ignoring baseline characteristics: Missing CGM data will be imputed by a randomly selected CGM data from the same arm, ignoring baseline characters during the same period of sensor wear.
- CGM data gap filled within the arm, considering baseline characteristics: Missing CGM data will be imputed by selected CGM data from the same arm, considering baseline characters such as age, gender and duration of diabetes during the same period of sensor wear.

13.8. Exploratory analysis on the Cohort B with MDI+RT-CGM arm

Mean HbA1c change from baseline to end of study (6 month) between control arm (ΔHbA1c MDI therapy + CGM) and treatment arm (ΔHbA1c AHCL) will be compared using linear mixed model on ITT population for exploratory purpose.

All Secondary endpoints, ancillary endpoints and safety endpoints analyses comparing MDI + FGM versus AHCL arms will also be performed for exploratory analysis comparing MDI + CGM versus AHCL arms.

A detailed statistical analysis will be outlined in a separate statistical analysis plan (SAP). Additional ad-hoc analysis may also be performed and will be described as such in the report of study results.

Any deviation from the original statistical plan including justification will be documented in the final study report.

14. Ethics

14.1. Statement(s) of Compliance

This clinical study will be conducted in compliance with the principles originating from the Declaration of Helsinki, the international standard ISO 14155:2020 ('Clinical Investigation of medical devices for human subjects'), laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

The study will also be conducted in compliance with the principles of good clinical practice (GCP) meaning that the study design, conduct, performance, monitoring, auditing, recording, analysis and reporting will assure that the data and results are credible and accurate and that the rights, safety and well-being of subjects are protected. GCP includes review and approval by an independent ethic committee (EC)/IRB and Regulatory authority before initiating the investigation, ongoing review of the investigation by an EC/IRB and RA and obtaining and documenting the freely given informed consent of the subject (or the subject's legally authorized representative) before their participation in the investigation.

All principles originating from the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC/IRB and RA approvals, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

The study will be registered in a publicly accessible database (clinicaltrials.gov). The sponsor shall avoid improper influence on, or inducement to the subject, monitor, any investigator(s) or other parties participating in, or contributing to, this study.

Following ISO14155:2020, legally incompetent and illiterate persons, or vulnerable populations will not be included in this clinical study.

14.2. EC/IRB approval

This CIP, any subsequent amendments to this CIP, the PIC form, subject material, and any form of subject recruitment information (e.g. advertisements), if applicable, relating to this study will be approved by the responsible EC/IRB.

The investigational center will not initiate any subject activities until EC/IRB approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

14.3. Regulatory submission

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements.

If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

Other documents that are referred to in this CIP will be made available upon request.

14.4. Investigator responsibilities

This study will be conducted at the investigational centers where all study-related activities will be performed and will be led by a PI. Per ISO14155:2020, an investigator means "individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions."

The investigator's responsibilities include but are not limited to:

- Conduct of the investigation in accordance with the CIP and Clinical Trial Agreement, applicable regulations, and any conditions of approval imposed by the reviewing EC/IRB or regulatory authority requirements
- Conduct of investigation in accordance to International guidelines for clinical trials on medical devices ISO 14155:2020
    - To supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    - To protect the rights, safety, and welfare of study subjects.
- Protecting the rights, safety, and welfare of subjects under the investigator's care
    - Providing reasonable medical care for study subjects for medical problems that arise during participation in the trial that are, or could be, related to the study intervention
    - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
    - Adhering to the CIP so that study subjects are not exposed to unreasonable risks
- Controlling devices under investigation

- Investigator is responsible for providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- Ensuring that the requirements for obtaining informed consent are met in accordance with ISO
- Disposing of device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- Allowing study devices to be used only with subjects under the investigator's supervision and to supply study devices only to persons authorized to receive it
- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the investigator's part of an investigation, to include:
    - all relevant correspondence with another investigator, an EC/IRB, the sponsor, a monitor, regulatory authorities, including required reports.
    - records of receipt, use or disposition of study devices
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
- Preparation and submission to Medtronic and, when required, regulatory agency and the reviewing EC/IRB, the following complete, accurate, and timely reports:
    - any reportable AEs (see Section 0) occurring during an investigation
    - progress reports on the investigation as required by the regulatory agency and EC/IRB
    - any deviation from the CIP made to protect the life or physical well-being of a subject in an emergency
    - any use of the device without obtaining informed consent
    - any further information requested by the regulatory agency and EC/IRB about any aspect of the investigation
    - any other records the regulatory agency requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation
- Permitting regulatory authorities to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include entry and addressing discrepancies in a timely fashion and approving selected eCRFs.

Only authorized study personnel as listed on the Delegation of Authority Log are permitted to consent subjects, receive, dispense, dispose of and return investigational products, conduct subject visits, insert devices, and enter data on eCRFs. These tasks may be delegated by the investigator. However, the

investigator is ultimately responsible to ensure investigational center-staff are qualified and perform the tasks that have been delegated to them correctly. In addition, the investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

The investigator's signature on the Investigator Statement confirms that the investigator is familiar with the CIP in its entirety and agrees to conduct this study in accordance with the provisions of the CIP and all applicable regulations. The investigator, prior to the initiation of any study related activity, will sign the Investigator Statement. If the sponsor discovers that an investigator is not complying with the Investigator Agreement, CIP, or other regulatory requirements, the sponsor shall promptly secure compliance or discontinue that investigator's participation in the study.

14.5. Role of the sponsor's representatives

Sponsor's representatives may provide Study specific training to the site personnel conducting study activities. Sponsor's representatives may also provide technical support under supervision of the PI following routine practice in the participating countries (i.e. pump or CGM training) and for study specific activities (i.e. data uploads, IT support). In the applicable participating sites where sponsor is involved in subject device trainings, the sponsor's representatives providing technical support will be listed on the sponsor technical support list. No data entry on the eCRF shall be performed by Medtronic personnel or their representatives at investigational centers.

14.6. Subject compensation and indemnification

The subjects will not receive any compensation for participation in this study. Travel fees to the site may be reimbursed for study specific visits if required by local regulations.

Insurance coverage is described in section 15.6 Liability.

15. Study Administration

15.1. Investigator Qualification

The following requirements will be evaluated for each investigator considered for participation in the clinical study:

- Investigator/site is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures (Endocrinology or Diabetology expertise)
- Investigator/site has Medtronic MiniMed 640G or 670G System experience, including CareLink usage
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration, including Internet access

- Investigator/site has access to an adequate number of eligible subjects
- Investigator/site has past experience in conducting clinical studies
- Investigator/site has interest in participating in pre-market interventional studies with devices
- Investigator/site has the ability to comply with applicable IRB/EC and regulatory requirements
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions

15.2. Training of Clinical Staff

In order to conduct the study, investigational center staff that have the appropriate medical training is required. Training of the investigational center staff on the conduct of the study and system being studied will be initiated before the CIP is implemented. All participating physicians will be familiarized with the system. Other members of the investigational center staff may require training depending on their role listing in the Delegation of Authority Log.

The PI is responsible for ensuring that investigational center staff are trained to perform their assigned duties per the Delegation of Authority Log. Individual investigational center staff must be appropriately trained prior to performing study related tasks.

15.3. Monitoring

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated informed consent forms have been obtained from each subject at the point of enrollment and that AEs discussed in Section 11 were reported via completion of the Adverse Event CRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

15.3.1. Accessibility of investigational center staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the electronic Case Report Form (eCRF).

15.3.2. Direct Access to Source Data/Documents

The subject's medical file, CareLink™ Personal For Clinical Research software data, and source worksheets are handled as source data.

Medtronic clinical representatives or delegates will be granted access by the investigational center to all source documents including electronic source documents, if applicable, for the purposes of monitoring,

audit, or inspection. Source data access should be prepared by investigational center staff prior to any visit. If applicable, where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational center team with a statement that it is a true and complete reproduction of the original source document ("certified copy").

15.3.3. Audits and investigational center inspections

In addition to regular monitoring visits, Medtronic may conduct quality audits at participating investigational centers. The purpose of an audit is to verify the adequate performance of the clinical study related activities independent of the employees involved in the clinical study, verify adherence to external regulations and internal policies and procedures; assess adequacy and effectiveness of clinical policies and procedures; assure compliance with critical study document requirements; confirm integrity and accuracy of clinical study data; and protect the safety, rights and welfare of study subjects.

Regulatory authorities may also perform inspections at participating investigational centers. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory authorities direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC/IRB review, and regulatory inspections.

15.4. Data Management

15.4.1. Data collection

15.4.1.1. Electronic Case Report Forms (eCRFs)

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents, such as subject medical records, must be consistent with the source documents and discrepancies need to be justified in a documented rationale.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigational center staff as specified on the Delegation of Authority Log included in the Investigator Site Binder. The OC-RDC system maintains an audit trail on entries, changes, and corrections in the eCRFs.

A copy of the eCRFs to be used in this clinical study is available under a separate cover, upon request to the Sponsor and in the Investigator Site File.

Investigational centers will be trained in the use of eCRFs. Access to final eCRFs for study conduct will be granted after training is performed and prior to patient's enrollment.

15.4.1.2. Paper Study Worksheets

All investigational centers will receive paper worksheets, which specify the required data collection in the CRFs, and some additional instructions to ensure correct completion. The study worksheets are a supplement of the patient's hospital/clinic file and completed worksheets will be considered as source documents. Only authorized persons can complete the worksheets as specified on the Delegation of Authority Log included in the Investigator Site File.

15.4.1.3. Medtronic CareLink™ Personal Therapy Management Software for Diabetes System

The MiniMed™ insulin pump data needs to be uploaded in Medtronic's CareLink database by the investigator or designated investigational site staff and subjects at home.

The data in the different databases are linked to each other via the SIDs to prevent subject's identification by the sponsor and allow data aggregation.

15.4.1.4. Download Utility Software

The Download Utility Software for use with the Guardian Link 3 Transmitter is a computer-based program used to set time, upload data and clear data for the Guardian Link 3 Transmitter when used in a blinded mode (described in section 7.4). Communication between the Transmitter and the computer is done via the specific Dock with USB cable. Once the data is downloaded, each site uses a specific username and password to access the site's database and upload the device data for each subject.

Refer to the Download Utility guidelines for more details.

15.4.1.5. Patient Questionnaires

The questionnaires will be provided in local language in the countries. The data will initially be collected on paper questionnaires that will be kept at the site.

The investigator, or designated site personnel, will then copy the answers of the subject from the paper questionnaires into the OC-RDC system. It is important that the investigator, or designated site personnel

verifies the questionnaires for completeness before subject leaves the site, because missing answers for some questions would prevent calculations of total scores.

15.4.2. Time windows for completion and submission of Case Report Forms

It is expected that eCRFs are completed in a timely manner, with the exception of reportable events (see Table 7), which need to be recorded immediately after awareness of the investigational site staff on the *Adverse Event* or *Device Deficiency* eCRFs. After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay. Exceptions to this rule apply for CRF forms that need to be accessed on multiple occasions before they can be finalized (*i.e. Device/ Consumables Accountability* eCRF*)*.

15.4.3. Data review and processing

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study.
Collected data will be reviewed for completeness, correctness, and consistency, as per the monitoring plan. In case of issues, queries will be entered on the respective eCRF for the investigator to complete, correct, or comment on the data.

15.5. Confidentiality

The investigator will ensure that the subject's anonymity is maintained. All records and other information about subjects participating in this clinical study will be treated as confidential. Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (study - site - subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject ID code in order to maintain subject confidentiality. All records will be kept in a secure environment and all computer entry and networking programs will be done with coded numbers only.
The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. Study data may also be made available to third parties, e.g., in the case of an audit or inspection performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed.

Subjects will not be identified in any publicly released reports of this study. Only anonymized data will be analysed and published.

15.6. Liability

The Medtronic International Trading Sàrl is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB or regulatory authority.

15.7. CIP Amendments

An investigator or study team member can propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device/product or investigational device/product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic can decide to review the CIP based on new information (i.e. from an investigator, the CEC or the study team) and will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities for their approval and to the investigators to obtain approval from their EC/IRB. The investigator will only implement the amendment after approval from the EC/IRB, regulatory authority and sponsor. Administrative amendments to the CIP will be submitted to the EC/IRB for notification. Furthermore, investigators shall sign any approved amendment for agreement.

15.8. Investigational Center Compensation

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

15.9. Record Retention

The Principal Investigator will retain all records and documents pertaining to this study in accordance with local law and regulations for a minimum period of 10 year (or longer if local laws require) after market-release in his/her region or termination of the study, whichever is longer. They will be available for inspection by the appropriate regulatory authorities. In addition, the investigator will retain the source documents from which the information entered on the eCRF was derived. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials and will ensure

that essential study documents are not destroyed until written permission has been obtained from Medtronic.
Medtronic will retain the study records according to Medtronic policy.

15.10. Publication and Use of Information

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites.

Medtronic intends to publish the results of the clinical study in a scientific journal.

A separate Publication Plan will describe the publication strategy and processes for publications of the study.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is in accordance with the International Committee of Medical Journal Editors (ICMJE) published guidelines, as agreed upon by the editors of all major medical journals.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The contents of this CIP, documentation, and results pertaining to this study are confidential and may not be published or disclosed without the written consent of Medtronic.

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The results for this study will be published on ClinicalTrials.Gov.

15.11. Suspension or Early Termination

15.11.1. Early study suspension or termination

Sponsor or Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, lack of enrollment, if interim analysis indicates that the results significantly differ from expectations relative to study objectives or statistical endpoints, or because of a business decision). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly notify the Regulatory Authority and inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects, as applicable by local laws and regulations.

15.11.2. Early Investigational Center suspension or termination

Sponsor, EC/IRB or a Regulatory Authority may decide to suspend or prematurely terminate an investigational center (e.g. in case of non-compliance to the CIP, lack of enrollment). If an investigational center is suspended or prematurely terminated, sponsor shall promptly inform the investigator(s) and the Regulatory Authority of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects, as applicable by local laws and regulations.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify, or immediately stop the clinical study in the respective investigational center and immediately inform the sponsor and EC/IRB, if applicable.

15.11.3. Subject follow-up in case of termination

In case of early investigational site suspension or termination, all subjects should be called to plan an Early Termination visit (described in section **9.6**) at the site. All efforts will be made to complete and report all study observations at the time of termination. The subject will return the study devices to the site.

15.12. Study Close-Out

At the time of a study close-out, the investigators will be notified by the sponsor. Appropriate notification and final study report will be provided to EC/IRB and Regulatory Authority, if required per local laws and regulations.

16. References

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17. Appendices

17.1. Names and addresses

17.1.1. Investigational Centers Information

The names and addresses of investigators and participating investigational centers will be kept under separate cover. This list will be provided to the participating investigators and sponsor shall inform the investigators in case changes occur in the list of participating sites. The most current list is available upon request.

17.1.2. Monitors Contact Information

The names and addresses of monitors will be kept under separate cover. This list will be provided to the participating investigators and sponsor shall inform the investigators in case changes occur in the list. The most current list is available upon request.

17.1.3. Sponsor Contact Information

The names and addresses of sponsor team will be kept under separate cover. The most current list of the contact persons is available upon request.

17.1.4. Vendors Contact Information

The names and addresses of vendors providing services for the study will be kept under separate cover. The most current list of the contact persons is available upon request.

17.2. Labelling and IFUs of Devices

The current labelling and IFU for the study devices will be provided to the investigators in a separate cover.

17.3. Sample Informed Consent Form

Informed Consent template is provided under a separate cover upon request to the Sponsor.

17.4. Sample CRF

Case Report Form is provided under a separate cover upon request to the Sponsor.

17.5. Sample Investigator Agreement

Sample Investigator Agreement will be provided under a separate cover upon request to the Sponsor.

17.6. List of Consumables and Accessories

INFUSION SETS	EUROPE
MMT-399	MiniMed™ Quick-set™ 60cm tubing with 6 mm cannula (box of 10)
MMT-387	MiniMed™ Quick-set™ 80cm tubing with 6 mm cannula (box of 10)
MMT-398	MiniMed™ Quick-set™110cm tubing with 6 mm cannula (box of 10)
MMT-397A	MiniMed™ Quick-set™60cm tubing with 9 mm cannula (box of 10)
MMT-386	MiniMed™ Quick-set™ 80cm tubing with 9 mm cannula (box of 10)
MMT-396	MiniMed™ Quick-set™110cm tubing with 9 mm cannula (box of 10)
MMT-921/941	MiniMed™ Mio™ 45cm tubing with 6mm cannula (Pink/Blue) (box of 10)
MMT-923/943	MiniMed™ Mio™ 60cm tubing with 6mm cannula (Pink/Blue) (box of 10)
MMT-965	MiniMed™ Mio™ 80cm tubing with 6mm cannula (box of 10)
MMT-975	MiniMed™ Mio™ 80cm tubing with 9mm cannula (box of 10)
MMT-368	MiniMed™ Silhouette™ 45cm tubing with 13mm cannula (box of 10)
MMT-381	MiniMed™ Silhouette™ 60cm tubing with 13mm cannula (box of 10)
MMT-383	MiniMed™ Silhouette™ 80cm tubing with 13mm cannula (box of 10)
MMT-382	MiniMed™ Silhouette™ 110cm tubing with 13mm cannula (box of 10)
MMT-378	MiniMed™ Silhouette™ 60cm tubing with 17mm cannula (box of 10)
MMT-384	MiniMed™ Silhouette™ 80cm tubing with 17mm cannula (box of 10)
MMT-377	MiniMed™ Silhouette™ 110cm tubing with 17mm cannula (box of 10)
MMT-864	MiniMed™ Sure-T™ 60cm tubing with 6mm cannula (box of 10)
MMT-866	MiniMed™ Sure-T™ 80cm tubing with 6mm cannula (box of 10)
MMT-874	MiniMed™ Sure-T™ 60cm tubing with 8mm cannula (box of 10)
MMT-876A	MiniMed™ Sure-T™ 80cm tubing with 8mm cannula (box of 10)
MMT-884	MiniMed™ Sure-T™ 60cm tubing with 10mm cannula (box of 10)
MMT-886	MiniMed™ Sure-T™ 80cm tubing with 10mm cannula (box of 10)
MMT-905	MiniMed™ Mio™ 30 60cm tubing with 13mm cannula (box of 10)
MMT-906	MiniMed™ Mio™ 30 100cm tubing with 13mm cannula (box of 10)
MMT-242	MiniMed™ Mio™ Advance (box of 10)

INFUSION SET	INSERTION DEVICES
MMT-395	MiniMed™ Quick-serter™ (for use with Quick Set Infusion Sets)
MMT-385	MiniMed™ Sil-serter™ (for use with Silhouette Infusion Sets)

RESERVOIRS

MMT-326A	1.8 mL reservoirs (box of 10)
MMT-332A	3.0 mL reservoirs (box of 10)

OTHER

-	CONTOUR® NEXT Test Strips
-	CONTOUR® Solution
ACC-LR6	AA Battery (Alkaline)
MMT-174	Tape HMS-174 ADH IV3000 1-hand 13L
7005739-006	Standard tape
HMS-180	Skin Tac Adhesive Wipe (box of 50)
MMT-173	Skin preparation wipes
ACC-1601	Belt clip
ACC-410BK	Leather case
MMT-7747	USB cable and wall-powered adapter
-	Urinary pregnancy test, if needed

Product references may be updated per company procedures throughout the study. The most updated list of references will be kept separately.

17.7. Sample Questionnaires

The questionnaires are available in local language and will be provided under a separate cover upon request to the Sponsor.

17.8. CIP327 Study Visit Procedures Table

The Study Visit Procedures Table is provided under a separate tool describing all study requirements.

18. Version History

Version	Summary of Changes	Author(s)/Title
A	'Not Applicable, New Document'	[redacted]/ Sr. Clinical Specialist
B	Correction of few typos. Removed "draft" watermark on pages 53-57. Corrected visit schedule at Visit 12 and 13 on Figure 2 and 8 and in study procedures to match with corrected schedule for Visit 12 (V11E+1m) and visit 13 (V12+3m). Addition that subject will stop FGM/CGM at visit 6A upon CGM start with AHCL system throughout the protocol.	[redacted]/ Sr. Clinical Specialist

C	The statement "*as per investigator judgment"* was added to Exclusion criteria 9 for clarification purpose. "Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, *as per investigator judgment."* Section 8.1 "Study Population" was further detailed, specifying the 2 cohorts of the study : *The study will include subjects in two different cohorts, as follow:* ***Cohort A** with subjects on **MDI + FGM*** ***Cohort B** with Subjects on **MDI + Real-Time CGM*** Approximately 84 MDI + FGM subjects will be enrolled *in cohort A* to achieve approximately 70 subjects randomized and 64 subjects completing the 6-month study phase. *The primary analysis will be conducted on cohort A.* In addition, approximately 40 MDI + RT-CGM subjects will be enrolled *in cohort B* to achieve approximately 34 subjects randomized and 30 subjects completing the 6-month study phase. *An exploratory analysis will be conducted on cohort B.* Section 9.10: Randomization and Treatment Assignment was rephrased and clarified, adding text in italic: "Treatment assignment will be randomized by cohort. " Part which is not in line with final randomization process was deleted: *"In case technical issues occur with the electronic CRF (i.e. Internet access, system maintenance), a randomization list will be generated by the statistician and the statistician will be able to communicate the randomization arm to the study team and site staff."* Table 6: corrected typo at Visit 11E – Window 14 days instead of 10 days. Section 13.3. Sample Size Considerations: Clarification was made to the minimal/maximal numbers of patients, changed from percentage to actual numbers "a minimum of 4 ~~(5%)~~ and a maximum of 20 ~~(23%)~~ of the total subjects of the cohort should be randomized (~~enrolled~~) at each site, with the current sample size. Section 13.4. Sample size reassessment - Interim Analysis in Cohort A: The following sentence was added for clarification: *"Early stopping is only considered in case of futility. No sample size decrease is considered for efficacy."* A new section *13.7. Handling Missing Data* was added for clarification: *The main analysis for the primary endpoint (HbA1c) is based on a random effect model that uses available data and accounts for missing at random. In addition, sensitivity analyses will be performed. Sensitivity analysis includes Per Protocol population (or those subjects who completed study) analysis, multiple imputation*	[redacted]/ Sr. Clinical Specialist

	analysis and Last Observation Carry Forward (LOCF) analysis by replacing missing values by baseline value for subjects that withdraw/drop-out.	
D	In Synopsis – Product status, Tester number was corrected to MMT-7736L (correcting mistaken 7726 number) In Section 11.2, the note in the definition of Serious Adverse Event (SAE) for in-patient hospitalization referring to 24 hours period was removed: ~~*For the purpose of this study, In-patient Hospitalization is defined as: admission to the hospital for a period of 24 hours or more based on urgent medical need rather than planned admission.*~~ Section 13.7. Handling Missing Data as revised to: *Primary endpoints and Secondary endpoints will be collected at baseline, end of 3 months and end of 6 months .The main analysis is based on ITT (Intention to Treat) using a random effect model that uses available data and accounts for missing at random. In addition, sensitivity analyses will be performed.* *For the primary analysis (change of A1c), if A1c at 3 months or 6 months is not available in subjects that drop-out of the study, the following sensitivity analyses will be carried out:* • *Per Protocol Dataset* • *Baseline Observation Carry Forward (BOCF)* • *Data will be imputed by selected A1c data from the same arm considering baseline characteristics such as age, gender and duration of diabetes* *For the secondary endpoints, as suggested by International Consensus Group (ICG), during the two weeks period of SG comparison at 3 months and 6 months between control and treatment arm, a minimum number of 2880 SG values (288 SG values/day × 10 days out of 14 days) is required to evaluate the glycemic outcome. For those subjects with less than 2880 SG during the two weeks of sensor wear, the following sensitivity analysis will be carried out to mitigate the impact of data loss:* • *CGM data gap filled within the same subject: Missing CGM data in one arm will be imputed by randomly replaced CGM data in the same subject during the same period of sensor wear.* • *CGM data gap filled within the arm, ignoring baseline characteristics: Missing CGM data will be imputed by a randomly selected CGM data from the same arm, ignoring baseline characters during the same period of sensor wear.* • *CGM data gap filled within the arm, considering baseline characteristics: Missing CGM data will be imputed by selected CGM data from the same arm, considering baseline characters such as age, gender and duration of diabetes during the same period of sensor wear.*	[redacted]/ Sr. Clinical Specialist

E	**Version E** was created to comply with the German regulatory authority requests, to clarify the study design, the separated cohorts (A and B) and the analysis. **Page 1:** Per MDR requirements, the EU-based Legal representative of the Sponsor was added : Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands **Study Title/Study type** was updated on pages 1 and 11, 12 : The following sentence was added following: "A Prospective, Open-label, Multi-center, Adaptive, Confirmatory and Randomized Controlled Study" **Synopsis Study type** was updated accordingly to title update. **Randomization** section was updated, adding the words "confirmatory" for the Cohort A and "exploratory" for the Cohort B, with the sentence "Each cohort will have a separate randomization." **Synopsis Sample Size and Investigational Sites and Section 8.1** have been updated to clarify the number of patients to be enrolled in the study in each cohort separately: Deleted ~~"A total of approximately 124".~~ Cohort A and Cohort B were moved to the beginning of the sentences. In section 8.1: Deleted "~~in order to have approximately 100 subjects complete the study"~~ **Visit schedule overview:** Visit 7B was changed to green (Onsite only). **Synopsis (Page 20) and Primary Endpoint (Section 5.3.1, Page 26) : Primary Endpoint** was updated: "*Confirmatory test*" was added and "*evaluated*" was replaced by "*performed*" for more clarity on the analysis. **Synopsis (Page 20) and Secondary Endpoints (Section 5.3.2, Page 26) : Secondary Endpoints** were updated and reorganized to describe the tests that will be conducted, in alignment with the Convention for evaluation of Time in ranges with CGM data (Danne 2017). • Deleted "and categorized by daytime (06:01 to 23:59), night-time (00:00 to 06:00) and overall (24h)". Secondary endpoints will be analyzed overall. Daytime and Night-time assessments are moved to ancillary endpoints. • % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) • % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) • % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) • % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L) • % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L) **Synopsis (Page 21) and Ancillary Endpoints (Section 5.3.3, Page 27):** **Ancillary Endpoints:** The endpoints that are part of the secondary analysis were removed for consistency.	[redacted]/ Sr. Clinical Specialist

	Combined Number of biochemical hypoglycemic events with SG < 54 mg/dL and < 70 mg/dL into 1 row. Added the following ancillary endpoints: ▪ % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) ▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) ▪ % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L) ▪ % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L) The above five endpoints will be categorized by daytime (06:01 to 23:59) and night-time (00:00 to 06:00). The following endpoints were split for more clarity: ▪ Diabetes-related number and mean duration of hospitalizations, number and mean duration intensive care unit (ICU) care, number of emergency room admissions, number of events requiring ambulance assistance, *"categorized by reason of diagnosis"* (*part added*) ▪ Number of lost days from school or work **Section 6:** Added sentence "*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."* **Section 8.1:** The word "*confirmatory*" was added to the sentence: The primary and "*confirmatory*" analysis will be conducted on cohort A. **Section 9.1:** Last sentence was updated to add *"which may impact patient's safety":* Participants who are not compliant with the arranged contacts, *which may impact patient's safety,* may be discontinued at the discretion of the investigator. **Section 9.2 (p. 45) : Visit 1 and section 9.8.5 (p. 65):** The reference to external web-based calculator was removed: ~~Usage of the web-based calculator is recommended (Cockroft): https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation.~~ "The sites will follow routine practice for evaluation of the creatinine clearance" was added. **Section 9.10: Randomization.** Sentence was rephrased for more clarity from "~~Treatment assignment will be randomized by cohort.~~" to Each cohort will have a separate randomization. **Section 11.3. Adverse Event and Device Deficiency Reporting Requirements** was revised to describe further Reporting To Regulatory Authority and Ethics Committee from Investigators and Sponsor. Added the new **Table 8: Adverse Event and Device Deficiencies Reporting Requirements by Medtronic to Regulatory Authorities & EC.**	

	Added "In addition, Medtronic shall prepare and submit complete, accurate, and timely study reports, as per local reporting requirements." **Section 13.5. Analysis of Primary Endpoint:** *Added "confirmatory"* to the sentence: This "*confirmatory*" analysis will be performed on the Intent to Treat (ITT) basis. **Section 13.6 Analysis of Secondary Endpoints:** Revised entire section to detail the analysis, according to the updated secondary endpoints listed in section 5.3.2. ~~The mean of the below listed secondary endpoints during the study phase will be compared between the arms like primary endpoint analysis.~~ Analysis on secondary endpoints listed in section 5.3.2 will be performed using ~~A two-sided test using linear mixed model~~ a linear mixed model on the ITT population. ~~The secondary endpoints are day time, night time and overall (24h)~~ This is a confirmatory trial for primary and secondary endpoints in cohort A as described in following sequential testing. If the primary endpoint analysis is significant, the procedure tests hierarchically the ordered hypotheses in sequence at level α=0.05 until one of the hypotheses is non-rejected. ▪ % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) Non-inferiority test with non-inferiority margin of 6% ▪ (the margin of 6% corresponds to approximately 90 minutes per day which is considered as a clinically relevant reduction in time spent in hyperglycemia). ▪ % Time spent in hyperglycemic range with SG > 250 mg/dL (13.9 mmol/L) Superiority test ▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) Non-inferiority test with non-inferiority margin of 6% ▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L) Superiority test ▪ % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) Non-inferiority test with non-inferiority margin of 6% ▪ % Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L) Superiority test ▪ % Time spent in hypoglycemic range with SG < 54 mg/dL (3.0 mmol/L) Non-inferiority test with non-inferiority margin of 2% (the margin of 2% corresponds to approximately 30 minutes per day increase which is considered as a clinically relevant reduction in time spent in level II hypoglycemia) ▪ % Time spent in hypoglycemic range with SG < 70 mg/dL (3.9 mmol/L) Non-inferiority test with non-inferiority margin of 5% (the margin of 5% corresponds to 72 minutes per day which is considered as a clinically relevant reduction in time spent in level 1 hypoglycemia). ▪ ~~% Time spent within range with sensor glucose (SG) between 70 - 180 mg/dL (3.9-10.0 mmol/L)~~	

	~~▪ Number of biochemical severe hypoglycemic events < 54 mg/dL (defined as sensor values < 54 mg/dL per 15 consecutive minutes)~~ ~~▪ % Time spent in hyperglycemic range with SG > 180 mg/dL (> 10.0 mmol/L)~~ Superiority test for % Time spent in hypoglycemic range with SG < 54 mg/dL, < 70 mg/dL and analyses on the ancillary endpoints listed in section 5.3.3 and safety endpoints listed in section 5.3.2.1, ~~between-arm comparison~~ may be performed for exploratory purpose and significance of these tests will not be claimed. Linear mixed model will be used for the endpoints with repeated measures and analysis of variance will be used for single measurements. **Section 13.7 Handling Missing data section:** Deleted paragraph left by mistake in Version D update: ~~The main analysis for the primary endpoint (HbA1c) is based on a random effect model that uses available data and accounts for missing at random. In addition, sensitivity analyses will be performed. Sensitivity analysis includes Per Protocol population (or those subjects who completed study) analysis, multiple imputation analysis and Last Observation Carry Forward (LOCF) analysis by replacing missing values by baseline value for subjects that withdraw/drop-out.~~	
F	**Section 11.3 Adverse Event and Device Deficiency Reporting Requirements - Table 7:** Device Deficiency (DD) were moved to second row for reporting in a timely manner by the Investigator to Medtronic as per Medtronic standard requirements. **Section 11.3 and Table 8:** The reference was added "For Germany, refer to German Local Amendment A, or subsequent versions, for more details", as per Bfarm requirements. **Section 11.3.2. Reporting of Device Deficiencies** updated per Bfarm requirements to clarify the definition of Device Deficiencies with SADE potential and the reporting requirements: Deleted: ~~Device deficiencies that did not lead to an Adverse Event, but could have led to a SADE require immediate reporting (see section 0)~~ ~~a) if either suitable action had not been taken,~~ ~~b) if intervention had not been made, or~~ ~~c) if circumstances had been less fortunate,~~ Replaced by: Device deficiencies that did not lead to an Adverse Event, but could have led to a SADE: a) if either suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate	[redacted]/ Sr. Clinical Specialist

	also defined as Device Deficiencies with SADE potential require immediate reporting to the sponsor via completion of the applicable CRF, to IRB/EC and to regulatory authority per local reporting requirements ISO14155:2011 (Refer to Table 9). For Germany, refer to German Local Amendment A, or subsequent versions, for more details. Adding : All Device deficiencies will be reported to Investigators, Regulatory Authorities and IRB/IEC as part of the Study report(s).	
G	**Version G** was developed to address sites and subjects' needs under pandemic, especially to allow remote visits throughout the study, as safety measures. *The ICF and CRFs documents are updated according to the changes of version G. There is no anticipated impact on performance, effectiveness, or safety or other endpoints related to this amendment.* Inclusion criteria 4 was revised to facilitate recruitment under pandemic: Subject has been followed and treated by the investigator at this investigational site for at least ~~6~~ 3 months prior to screening and subject has already undergone local educational therapeutic programs. Exclusion criteria 3 was revised to avoid repeated/additional blood test under pandemic : Subject has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ ~~3~~ 12 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations. Synopsis - Study Procedures and Assessments Added "Under pandemic situation, all the visits can be conducted remotely (via phone or video call) and organized accordingly (see details below) per Investigator decision." Visit schedule overview Figures (2 and 8) have been updated: Added symbol and note "¤ Visits allowed to be conducted remotely in pandemic period" in the figure with light color code to indicate remote visit option for all visits. Visit 2 window has been updated to allow more flexibility: visit can be planned at Visit 1 +7 days with the new window of minimum + 3 days after visit 1, as long as HbA1c results have been received. Section 9 has been fully revised to describe the visit with new remote organization accordingly (shipments of supplies and documents, virtual trainings, remote blood tests). Section 9.1: Added "Under pandemic situation, all the visits can be conducted remotely (via phone or video call) and organized accordingly (see details below), per Investigator decision. Investigator may decide to conduct a remote visit during pandemic to maintain safety and when onsite visit is not possible as it would expose subject and staff to increased risks. Rationale will be documented in the source files."	[redacted]/ Sr. Clinical Specialist

	Section 9.5 and 9.6: Added "This visit can be conducted onsite or remotely." Section 9.9: Added text to specify Remote informed consent process. "Documentation can be sent by mail to the subject (two copies of the PIC will be sent for signature). If the visit is conducted remotely in pandemic context, the investigator or his/her authorized designee will conduct the discussion via phone or video call." And "If applicable, (ie. during pandemic), the patient can send the signed consent back by regular mail to the site. Site will wait for the signed copy before proceeding with any study related procedure. Once received, the investigator or authorized designee will date and sign." New section 10.1.3.4. Remote follow-up was created: "In response to pandemic situation, to continue study execution, visits can be conducted remotely (via phone or video call) as site staff have built up experience with virtual clinics to train and can follow-up their patients on insulin pump therapy, using virtual tools and videos. The same standard of care process can be followed in this study, with no additional risk for the patients. Investigators may decide to conduct a remote visit during pandemic to maintain safety and when onsite visit is not possible as it would expose subject and staff to increased risks. Rationale will be documented in the source files." Section 10.2. Risk-Benefit Rationale. Added sentence "Finally, in the context of pandemic, the risk of visiting the site for the subject has been mitigated via the setup of remote visits." Section 13.3.1 and 13.3.2: updated email address to rs.mc2safetyportfoliodiabetespainbrain@medtronic.com Appendix 17.6: Updated to new model number MMT-876A for MiniMed™ Sure-T™ 80cm tubing with 8mm cannula (box of 10) (instead of MMT-876).	
H	**Version H** was developed to update the protocol to the new standard ISO 14155:2020. *There is no anticipated impact on performance, effectiveness, or safety or other endpoints related to this amendment.* Reference to the *International Standard ISO 14155 was updated throughout the document to new version dated 2020 instead of 2011.* Synopsis: Section "**Sponsor**" Added "(*Sponsor is the funding source*)", per new ISO 14155:2020 requirement. Updated **Visit schedule overview Figures (2 and 8)** for clarity on the picture : The optional remote visits related to pandemic are shown with the symbol and note "¤ Visits allowed to be conducted remotely in pandemic period" to indicate remote visit option for all visits in case of pandemic.	[redacted]/ Sr. Clinical Specialist

	Synopsis Section "**Objective**" and **section 5.1** The word "Superiority" is replacing "efficacy" for more clarity on the design, per new ISO 14155:2020 The primary objective of the study is to evaluate the **superiority** ~~efficacy~~ on glycemic control of the AHCL system versus MDI + FGM in patients with Type 1 Diabetes. Page 23: **Table 1: AHCL clinical studies** "Dr. De Bock" and "FLAIR" studies updated to status "completed" Added new **Section 7.2 Comparator,** per new ISO 14155:2020 "Subject enrolled in the study are treated with any Multiple Daily Injection device and Flash or Continuous Glucose Monitoring systems. Subject can use any model, as prescribed per standard of care prior to screening, through the commercial pathway. There is no device accountability requirement for the comparator for the purpose of this study. Subjects will continue to use it as needed throughout the study, as per randomization assignment. Examples of Flash Glucose Monitoring Systems: Abbott Freestyle Libre 1 or 2. Examples of Continuous Glucose Monitoring systems: Dexcom G4, G5, G6; Medtronic Guardian Connect; Sugarbeat. Any other model that may be/become available for prescription during the study can also be used." **Tables 5 and 6 on STUDY PROCEDURES** were updated by adding one row for Pandemic measure ("remote option") for more clarity on the organization of the visits. **Section 9.7. Study Exit** Added **"the subjects will be exited from the study"** for clarity per new ISO 14155:2020. "After the study has been completed (at Visit 13 or in case of early termination), **the subjects will be exited from the study**. The subjects will continue to be treated following the routine practice of each center." **Section 9.8.1.1 HbA1c at central laboratory** Added sentence per new ISO 14155:2020 **"The blood sample will be destroyed according to the Central laboratory procedure after analysis."** **Section 9.8.2. AHCL use** Added sentence for clarification on the recommended device usage per protocol "**The recommended settings for the Auto Mode during the study are the following:** **Auto Basal Target: 100 mg/dL (5.6 mmol/L)** **Active Insulin Time: 2h"** **Section 9.8.Creatinine Clearance**	

	Added sentence per new ISO 14155:2020 "**following local lab procedures for blood sample collection and disposition".** **Section 9.10 Randomization and Treatment Assignment** Added sentences to describe bias minimization per new ISO 14155:2020 **"Block randomization was chosen in order to preserve a 1:1 randomization ratio as much as possible, while minimising the likelihood of predicting treatment allocation to the next participant.** **Confounding is addressed by the random allocation, with the aim that any confounding variable should be equally distributed in the two groups to give balanced groups."** **Section 10.1.1. Potential risks associated with the use of the investigational device** Regarding "Risks with hypoglycemia and hyperglycemia", in column "Prevention and mitigation include": the text "*Patients will receive*" was added for clarity of who is receiving the training: "**Patients will receive** training prior to study device use and diabetes management principles". **Section 11.2. Definitions and Classification** Updated all definitions of Adverse Events and Device Deficiencies per new ISO 14155:2020 **Adverse Event (AE):** ~~*(ISO14155:2011)*~~ new reference to *ISO 14155:2020, 3.2* Added sentence to the definition of AE "**and whether anticipated or unanticipated."** Updated NOTE 3, adding "or comparators": For users or other persons, this definition is restricted to events related to investigational medical devices "**or comparators"**. **Adverse Device Effect** (ADE):~~*(ISO14155:2011)*~~ new reference to *ISO 14155:2020, 3.1.* Added "**NOTE 3: this includes 'comparator' if the comparator is a medical device**." **Serious Adverse Event (SAE):** ~~*(ISO14155:2011)*~~ new reference to ISO 14155:2020, 3.45. Definition rephrased and updated with the following changes **b)** added **" in users or other persons as defined by one or more of the following** ~~that either resulted in~~**:** […] **2)** added **"including chronic disease"** **4)** added **"including physical or mental impairment"** **Serious Adverse Device Effect (SADE):** ~~*(ISO14155:2011)*~~ new reference to ISO 14155:2020, 3.44.	

	Unanticipated Serious Adverse Device Effect (USADE): ~~*(ISO14155:2011)*~~ new reference to *ISO 14155:2020, 3.51.* Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current ~~version of the~~ risk ~~analysis report~~ "**assessment".** NOTE~~Anticipated serious adverse device effect~~ **1:** ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk ~~analysis report~~ "**assessment".** New definition added**: "Serious Health Threat** *(ISO 14155:2020, 3.46)* **Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons** **NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals."** **Device deficiency:** ~~*(ISO14155:2011)*~~ new reference to *ISO 14155:2020, 3.19.* added **"usability"** to the definition. NOTE 1: DD include malfunctions, use errors ~~and inadequate labelling~~ **and inadequacy in the information supplied by the manufacturer including labeling.** **NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator.** Added full section on "**Relatedness**" per new ISO requirements: **Relatedness:** Device Related: An AE that results from the presence or performance (intended or otherwise) of the device. Procedure Related: An AE that occurs due to any study procedure (ie. Blood draw). **Section 13.5. Analysis of Primary Endpoint** Added text for clarity per new ISO 14155:2020: This confirmatory analysis "**aims at demonstrating the superiority of AHCL and**" will be performed on the Intent to Treat (ITT) basis. **Section 15.2. Training of Clinical Staff** […] All participating physicians ~~and coordinators~~ will be familiarized with the system. The word "coordinators" was removed from the sentence. Coordinators are trained on the system only if applicable per delegation of tasks, per Study training plan.	

	Section 17.6. List of Consumables and accessories: Reference MMT-397 was updated to MMT-397A for MiniMed™ Quick-set™60cm tubing with 9 mm cannula, per company procedure. The following sentence was added to clarify that future reference updates may occur: "Product references may be updated per company procedures throughout the study. The most updated list of references will be kept separately." Version history of CIP G was updated to clarify impact of the update and other study documents updates, per new ISO recommendation "*The ICF and CRFs documents are updated according to the changes of version G.* *There is no anticipated impact on performance, effectiveness, or safety or other endpoints related to this amendment. "*	