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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan (CIP)/Study Title	EvaLuation of th**E** Mi**N**iMed 780G System i**N** **Y**oung Paediatric Subjects (2-6 years old) with Type 1 Diabetes in a Home Setting (LENNY)
CIP Identifier	342
EUDAMED Number	CIV-SI-23-02-042435
Study Product Name	MiniMed™ 780G Insulin Pump system with Guardian™ Sensor 4 Sensor MiniMed™ 780G BLE 2.0 Insulin Pump system with Disposable Sensor 5
Description of CIP	This study will evaluate the safety and performance of the MiniMed 780G system in paediatric subjects (2-6 years old) with type 1 diabetes in Europe.
Sponsor	Medtronic International Trading Sàrl [redacted]
Europe-based Legal representative of the Sponsor	Medtronic Bakken Research Center [redacted]
Document Version	E
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1 Glossary

Abbreviations	
ADE	Adverse Device Effect
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AIT	Active Insulin Time
ASADE	Anticipated Serious Adverse Device Effect
AUC	Area Under Curve
BG	Blood Glucose
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CEC	Clinical Event Committee
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
CV	Coefficient of Variation
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
DoH	Declaration of Helsinki
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
EOS	End of Study
ER	Emergency Room
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDF	International Diabetes Federation
IFU	Instructions For Use
ISO	International Organization for Standardization
ITT	Intention to Treat
IV	Intravenous
MC2	Medtronic Core Clinical Solutions
MDI	Multiple Daily Injections

Abbreviations	
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
NGSP	National Glycohemoglobin Standardization Program
PC	Personal Computer
PI	Principal Investigator
PP	Per Protocol
QC	Quality Control
RA	Regulatory Authority
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SBL	Suspend Before Low
SD	Standard Deviation
SDS BMI	Standardized BMI
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SOP	Standard Operating Procedure
T1D	Type 1 diabetes
TDD	Total Daily Dose
TIR	Time in Range
TLS	Transport Layer Security
USADE	Unanticipated Serious Adverse Device Effect

Definitions	
Auto Mode/SmartGuard	Auto Mode (referred to as SmartGuard in the user guide) , is a feature in the MiniMed 780G system. In Auto Mode, the pump automatically adjusts basal insulin delivery to regulate glucose levels to a target sensor glucose amount. It also features automatic correction boluses.
Manual Mode	Manual Mode refers to when the function of the MiniMed 780G system when Auto Mode is not active.
Suspend before low	Suspend before low is a feature in the MiniMed 780G system. When Suspend before low is activated, the pump temporarily stops delivering insulin when the sensor glucose is at or within 70mg/dL above the set low limit and is predicted to reach or fall below a level that is 20mg/dL above the set low limit in 30 minutes.
Suspend on low	Suspend on low is a feature in the MiniMed 780G system. Suspend on low feature stops insulin delivery when SG readings reach or fall below the set low limit. When a Suspend on low event occurs, insulin delivery is suspended.

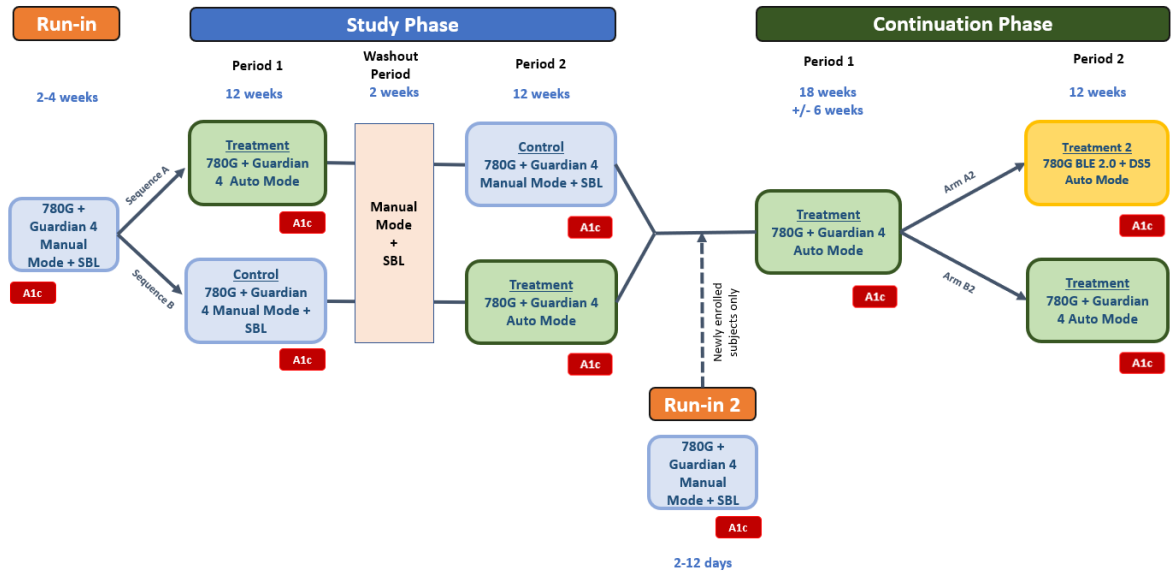
2 Synopsis

Title	EvaLuation of thE MiNiMed 780G System iN Young Paediatric Subjects (2-6 years old) with Type 1 Diabetes in a Home Setting (LENNY)
Clinical Study Type	Pre-market, interventional, prospective, open-label, multi-center, randomized crossover study
Indication under investigation	Type 1 diabetes (T1D) in paediatric population (2-6 years old)
Sponsor	Medtronic International Trading Sàrl [redacted]
EU-based Legal Representative of the Sponsor	Medtronic Bakken Research Center [redacted]
Study Products	**Study Products for Study Phase:** The following CE-marked products evaluated in this study are considered investigational for the study population: ▪ MiniMed™ 780G Insulin Pump (MMT-1895 and MMT-1896) ▪ Guardian™ 4 Sensor (MMT-7040) ▪ Guardian™ 4 Transmitter Kit (MMT-7840) **Study Products for Continuation Phase**: Based on the randomization, the following products will be used. The following CE-marked products evaluated in this study are considered investigational for the study population: ▪ MiniMed™ 780G Insulin Pump (MMT-1895 and MMT-1896) ▪ Guardian™ 4 Sensor (MMT-7040) ▪ Guardian™ 4 Transmitter Kit (MMT-7840) The following non-CE-marked products evaluated in this study are considered investigational for the study population: ▪ MiniMed 780G BLE 2.0 Insulin Pump (MMT-1895 and MMT-1896) ▪ Disposable Sensor labeled as DS5 and referred as DS5 throughout this CIP (MMT-5100) Commercialized devices, consumables and accessories will be provided during the study (detailed list in **Section 6.2** and **Appendix 18.7**).
Purpose	The purpose of this study is to demonstrate the safety and performance of the MiniMed™ 780G system in paediatric subjects (2-6 years old) with type 1 diabetes in a home setting.

Objective(s)	The objective of this study is to evaluate the safety and performance of the MiniMed™ 780G system in Auto Mode **firstly** in comparison to the MiniMed™ 780G system in Manual Mode with Suspend before low activated (currently available standard therapy) and **secondly** in comparison to the new MiniMed™ 780G BLE 2.0 system with DS5 sensor in Auto Mode among paediatric population (2-6 years old).
Study Design	This study is a pre-market, prospective, open-label, multi-center, randomized crossover trial in paediatric subjects aged 2-6 years with type 1 diabetes. The study consists of a run-in phase, a study phase and a continuation phase (see **Synopsis Figure 1** for an overview). **Run-in Phase (Visit 2-3):** The purpose of the run-in phase (2 to 4 weeks) is to train subjects on the MiniMed™ 780G system and to collect 2 weeks of baseline data. At the end of Run-in Phase, subjects will be randomized into 2 sequences (A and B). **Study Phase (Visit 3A-11):** During the study phase, each sequence consists of 2 phases of 12 weeks each separated by a 2-week washout phase for a total of 26 weeks. • Sequence A: subjects will start using the MiniMed™ 780G system in Auto Mode for 12 weeks. The washout phase of 2 weeks will be followed by a 12-week phase where subjects will use MiniMed 780G system in Manual Mode with Suspend before low (SBL) activated. • Sequence B: subjects will continue to use MiniMed™ 780G system in Manual Mode with SBL activated for 12 weeks. After a washout phase of 2 weeks, subjects will start to use the MiniMed 780G system in Auto Mode for a 12-week phase. During the washout period, all subjects will use MiniMed™ 780G system in Manual Mode with SBL activated. **Run-in Phase 2 (Visit 2a-3a):** The purpose of the run-in phase 2 (2 to 12 days) is to collect a minimum of 2 days baseline data for the subjects that will enroll only for the continuation phase (only applicable based on the interim analysis outcome). **Continuation Phase (Visit 12-15):** For the duration of the continuation phase. enrolled subjects will enter the continuation phase period 1 and will use MiniMed 780G system in Auto Mode. At the end of the continuation phase period 1, subjects will be randomized into 2 arms (A2 and B2) and enter period 2 for 12 weeks. • Arm A2: Subjects will start using the MiniMed™ 780G BLE 2.0 system with the DS5 sensor for 12 weeks • Arm B2: Subjects will continue to use MiniMed™ 780G system in Auto Mode for 12 weeks

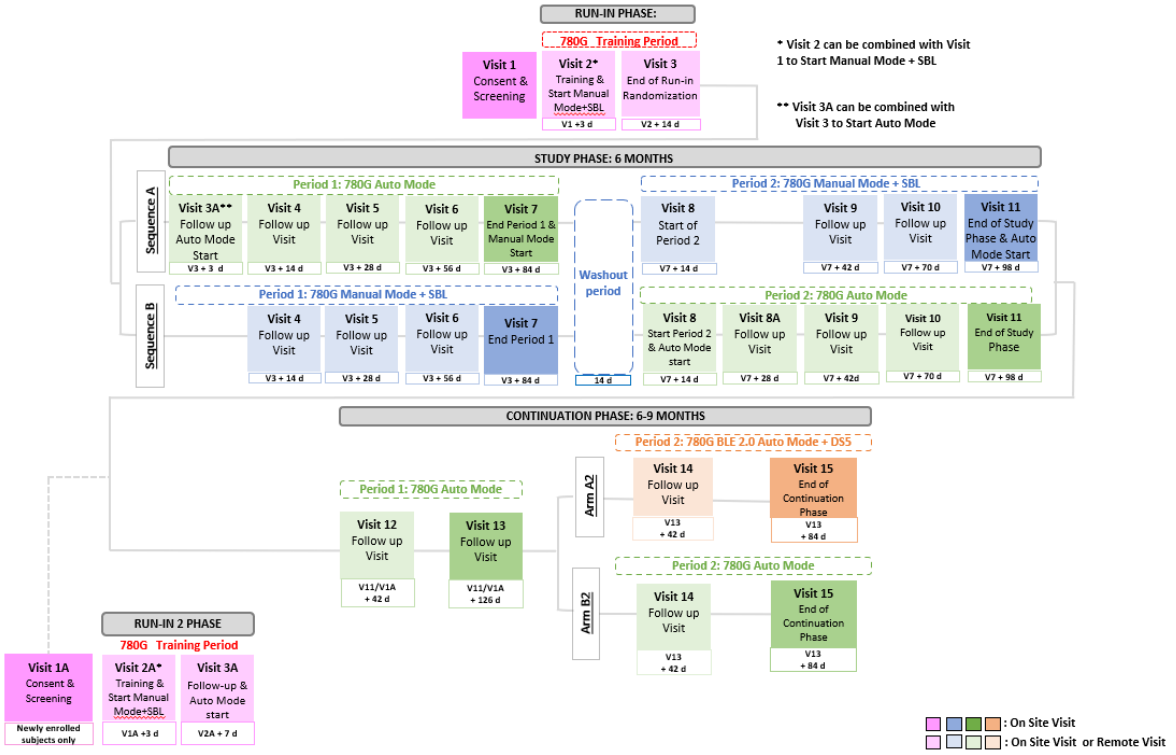
	See **Section 5** for more details.

Synopsis Figure 1. Study Design



Study Visit Schedule	Subjects may participate in up to 15 planned study visits, as presented in **Synopsis Figure 2**. A remote office visit (audio visual) may be performed for office visits in cases where an in-person office visit is not possible. For detailed information, see **Section 9**. Subjects who enroll only at the start of the continuation phase can participate in up to 7 planned study visits.

Synopsis Figure 2. Visit Schedule



Sample Size & Investigational Centers	Approximately 100 subjects with type 1 diabetes age 2-6 years will be enrolled at up to 18 investigational centers across Europe to achieve approximately 80 subjects randomized and have 72 completing the study phase and 64 completing the continuation phase. During the Continuation Phase period 1, the sample size will be re-estimated based on an interim analysis which will evaluate HbA1c Standard Deviation. Based on the interim analysis result, enrollment for the Continuation phase only will be opened.
Duration	The study is anticipated to last approximately 23 months from first investigational center initiation to study completion. The study will target 4 months to complete enrollment. Individual subject participation is expected to be approximately 14 months from the run-in phase to end of study participation or 6-9 months for subjects enrolled for the continuation phase only.
Inclusion Criteria	1. Aged 2 – 6 years at time of screening 2. Has a clinical diagnosis of type 1 diabetes for ≥6 months prior to screening as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 3. Is on MDI therapy or CSII with or without CGM prior to screening

	4. Has a glycosylated hemoglobin (HbA1c) <11% (97 mmol/mol) at time of screening visit as processed by a Local Lab) 5. Is using or willing to switch to one of the following commercialized available insulins: • Humalog™ (insulin lispro injection) • NovoLog™/ NovoRapid™ (insulin aspart) 6. Must have a minimum daily insulin requirement (Total Daily Dose) of ≥6 units 7. Parent(s)/legal guardian(s) willing to upload data from the pump system, must have Internet access, a compatible computer or mobile phone that meets the requirements for uploading the study pump data at home. 8. Is living with one or more parent(s)/legal guardian(s) knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 9. Investigator has confidence that the parent(s)/legal guardian(s) can successfully operate all study devices and is capable of adhering to the protocol 10. Subject and parent(s)/legal guardian(s) willingness to participate in all training sessions as directed by study staff. 11. Subject's parent(s)/legal guardian(s) must be willing and able to provide written informed consent.
Exclusion Criteria	1. Has Addison's disease, growth hormone deficiency, hypopituitarism or definite gastroparesis, untreated coeliac disease, untreated thyroid disorder, or poorly controlled asthma, per investigator judgment. 2. Is using any anti-diabetic medication other than insulin at the time of screening or plan on using during the study (e.g., pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors). 3. Has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study. 4. Has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ 6 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft, CKD-EPI or MDRD equations. 5. Has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 6. Is under Control IQ or CamAPS FX, Omnipod 5 or other advanced hybrid closed loop therapy (e.g. DIY, MiniMed 780G) in the previous 3 months before enrollment. Note: For the continuation phase only, subjects using MiniMed 780G can be enrolled. 7. 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.

	8. Has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment. 9. History of >1 DKA event not related to illness or initial diagnosis in the last 3 months. 10. Parent(s)/legal guardian(s) are part of research staff involved with the study. 11. Parent(s)/legal guardian (s) are illiterate
Statistical Analysis for Endpoints and Hypothesis	**<u>Primary Endpoint – Study Phase</u>** The primary endpoint for study phase is the between-treatment difference in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L). The endpoint will be assessed for non-inferiority with an absolute margin of 7.5% time in target range. **<u>Secondary Endpoints – Study Phase</u>** The secondary endpoints will be the between-treatment difference in the study phase for: • Mean HbA1c at the end of each 12-week period, non-inferiority with an absolute margin of 0.4% HbA1c. • % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]), simple superiority test. • Mean HbA1c at the end of each 12-week period, simple superiority test. **<u>Primary Endpoint – Continuation Phase</u>** The primary endpoint for continuation phase is the between-treatment difference in the mean HbA1c (%) at the end of 12-week continuation phase period 2. The endpoint will be assessed for non-inferiority with an absolute margin of 0.4% HbA1c. **<u>Secondary Endpoints – Continuation Phase</u>** The secondary endpoints will be the between-treatment difference in the continuation phase period 2 for: • Mean HbA1c at the end of the 12-week continuation phase period 2, simple superiority test. • % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]) during the end 12-week continuation phase period 2, non-inferiority with a margin of 7.5%.

	• % Time spent in target range (70 to 180 mg/dL [3.9-10.0 mmol/L]) during the end 12-week continuation phase period 2, simple superiority test. **Safety Endpoints** The following safety endpoints will be assessed for each treatment during each period in the study phase and continuation phase: • Number of severe hypoglycemic events • Number of Diabetic Ketoacidosis events (DKA) • Number of Serious Adverse Events (SAEs) • Number of Serious Adverse Device Events (SADEs) • Number of Unanticipated Serious Adverse Device Events (USADEs)
Final Report	The study results will be summarized and presented in the final report.

3 Introduction

3.1 Background

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

In T1D, glycemic control is influenced by numerous factors, such as insulin dosage, insulin absorption, timing, physiological/ lifestyle factors such as exercise, food intake, hormones and illness. The use of sensor-augmented pump therapy with predictive low-glucose suspend features, available in the commercialized MiniMed 640G System, in which the pump stops insulin delivery when an algorithm predicts glucose levels to drop below the prespecified low-glucose threshold, is accompanied by improvements in glycemic control in children, but the management of the therapy remains challenging in the young children due to high variability of insulin requirements, marked insulin sensitivity and unpredictable eating and activity patterns.

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

Several studies have been completed and are ongoing on the AHCL MiniMed 780G system to demonstrate its safety and effectiveness in children, adolescents and adults (**Table 1**). In a pivotal study, it was demonstrated that the MiniMed 780G system helped children over 7 years old to reach better time in range (TIR) and better mealtime glycaemia without increasing time below range (TBR), severe hypoglycemia or ketoacidosis [2]. Furthermore, real-life data analysis in 3,211 users, reporting age <15, demonstrated a GMI of 6.8±0.3%, TIR of 73.9±8.7%, and TBR (70 mg%) of 3.2%, while spending 92.7% of time in AHCL[3].

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

In the continuation phase, an advanced MiniMed 780G system will be used. The system is comprised of the MiniMed 780G BLE 2.0 insulin pump used in combination with the DS5 sensor, which combines the glucose sensor and transmitter into one disposable device thereby simplifying the insertion process. Additionally, the user will no longer need to charge the transmitter, reducing user burden. The modifications to the MiniMed 780G insulin pump include DS5 sensor compatibility, communication enhancements to the mobile app, and improved adaptation process and insulin on board calculation.

Table 1. AHCL Clinical Studies

Study	Design	Primary Endpoints	Status
[redacted] New Zealand	4 weeks; randomized vs predictive low glucose suspend, two-sequence cross-over with 60 subjects >7 – 70 years old with Type 1 Diabetes	Safety and Effectiveness Time in Range 3.9-10 mmol/L and Time in Hyperglycemia >10 mmol/L	Completed
Medtronic study United States	12 weeks; single arm in 250 subjects >7 years old with Type 1 Diabetes	Safety, HbA1c	Completed
[redacted] Finland	3-month study, single arm in 35 subjects 2-6 years old with Type 1 Diabetes in Finland	Time in Ranges	3 months completed 12 months ongoing
Medtronic ADAPT Study UK, France, Germany	6-month study and 6 months continuation, randomized vs multiple daily injections with CGM, >18 years old with Type 1 Diabetes	Safety and Effectiveness, HbA1c, Time in Ranges	Completed
HyCLIP Study Australia	4 month; randomized vs standard therapy children age 2 to ≤7 years	Time in Range	Ongoing
Medtronic CIP337 Study USA	4-month; single arm in 250 subjects >7 years old with Type 1	Safety and Effectiveness	Ongoing

3.2 Purpose

The purpose of this study is to demonstrate the safety and performance of the MiniMed 780G system in paediatric subjects (2-6 years old) with type 1 diabetes in a home setting.

4 Objectives and/or Endpoints

4.1 Objectives

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

4.2 Study Phase Endpoints

4.2.1 Primary Endpoint

The primary end point is the between-treatment difference in the percentage of time that the sensor glucose measurement is in the target range, 70 to 180 mg/dL (3.9-10.0 mmol/L).

The endpoint will be assessed for non-inferiority with an absolute margin of 7.5% time in target range.

4.2.2 Secondary Endpoints

The secondary endpoints will be the between-treatment difference in the study phase for:

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

4.3 Continuation Phase Endpoints

4.3.1 Primary Endpoint

The primary end point for continuation phase is the between-treatment difference in the mean HbA1c at the end of the 12-week continuation phase period 2.

The endpoint will be assessed for non-inferiority with an absolute margin of 0.4% HbA1c.

4.3.2 Secondary Endpoints

The secondary endpoints will be the between-treatment difference in the continuation phase period 2 for:

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

4.4 Safety Endpoints

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

- Number of severe hypoglycemic events
- Number of Diabetic Ketoacidosis events (DKA)
- Number of Serious Adverse Events (SAEs)
- Number of Serious Adverse Device Events (SADEs)
- Number of Unanticipated Serious Adverse Device Events (USADEs)

5 Study Design

This study is a pre-market, prospective, open-label, multi-center, randomized crossover trial in paediatric subjects (2-6 years old) with type 1 diabetes. The study consists of a run-in phase, a study phase and a continuation phase (see **Figure 3** for an overview).

Run-in Phase (Visit 2-3):

The purpose of the run-in phase (2 to 4 weeks) is to train subject's parent(s)/legal guardian(s) on the MiniMed 780G system in Manual Mode with Suspend before low activated and to collect 2 weeks of baseline data. At the end of Run-in Phase, subjects will be randomized into 2 sequences (A and B).

Successful completion of run-in phase requires sensor usage ≥70% over the previous 2 weeks during the run-in phase. If this is not achieved (e.g. sensor felt off) the run-in phase can be extended for another 7 to 14 days to achieve sensor usage ≥70%.

Study Phase (Visit 3A-11):
During the study phase, each sequence consists of 2 phases of 12 weeks each separated by a 2-week washout phase for a total of 26 weeks.

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

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

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

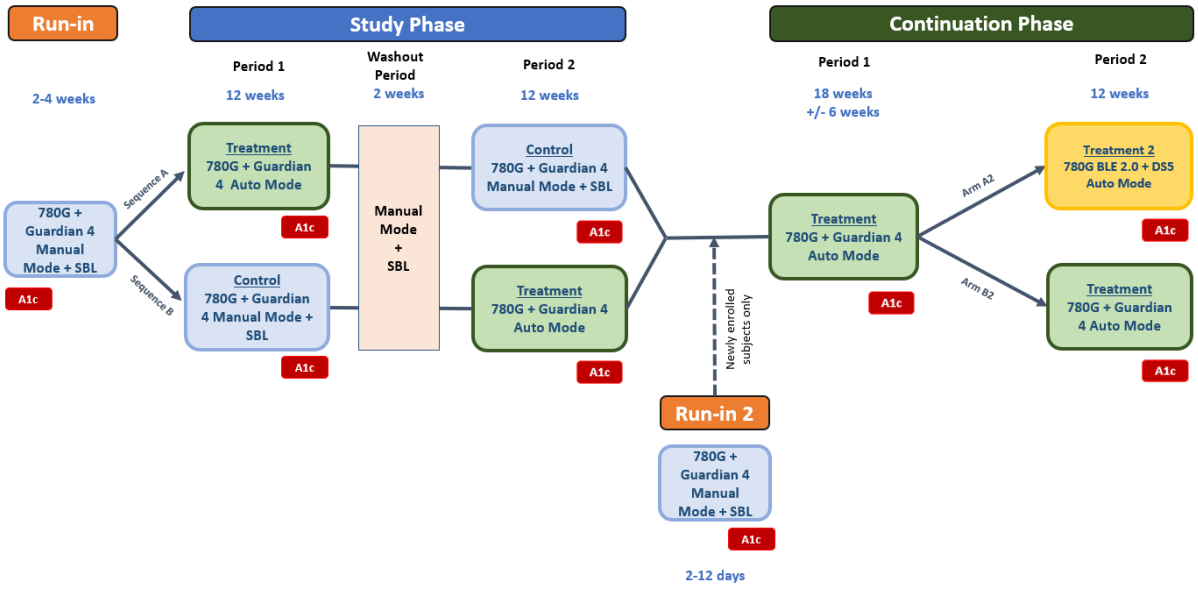
Continuation Phase (Visit 12-15):
The continuation phase consists of 2 periods.

Enrolled subjects will enter the continuation phase period 1 and will use MiniMed 780G system in Auto Mode for 18 weeks +/- 6 weeks. At the end of the continuation phase period 1, subjects will be randomized into 2 arms (A2 and B2).

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

Based on the interim analysis results, enrollment may be re-opened for the Continuation phase with a dedicated run-in 2.

Figure 3. Study Design



5.1 Duration

The study is anticipated to last approximately 23 months from first investigational center initiation to study completion. Individual subject participation is expected to be approximately 14 months from the run-in phase to end of study participation or 6-9 months for subjects enrolled for the continuation phase only.

5.2 Rationale

Previous clinical investigations (**Table 1**) and real-world usage have confirmed safe usage of the MiniMed 780G system for people living with type 1 diabetes. However, data on very young children of 2 years of age and older remains limited and therefore this study assesses the safety and performance in this young age group.

6 Product Description

6.1 Intended Use

In this study, the MiniMed 780G system will be used by people 2-6 years old with type 1 diabetes who require at least 6 units of insulin per day.

6.2 General Overview of the MiniMed 780G System

Study Phase and Continuation Phase Period 1 + Arm B2: The system is composed by commercially available products used outside their approved indication and commercially available components which will be used within their intended use according to the labeling and instruction for use (for additional details please refer to **Table 2**).

The MiniMed 780G insulin pump is approved (CE-Marked) with the indication for use by patients aged 7-80 years with Type 1 Diabetes, whose total daily dose of insulin is 8 units per day or more. In the

study, the MiniMed 780G insulin pump will be used by 2-6 years old children with Type 1 Diabetes who require at least 6 units of insulin per day, therefore its use will be considered outside its approved indication. Guardian 4 Sensor and Guardian 4 Transmitter are approved (CE-Marked) with the indication for use by patients aged 7 years and older. During the study, Guardian 4 Sensor and Guardian 4 Transmitter will be used by 2-6 years old children with Type 1 Diabetes, therefore their use will be considered outside their approved indication.

Continuation Phase Arm A2: The system is composed by investigational products, MiniMed 780G BLE 2.0 insulin pump and DS5 Sensor.

Table 2. MiniMed 780G Insulin Pump: System Components and Consumable Materials

Device name*	MDT Model number	Device Regulatory Status
MiniMed 780G Insulin Pump**	MMT-1895 and MMT-1896 (kits) MMT-1885 and MMT-1886 (pump only)	CE-Marked, used outside of its approved indication
MiniMed 780G BLE 2.0 Insulin Pump**	MMT-1895 and MMT-1896 (kits) MMT-1885 and MMT-1886 (pump only)	Investigational
Guardian 4 Sensor	MMT-7040	CE-Marked, used outside of its approved indication
Guardian 4 Transmitter**	MMT-7840 (kits) MMT-7841 (transmitter only)	CE-Marked, used outside of its approved indication
DS5 Sensor	MMT-5100	Investigational
One-Press Serter**	MMT-7512	CE-Marked
Charger**	MMT-7715	CE-Marked
Tester**	MMT-7736L	CE-Marked
CareLink Personal	MMT-7333	CE-Marked
CareLink system	MMT-7350	CE-Marked
Roche Accu-Chek Guide Link Glucose Meter***	08116083016 (Italy) 08116113018 (United Kingdom) 08116113343 (Slovenia) 08116113370 (Finland) 08116083016 (France)	CE-Marked
MiniMed Clinical App	MMT-6103 Android; MMT-6104 IOS	Not a medical device
CareLink Clinical App	MMT-6113 Android; MMT-6114 IOS	Not a medical device
Blue Adapter	ACC-1003911	Not a medical device
Consumables and accessories	See **Appendix 18.7**	CE-marked

*For detailed information on the characteristics' materials, see device instructions for use (IFU).
** Devices may be distributed in kits.
***For additional country model numbers, refer to **Appendix 18.7**

Table 3. Estimated Numbers of Devices Per Subject During The Study

Item	Units per Subject Entire Study
MiniMed 780G Insulin Pump	1

Item	Units per Subject Entire Study
MiniMed 780G BLE 2.0 Insulin Pump) (Continuation Phase, Arm A2 only)	1
Guardian 4 Sensor (Boxes of 5)	10 (Arm A2) or 14 (Arm B2)
DS5 Sensor (Boxes of 5) (Continuation Phase, Arm A2 only)	4
Guardian 4 Transmitter Kit (includes serter, charger, and tester)	1
Extended infusion set (Boxes of 10)	6
Extended Reservoir (Boxes of 10)	14
Roche Accu-Chek Guide Link Study Meter	1
Roche Accu-Chek strips (Boxes of 50)	17
Blue Adapter	1

The Medtronic MiniMed™ 780G System is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) as well as for the continuous monitoring and trending of glucose levels via a sensor in the interstitial fluid under the skin.

MiniMed™ 780G system with SmartGuard™ technology adjusts insulin delivery based on SG value. The MiniMed 780G Pump receives the SG values and sensor integrity (SI) check from the Guardian 4 Transmitter, which is connected to the Guardian 4 Sensor. The glucose sensor measures glucose values in the tissue fluid. The glucose values are wirelessly sent to the insulin pump, and displayed along with glucose trend information, alerts, and alarms on the pump screen. The insulin pump also receives BG values from the Roche's Accu-Chek Guide Link BG meter for calibration. The insulin pump delivers a prescribed dosage of insulin through an infusion set. The insulin pump can automatically adjust the delivery of insulin using a mathematical equation, or algorithm that incorporates information from the CGM. The MiniMed 780G insulin pump operates in Manual mode when the SmartGuard feature is inactive.

The data are sent from the pump to a compatible consumer electronic device with the MiniMed Clinical app, to provide a secondary display for passive monitoring of CGM and pump data for the user.

The pump also transmits data to CareLink Personal/CareLink system software through the Blue Adapter or MiniMed Clinical app.

The MiniMed 780G Pump System interacts as follows:

- MiniMed 780G insulin pump and components (including Guardian 4 CGM) presented in **Figure 4**
- MiniMed 780G BLE 2.0 insulin pump with and components (including the DS5 sensor) presented in **Figure 5**

Figure 4. MiniMed 780G System and Components

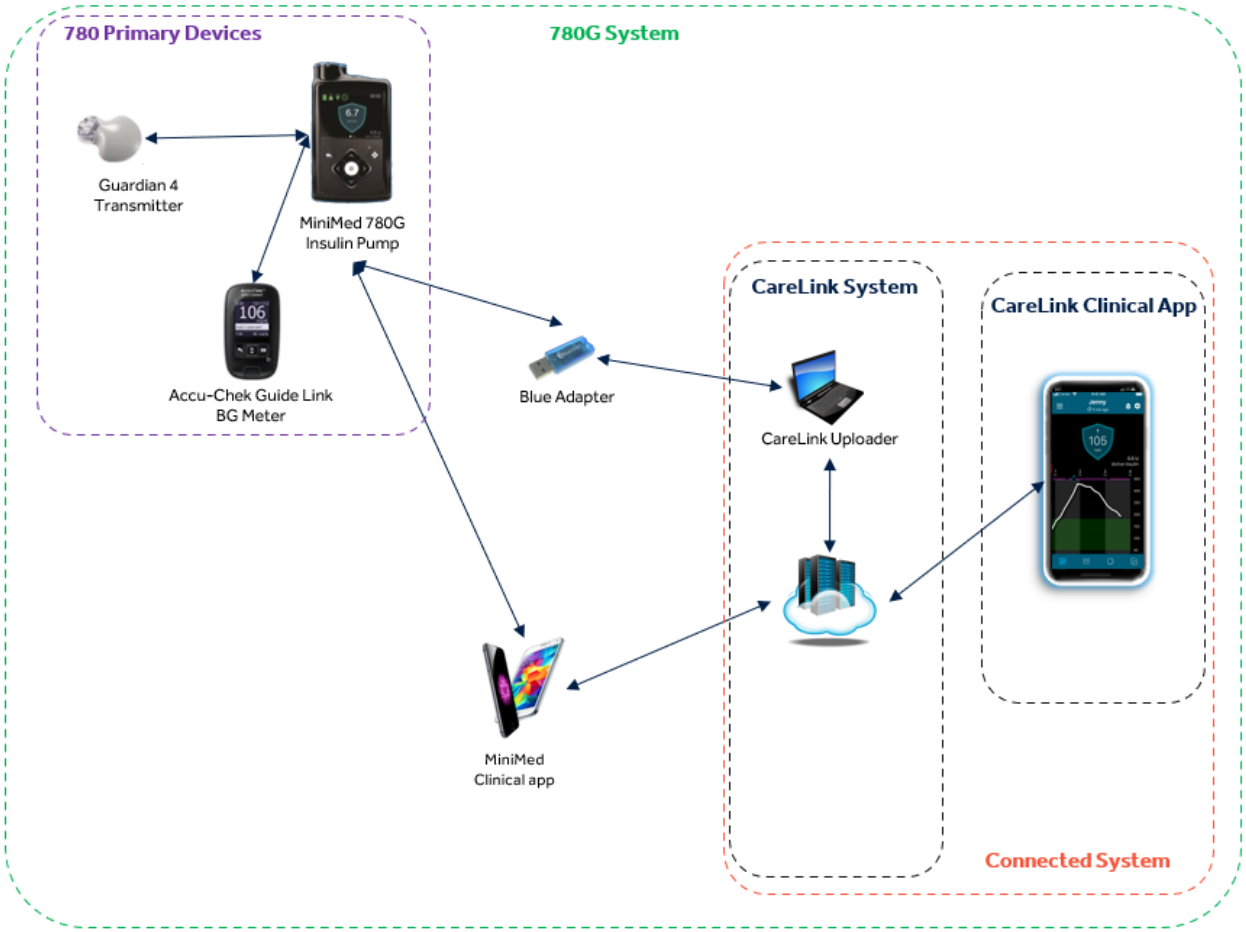
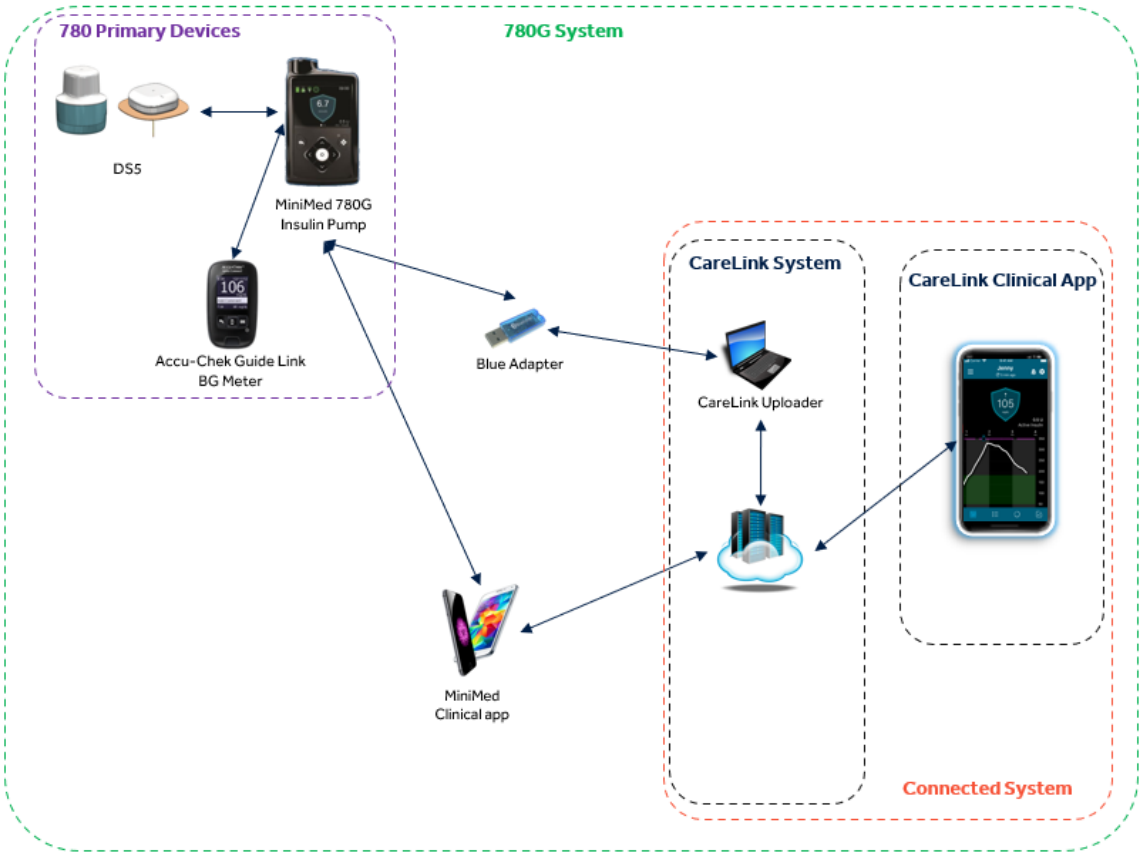


Figure 5. MiniMed 780G BLE 2.0 System with DS5 Sensor and Components (Continuation Phase Arm A2 only)



6.2.1 MiniMed 780G Insulin Pump / MiniMed 780G BLE 2.0 Insulin Pump

The MiniMed 780G Insulin Pump houses electronics, a pumping mechanism, a user interface, and a medication reservoir within the same physical device. The pump communicates via Bluetooth® Low Energy wireless communication protocol with the compatible devices in the MiniMed 780G System.

The MiniMed™ 780G Insulin Pump is intended for the continuous delivery of basal insulin at selectable rates, and the administration of insulin boluses at selectable amounts. When used with the CGM components (Guardian™ Sensor (4), Guardian™ Link (4) Transmitter, DS5 Sensor), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump system includes SmartGuard technology, which can be programmed to provide an automatic adjustment of insulin delivery based SmartGuard technology adjusts insulin delivery based on sensor glucose (SG) readings. The MiniMed 780G insulin pump operates in two modes: Manual mode and Auto Mode (SmartGuard). Manual Mode is active when the Auto Mode is inactive.

In Manual Mode, the system can be programmed by the user to deliver basal insulin at a pre-programmed constant rate. The system can automatically suspend delivery of insulin if the sensor glucose value falls below or is predicted to fall below a predetermined threshold (Suspend before low

and Suspend on low). The system will then also automatically resume delivery of insulin once sensor glucose values rise above or are predicted to rise above a predetermined threshold.

When Auto Mode is enabled on the MiniMed™ 780G insulin pump, the sensor glucose values received from the Guardian™ Link (4) Transmitter by the insulin pump will be used to automatically calculate the basal insulin dose. It will then deliver insulin to the patient, at five-minute intervals, to achieve glycemic control. In SmartGuard the system can automatically adjust basal insulin by continuously increasing, decreasing, or suspending delivery of insulin based on CGM values. Although SmartGuard feature can automatically adjust basal insulin delivery without input from the user, the user must still manually deliver insulin therapy during meals according to the user carbohydrate ratio. This ratio is determined by the Health Care Professional (HCP)/patient.

The MiniMed 780G BLE 2.0 insulin pump modifications include DS5 sensor compatibility, communication enhancements to the mobile app, and other performance enhancements.

Figure 6. MiniMed 780G Insulin Pump / MiniMed 780G BLE 2.0 Insulin Pump

6.2.2 Guardian 4 Sensor

The Guardian 4 sensor is a subcutaneous sensor that contains one microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The Guardian 4 sensor will be used with the 780G system. The sensor is an iteration of previously approved glucose sensors with design changes for supporting improved accuracy. It is intended to penetrate the skin at a 90-degree angle. The sensor is tubeless. 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.

6.2.3 Guardian 4 Transmitter

The Guardian 4 Transmitter is a portable, electrical current meter intended to process, store, and transmit glucose sensor values to the compatible insulin pump. The transmitter sends SG values and

SI data from the sensor to compatible insulin pumps via a Bluetooth Low Energy wireless communication protocol.

6.2.4 One-Press Serter

The One-Press Serter (**Figure 7**) referred to as the Serter in this protocol, is an insertion device that is used to ensure correct placement of the Guardian 4 sensor 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

6.2.5 Charger

The Charger (**Figure 8**) is used to recharge the Guardian 4 transmitter as needed. A fully charged battery provides up to 7 days of transmitter use. The system includes a battery charger that will recharge the device according to the user guide.

Figure 8. Charger

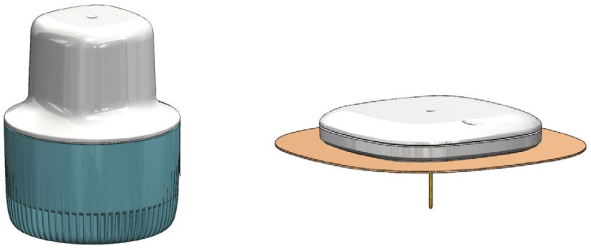
6.2.6 Tester

The Tester operates as a Guardian 4 sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation.

6.2.7 DS5 Sensor

The Disposable Sensor 5 Sensor (DS5) (**Figure 9**) is a disposable integrated sensor-transmitter platform which does not require calibration and is non-adjunctive. The sensor is packaged into a single-use insertion device, called the inserter, resulting in an all-in-one device out of the box. The inserter is designed to simplify the insertion process. The sensor flex is inserted subcutaneously with an introducer needle, which is retracted by the inserter upon removal.

Figure 9. DS5 Sensor



6.2.8 Roche Accu-Chek Guide Glucose Meter

The Roche's Accu-Chek Guide Link meter, referred to as the Study Meter throughout protocol, is a home BG meter designed to measure subject's capillary blood glucose level using the Accu-Chek® Guide Link by Roche and transmit BG values to the compatible insulin pumps via a Bluetooth Low Energy wireless communication protocol. The transmission of BG values from a compatible meter is an optional feature provided as a convenience to the user; it eliminates the need to manually enter BG values into the pump.

6.2.9 CareLink Personal Software

Medtronic CareLink Personal software is an internet-based software system which allows the device data to be uploaded and reviewed by the subject. The CareLink Personal software allows subject's parent/legal guardian to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters. The data is only accessible to the subject, caregivers, and investigational center staff. The data contained in CareLink Personal software is accessible to users using a standard browser, e.g. Google Chrome, on an Internet enabled personal computer (PC).

The CareLink Personal software use 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.

6.2.10 CareLink System Software

Medtronic CareLink system software is an internet-based software system used by investigators which allows the device data to be uploaded, viewed and easily evaluated by the physician. The CareLink system software allows retrospective review of device data and was developed for use by the investigational center staff. The CareLink system software allows the investigational center staff to manage, create, and request for approval to link the subject's account. The data contained in CareLink

system software is accessible to users using a standard browser, e.g. Google Chrome, on an Internet enabled PC.

The CareLink system software use standard 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.

6.2.11 Roche Accu-Chek Guide Glucose Meter

The Roche's Accu-Chek Guide Link meter, referred to as the Study Meter throughout protocol, is a home BG meter designed to measure subject's capillary blood glucose level using the Accu-Chek® Guide Link by Roche and transmit BG values to the compatible insulin pumps via a Bluetooth Low Energy wireless communication protocol. The transmission of BG values from a compatible meter is an optional feature provided as a convenience to the user; it eliminates the need to manually enter BG values into the pump.

6.2.12 Accessory Applications – MiniMed 780G system

6.2.12.1 MiniMed Clinical app

The MiniMed Clinical app is an accessory, which receives pump data via Bluetooth Low Energy wireless communication from the pump. The app provides a secondary display of data from the insulin pump on a compatible mobile device and provides users with the convenience to wirelessly transfer pump data to CareLink Personal/CareLink system software. The MiniMed Clinical app is not designed to control or monitor the performance of the insulin pump nor for direct monitoring of pump data. As a mirroring display, the app can provide alarms, alerts, messages and reminders from the insulin pump to the subject via the user interface. All alerts must be addressed on the insulin pump.

The app is available for Android™* (MMT-6103) and for iOS™* (MMT-6104) operating systems.

6.2.12.2 CareLink Clinical app

The CareLink Clinical app is an optional accessory which receives pump data wirelessly from the CareLink server. The CareLink Clinical app provides a mirroring display of the MiniMed Clinical app screen, for remote monitoring by a care partner (e.g., caregiver). The CareLink Clinical app is not designed to monitor the performance of the insulin pump nor for direct monitoring of pump data. As a mirroring display, the app can provide notifications to the care partner via the user interface.

The app is available for Android™* (MMT-6113) and for iOS™* (MMT-6114) operating systems.

6.2.13 Blue Adapter

The Blue Adapter is an optional accessory with Bluetooth technology that facilitates the communication between a PC and the insulin pump, via a Bluetooth Low Energy wireless communication protocol. The

Blue Adapter is an off-the-shelf non-medical device intended to transfer data to CareLink server. The Blue Adapter does not have any computation, diagnostic, monitoring or therapeutic function/benefit. Medtronic will provide the Blue Adapter as a convenience to subject's parent/legal guardian as an alternative for subjects when automatic uploads via the MiniMed Clinical are not possible.

6.2.14 Smartphone

Sponsor may provide a smartphone, if applicable.

6.3 Insulin

Subjects will use their own rapid-acting analogue insulin (Novolog/NovoRapid or Humalog) during the study.

6.4 Consumable Devices and Accessories

Commercially available and compatible infusion sets, reservoirs, serter devices, glucose meter accessories and other consumables and accessories will be provided to subjects for use in the study. See **Appendix 18.7.**

6.5 Packaging

The labelling of the investigational devices and commercially available 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.

6.6 Product Training Materials

The MiniMed 780G system is a commercially available device on which sites have already experience on. Complementary device training for the Investigational center staff will be organized prior to a clinical site's first subject enrollment. Training of the investigation center's staff will be provided by Medtronic educators and/or clinical team.

For specific study training requirements needed for activation please refer to **Section 15.1**.

6.7 Anticipated Product Changes

There are no changes anticipated for any of the products/device during the course of the study.

6.8 Product Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational devices used in a research trial. It is expected that all investigational devices will be used in the manner intended during the study and that they will be used only by (on) subjects who have had their parent/legal guardian consent to the subject's participation in the research study and by investigational center staff trained on the study.

Any investigational device being used in clinical research must be strictly accounted for and will not be shipped to any investigational center unless all of the necessary approvals (e.g., regulatory authority and EC) have been received.

The principal investigator (PI) or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational devices. Additional details regarding device accountability and device disposition requirements are provided in and **Table 4**.

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)	Investigational Center Return Device to Sponsor at Conclusion of Study
MiniMed 780G Insulin Pump (MMT1895 and MMT-1896)	Yes	Yes	Yes	Yes
MiniMed 780G BLE 2.0 Insulin Pump (MMT-1895 and MMT-1896)	Yes	Yes	Yes	Yes
Guardian 4 Sensor (MMT-7040)	Yes	No[3]	No	No[2]
DS5 Sensor (MMT-5100)	Yes	Yes	Only Unused	Only Unused
Guardian 4 Transmitter[1] (MMT-7840)	Yes	Yes	Yes	Yes
Roche Accu-Chek Guide Link Study Meter	Yes	Yes	Yes	No[2]
Mobile Phone, if applicable	Yes[4]	Yes	Yes	Yes

[1]Devices may be combined and distributed in kits.
[2]If subject/investigational center is unable to dispose, return unused products to sponsor for disposal.
[3]Only serialized devices will be tracked on Subject Device Identification eCRF. Consumables will be tracked only at site level.
[4]Acknowledgement of Receipt (site to sign packing slip) for Mobile Phone if applicable.

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

6.8.1 Receipt and Inventory of Study Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff will take 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 slips/invoices, noting any discrepancies, send a copy to the Medtronic Study Team as an Acknowledgment of Receipt and file in appropriate study binder
- Notify the Medtronic Study Team of any discrepancies

6.8.2 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/user guide/labeling.

6.8.3 Dispensing of Study Devices

Each time a serialized study device is dispensed to a subject by the investigator or authorized member of the research team, eCRF, and/or source documentation will be completed as required. Documentation may include:

- Device type
- Dispensing date
- Subject identification (ID)
- Serial number (where applicable)

6.8.4 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**. 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 the study closure or upon sponsor request.

Other consumable devices (e.g., alcohol wipes, study meter supplies, and tape), and accessories shipped in kits, supplies or materials may be returned to the sponsor, they may be retained by investigational centers for educational purposes only, or they may be disposed of appropriately by the investigational center staff.

Disposable and consumable devices 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.

All used and unused devices cannot be retained by the subject.

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

7 Study Site Requirements

7.1 Investigator/Investigation Site Selection

In order to conduct the study, it is required that the investigator and investigational center staff have the appropriate medical training.

The following requirements will be evaluated for each investigator/site 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 (Paediatric Endocrinology or Diabetology expertise with very young children)
- 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

7.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train investigational center staff on devices and study requirements.

If new members join the study investigational center team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including but not limited to the following:

- EC approval (and voting list, as required by local law) of the current version of the CIP Informed Consent Form (ICF), and report of prior investigations/IB
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure (if applicable)
- Curriculum vitae (CV) of investigators
- Documentation of delegated tasks
- Documentation of study training

In addition, all participating investigational center staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the PI prior to performing delegated study activities.

Medtronic will provide each study investigational center with documentation of study investigational center/investigator subject enrollment readiness; this letter must be received prior to subject enrollment.

8 Selection of Subjects

8.1 Study Population

Approximately 100 paediatric (aged 2-6 years of age) subjects with type 1 diabetes will be enrolled at up to 18 investigational centers across Europe in order to have approximately 72 subjects completing the study phase and 64 subjects completing the continuation phase.

Each participating investigational site should attempt to enroll approximately a minimum of 5 and a maximum of 20 subjects who meet all study eligibility criteria.

During the continuation phase period 1, the sample size will be re-estimated based on an interim analysis which will evaluate HbA1c Standard Deviation. Based on the interim analysis result, enrollment for the Continuation phase only will be opened.

8.2 Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Inform Consent Form (ICF).

A subject will be assigned a unique study subject ID via the eCRF, which is a 9-digit code (342XXXXXX). The first three digits refer to the CIP number (342), 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., 342002001 is subject 001 from investigational center 002).

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

During the continuation phase period 1, the sample size will be re-estimated based on an interim analysis which will evaluate HbA1c Standard Deviation. Based on the interim analysis result, enrollment for the Continuation phase only will be opened.

If enrollment needs to be opened for the Continuation phase, all active sites will be notified at the same time for the additional number of subjects to be enrolled.

8.3 Inclusion Criteria

1. Aged 2 – 6 years at time of screening
2. Has a clinical diagnosis of type 1 diabetes for ≥ 6 months prior to screening as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
3. Is on MDI therapy or CSII with or without CGM prior to screening
4. Has a glycosylated hemoglobin (HbA1c) < 11% (97 mmol/mol) at time of screening visit as processed by a Local Lab
5. Is using or willing to switch to one of the following commercialized available insulins:
   - Humalog (insulin lispro injection)
   - NovoLog/Novorapid (insulin aspart)
6. Must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 6 units
7. Parent(s)/legal guardian(s) willing to upload data from the pump system, must have Internet access, a compatible computer or mobile phone that meets the requirements for uploading the study pump data at home.
8. Is living with one or more parent(s)/legal guardian(s) knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff.
9. Investigator has confidence that the parent(s)/legal guardian(s) can successfully operate all study devices and is capable of adhering to the protocol
10. Subject and parent(s)/legal guardian(s) willingness to participate in all training sessions as directed by study staff.
11. Subject's parent/legal guardian must be willing and able to provide written informed consent.

8.4 Exclusion Criteria

1. Has Addison's disease, growth hormone deficiency, hypopituitarism or definite gastroparesis, untreated coeliac disease, untreated thyroid disorder, or poorly controlled asthma, per investigator judgment.
2. Is using any anti-diabetic medication other than insulin at the time of screening or plan of using during the study (e.g. pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors).
3. Has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
4. Has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤6 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft, CKD-EPI or MDRD equations.
5. Has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).
6. Is under Control IQ, CamAPS FX, Omnipod 5 or other advanced hybrid closed loop therapy (e.g. DIY, MiniMed 780G in Auto Mode) in the previous 3 months before enrollment. Note: For the continuation phase only, subjects using MiniMed 780G can be enrolled.
7. 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.
8. Has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment.

9. History of >1 DKA event not related to illness or initial diagnosis in the last 3 months.
10. Parent(s)/legal guardian(s) are part of research staff involved with the study.
11. Parent(s)/legal guardian(s) are illiterate

8.5 Randomization Criteria

8.5.1 Study Phase

If subjects meet the above criteria, as well as all the following criteria (assessed at the end of the run-in phase), they may continue to participate in the study phase:

- Subject has a percentage of Guardian 4 sensor use ≥70% over 2 weeks (based on sensor usage from the download of CareLink report over 2 weeks prior randomization).
- Subject has shown acceptable tolerance to sensor wear, per investigator judgment.
- Subject has shown compliance with study procedures, per investigator judgment.

Randomization will be performed at Visit 3 via the electronic CRF.

8.5.2 Continuation Phase

All subjects completing the study phase will participate to the continuation phase and will be randomized into two arms (A2 and B2) at the end of continuation phase period 1:

Randomization will be performed at Visit 13 via the electronic CRF.

For the newly enrolled subjects for the continuation phase only, subjects may continue to participate in the continuation phase period 2, if they meet the above inclusion/exclusion criteria, as well as all the following randomization criteria (assessed at the end of the continuation phase period 1):

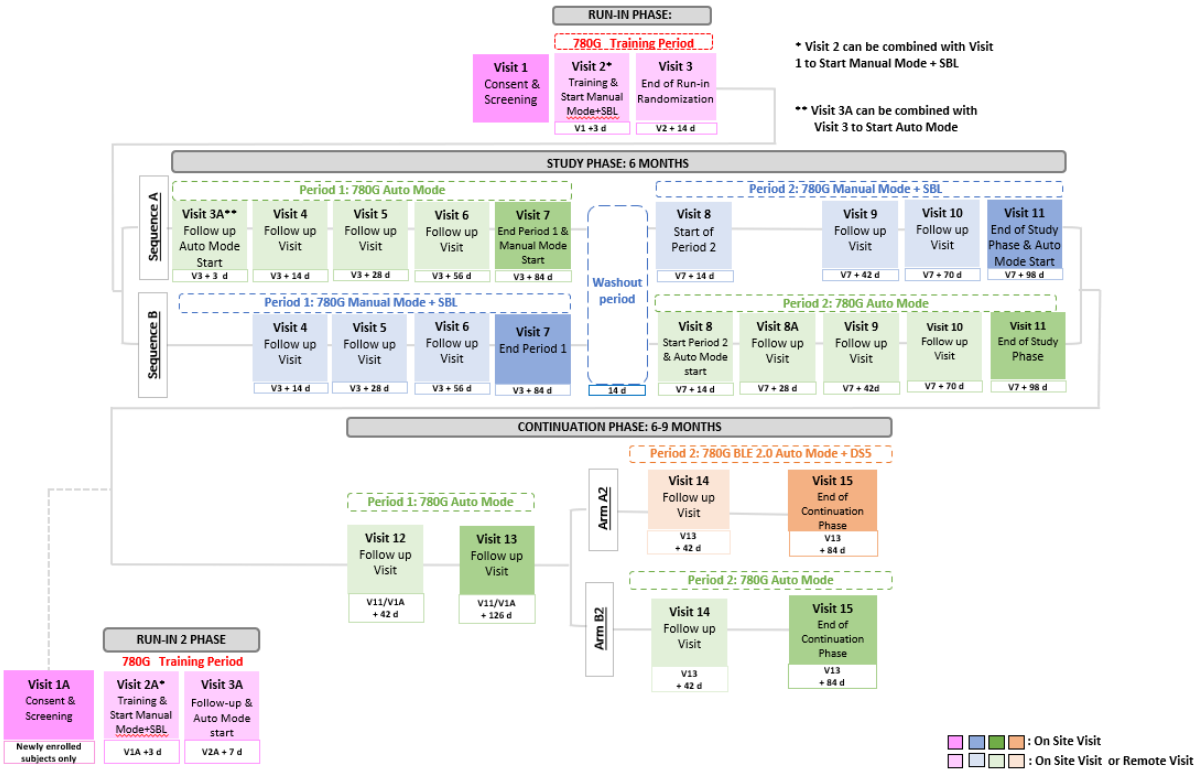
- Subject has a percentage of Guardian 4 sensor use ≥70% over 2 weeks (based on sensor usage from the download of CareLink report over 2 weeks prior the second randomization).
- Subject has shown acceptable tolerance to sensor wear, per investigator judgment.
- Subject has shown compliance with study procedures, per investigator judgment.

9 Study Procedures

9.1 Schedule of Events

Subjects may participate in up to 15 planned study visits, as presented in **Figure 10**. A remote office visit (audio visual) may be performed for office visits in cases where an office visit is not possible.

Figure 10. Visit Schedule



Prior to study start, Investigator or authorized designee must obtain written informed consent from the parents/legal guardian before any clinical study related activity (including screening) takes place and document informed consent process in the medical chart of the subject (Visit 1).

Subject enrolled will start the Run-in phase. During Run-in phase MiniMed 780G -system training program will be provided, including e.g. infusion set insertions/replacements, meal bolus procedure, what to do with significant illness, how to react on safety/alert notifications, when to perform BG measurements and when to contact site staff with the contact information provided.

During Run-in Phase subject will use 780G system in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L) (standard of care therapy- Visit 2). Study staff will conduct at the minimum a subject visit, 2 weeks

after Manual Mode + SBL has been started (Visit 3). Additional phone contacts or visits may be conducted (unscheduled visits), as needed.

Eligible subjects must successfully complete the run-in phase by demonstrating tolerance to sensor wear and sensor usage ≥ 70% in the last 2 weeks before being randomized. If this is not achieved (e.g. sensor felt off) the run-in phase can be extended for another 7 to 14 days.

Subject randomized in Sequence A will be trained on the use of MiniMed 780G system in Auto Mode (Visit 3A) and they will start to use the system with follow up visits at 2 weeks (Visit 4), 4 weeks (Visit 5) 8 weeks (Visit 6) and 12 weeks (Visit 7) after Auto mode Start.

At 12 weeks (Visit 7) subjects will stop Auto Mode and will start using the system in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L) for the washout period.

Following the end washout period (Visit 8), follow up visits will be done respectively every 4 weeks (Visit 9, 10 and 11). Additional phone contacts or visits may be conducted (unscheduled visits), as needed.

Subject randomized in Sequence B will continue to use the system in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L) with follow up visits will follow respectively at 2 weeks (Visit 4), 4 weeks (Visit 5) 8 weeks (Visit 6) and 12 weeks (Visit 7) after randomization. After the end of the washout period of 2-week, subject will start to use system in Auto Mode (Visit 8) and follow up visit will follow respectively every 2 weeks (Visit 8A), 4 weeks (Visit 9) 8 weeks (Visit 10) and 12 weeks (Visit 11) after Auto mode Start. Additional phone contacts or visits may be conducted (unscheduled visits), as needed.

All subjects who completed the Study Phase will enter the Continuation Phase and start using the 780G system in Auto Mode for 18 weeks +/- 6 weeks. After a second randomization subjects will be assigned to arm A2 (MiniMed 780G BLE 2.0 system and DS5 Sensor) or arm B2 and continue treatment for another 12 weeks. Follow-up visits will follow every 6 weeks respectively (Visit 12, 13, 14 ,15). Additional phone contacts or visits may be conducted (unscheduled visits), as needed.

Subjects who will start with the Continuation Phase will start using the 780G system in Auto Mode after Run-In 2 is completed.

Clinical Investigation Plan (CIP)-required procedures (Please refer to **Table 5** details) for this study that deviate from normal clinical practice (outside standard of care) include the following:

- Baseline blood draws for HbA1c testing
- Questionnaires

Schedule of Events for subjects enrolling for the entire study duration:

- **Visit 1 (Office): Consent & Screening**
  - Obtain subject's consent from parent/legal guardian
  - Determine if subject meets eligibility criteria
  - Collect demographic information (age, gender)
  - Review subject's Medical history:

- Date of Type 1 DM diagnosis
- Type of current Diabetes Treatment (MDI, CSII with or without CGM)
- Diabetes-related complications, if any
- Mean daily insulin dose
- Type of insulin used

- Measure/Collect height and weight
- Perform blood sample collection for creatinine clearance at local lab. If creatinine clearance test was performed ≤ 6 months prior to screening, only confirm date of collection at local lab and creatinine clearance value in medical chart. *Note: Creatinine clearance threshold for exclusion< 30 mL/min and must be calculated with the Cockcroft, CKD-EPI or MDRD equations. The sites will follow routine practice for evaluation of the creatinine clearance.*
- Perform blood sample collection for HbA1c at the Local Lab.
- Collect number of DKA in the last 3 months.

Run-In Phase:

- **Visit 2* (Office/Remote): Start Manual Mode + SBL [Visit 1 + 0-3 days (Window + 5 days)]**

  Note: Visit 2 and Visit 1 can be combined to start Pump Therapy in Manual Mode + SBL.
  - Train subject and parent(s)/guardian(s) on the MiniMed 780G system
  - Train the subject and parent(s)/guardian(s) on the use of pump therapy in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L)
  - Set-up subject CareLink Account.
  - CareLink Training
  - Start pump therapy in Manual Mode + SBL
  - Collection of sensor site location
  - Collection of questionnaires
  - Review adverse events or device deficiencies, if any.

- **Visit 3 (Office/Remote): End of Run-in & Randomization [Visit 2 + 14 days (Window + 14 days)]**
  - Ensure CareLink upload was done
  - Review Pump therapy/adjust settings (see **Table 6**)
  - Retrain subject on 780G system as needed
  - Collection of sensor site location
  - Review adverse events or device deficiencies, if any
  - Investigator will review randomization criteria

  If subject is eligible will be randomized to one of the two sequences:
  - Sequence A: start pump therapy in Auto Mode (Treatment)
  - Sequence B: continue pump therapy in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L) (Control)

  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.

Study Phase:

Sequence A Only:

- **Visit 3A** (Office/Remote): Auto Mode Start [Visit 3 +0- 3 days (Window + 2 days max)]**
  *** Note: Visit 3A and Visit 3 can be combined to start pump therapy in Auto Mode*
  - Train the subject and parent(s)/guardian(s) on the use of pump therapy in Auto Mode
  - Subject to start pump therapy in Auto Mode.
  - Collection of sensor site location
  - Ensure CareLink upload was done
  - Review pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed.
  - Review adverse events or device deficiencies, if any.

Sequence A and B:

- **Visit 4 (Office/Remote): Follow up visit [Visit 3+14 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed.
  - Review adverse events or device deficiencies, if any.

- **Visit 5 (Office/Remote): Follow up visit [Visit 3+28 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed.
  - Review adverse events or device deficiencies, if any.

- **Visit 6 (Office/Remote): Follow up visit [Visit 3+56 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed.
  - Review adverse events or device deficiencies, if any.

- **Visit 7 (Office/Remote): End of Period 1 [Visit 3 + 84 days (Window ± 5 days)]**
  - Perform blood sample collection for HbA1c at Local Lab.
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed
  - Measure/Collect height and weight.

- Collection of questionnaires
- Review adverse events or device deficiencies, if any.

For subjects randomized in Sequence A:

- Stop Auto Mode and start using Pump therapy in Manual Mode with SBL set at 65 mg/dL (3.6 mmol/L).
- Re-train the subject and parent(s)/guardian(s) on the use of pump therapy in Manual Mode as needed

- **Visit 8 (Office/Remote): Start of Period 2 [Visit 7 + 14 days (Window + 3 days max)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system therapy as needed.
  - Review adverse events or device deficiencies, if any.

For subjects subject randomized in Sequence B:

- Train the subject and parent(s)/guardian(s) on the use of pump therapy in Auto Mode
- To start Pump therapy in Auto Mode.

Sequence B Only:

- **Visit 8A (Office/Remote): Follow up visit [Visit 7 + 28 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed.
  - Review adverse events or device deficiencies, if any.

Sequence A and B:

- **Visit 9 (Office/Remote): Follow up visit [Visit 7 + 42 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed
  - Review adverse events or device deficiencies, if any.

- **Visit 10 (Office/Remote): Follow up visit [Visit 7 + 70 days (Window ± 5 days)]**
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed
  - Review adverse events or device deficiencies, if any.

- **Visit 11 (Office): End of Study Phase [Visit 7 + 98 days (Window ± 5 days)]**
  - Perform blood sample collection for HbA1c at local lab.
  - Ensure CareLink upload was done
  - Collection of sensor site location
  - Review Pump therapy/adjust settings (see **Table 6**).
  - Retrain subject on 780G system as needed
  - Measure/Collect height and weight.
  - Collection of questionnaires
  - Review adverse events or device deficiencies, if any

For subjects randomized in Sequence A:

- Start using Pump therapy in Auto Mode.
- Retrain the subject and parent(s)/guardian(s) on the use of pump therapy in Auto Mode if needed

Continuation Phase:

Schedule of Events for subjects enrolling for the Continuation phase only:

- **Visit 1A (Office): Consent & Screening (only applicable for subject entering the study for the continuation phase)**
  - Obtain subject's consent from parent/legal guardian
  - Determine if subject meets eligibility criteria
  - Collect demographic information (age, gender)
  - Review subject's Medical history:
    - Date of Type 1 DM diagnosis
    - Type of current Diabetes Treatment (MDI, CSII with or without CGM)
    - Diabetes-related complications, if any
    - Mean daily insulin dose
    - Type of insulin used
  - Measure/Collect height and weight
  - Perform blood sample collection for creatinine clearance at local lab. If creatinine clearance test was performed ≤ 6 months prior to screening, only confirm date of collection at local lab and creatinine clearance value in medical chart. *Note: Creatinine clearance threshold for exclusion< 30 mL/min and must be calculated with the Cockcroft, CKD-EPI or MDRD equations. The sites will follow routine practice for evaluation of the creatinine clearance.*
  - Perform blood sample collection for HbA1c at the Local Lab.
  - Collect number of DKA in the last 3 months.

Run-In Phase 2:

- **Visit 2A* (Office/Remote): Start Manual Mode + SBL [Visit 1A + 0-3 days (Window + 5 days)]**

  Note: Visit 2A and Visit 1A can be combined to start Pump Therapy in Manual Mode + SBL.

- Train subject and parent(s)/guardian(s) on the MiniMed 780G system
- Train the subject and parent(s)/guardian(s) on the use of pump therapy in Manual Mode + SBL set at 65 mg/dL (3.6 mmol/L)
- Set-up subject CareLink Account.
- CareLink Training
- Start pump therapy in Manual Mode + SBL
- Collection of sensor site location
- Collection of questionnaires
- Review adverse events or device deficiencies, if any.

- **Visit 3A (Office/Remote): Follow-up & Auto Mode start [Visit 2A + 7 days (Window +/- 5 days)]**
  - Switch to Auto Mode
  - Ensure CareLink upload was done
  - Review Pump therapy/adjust settings (see **Table 6**)
  - Retrain subject on 780G system as needed
  - Collection of sensor site location
  - Review adverse events or device deficiencies, if any

Schedule of Events for subjects enrolling for the entire study duration as well as for the Continuation phase only:

- **Period 1**
  - **Visit 12 (Office/Remote): Follow up visit [Visit 11/1A + 42 days (Window ± 5 days)]**
    - Ensure CareLink upload was done
    - Collection of sensor site location
    - Review Pump therapy/adjust settings (see **Table 6**).
    - Retrain subject on 780G system as needed
    - Review adverse events or device deficiencies, if any

  - **Visit 13 (Office): Follow up visit [Visit 11/1A + 126 days (Window ± 42 days)]**
    - Ensure subject's reconsent from legal/guardian on protocol C or subsequent version was obtained before Visit 13 procedures are performed (if applicable)
    - Ensure CareLink upload was done
    - Collection of sensor site location
    - Review Pump therapy/adjust settings (see **Table 6**).
    - Retrain subject on 780G system as needed
    - Review adverse events or device deficiencies, if any
    - Collection of questionnaires
    - Perform blood sample collection for HbA1c (Central Lab)
    - Randomize to one of the 2 arms:
      - Arm A2: Start pump therapy with MiniMed 780G BLE 2.0 system and DS5 Sensor in Auto Mode (treatment 2)
      - Arm B2: Continue pump therapy in Auto Mode (Treatment)

For subjects randomized in Arm A2:

- Train subject on MiniMed 780G BLE 2.0 system and DS5 sensor

- **Period 2**
  - **Visit 14 (Office/Remote): Follow up visit [Visit 13+ 42 days (Window ± 5 days)]**
    - Ensure CareLink upload was done
    - Collection of sensor site location
    - Review Pump therapy/adjust settings (see **Table 6**).
    - Retrain subject on MiniMed 780G system/MiniMed 780G BLE 2.0 system with DS5 sensor as needed
    - Review adverse events or device deficiencies, if any.

  - **Visit 15 (Office): End of Continuation Phase [Visit 13 + 84 days (Window ± 5 days)]**
    - Perform blood sample collection for HbA1c (Central Lab)
    - Ensure CareLink upload was done
    - Collection of sensor site location
    - Measure/Collect height and weight.
    - Return of devices
    - Collection of questionnaires
    - Review adverse events or device deficiencies, if any.

Table 5. Visit Details and Data Collection

Visit	1	2	3	3A	4	5	6	7	8	8A	9	10	11	1A	2A	3A	12	13	14	15
Visit Name	Consent & Screening	Start Manual Mode	End of Run-in & Randomization	Auto Mode Start	Follow-up	Follow-up	Follow-up	End of Period 1	Start of Period 2	Auto Mode Start	Follow-up	Follow-up	End of Study Phase	Consent & Screening	Start Manual Mode + SBL	Follow up & Auto Mode start	Start Continuation Phase - Period 1	End of Continuation phase Period 1 & randomization	Start of Period 2	End of continuation phase period 2 - End of Study
Visit Type	Office	O/R	O/R	O/R	O/R	O/R	O/R	Office	O/R	O/R	O/R	O/R	Office	Office	O/R	O/R	O/R	O	O/R	Office
Target date	-	V1 + 0-3d	V2 + 14d	V3 + 0-3d	V3 + 14d	V3 + 28d	V3 + 56d	V3 + 84d	V7 + 14d	V7 + 28d	V7 + 42d	V7 + 70d	V7 + 98d		V1a + 0-3d	V2 + 7d	V11/1A + 42d	V11/1A + 126d	V13 + 42d	V13 +84d
Window	-	+ 5d	+ 14d	+ 2d	± 5d	± 5d	± 5d	± 5d	+3d	± 5d	± 5d	± 5d	± 5d		+ 5d	± 5d	± 5d	± 42d	± 5d	± 5d
Informed consent	X													As needed						
Eligibility criteria	X													X			X[2]			
Review of Randomization Criteria			X															X		
Randomization			X															X		
Demographics	X													X						
Medical history	X													X						
Height and weight	X							X					X	X						X
HbA1c (Local lab)	X							X					X	X						X
HbA1c (Central lab)																		X		X
Creatinine test (Local lab)	X													X						
DKA in the last 3 Months	X													X						

Visit	1	2	3	3A	4	5	6	7	8	8A	9	10	11	1A	2A	3A	12	13	14	15
Visit Name	Consent & Screening	Start Manual Mode	End of Run-in & Randomization	Auto Mode Start	Follow-up	Follow-up	Follow-up	End of Period 1	Start of Period 2	Auto Mode Start	Follow-up	Follow-up	End of Study Phase	Consent & Screening	Start Manual Mode + SBL	Follow up & Auto Mode start	Start Continuation Phase - Period 1	End of Continuation phase Period 1 & randomization	Start of Period 2	End of continuation phase period 2 - End of Study
Visit Type	Office	O/R	O/R	O/R	O/R	O/R	O/R	Office	O/R	O/R	O/R	O/R	Office	Office	O/R	O/R	O/R	O	O/R	Office
Target date	-	V1 + 0-3d	V2 + 14d	V3 + 0-3d	V3 + 14d	V3 + 28d	V3 + 56d	V3 + 84d	V7 + 14d	V7 + 28d	V7 + 42d	V7 + 70d	V7 + 98d		V1a + 0-3d	V2 + 7d	V11/1A + 42d	V11/1A + 126d	V13 + 42d	V13 +84d
Window	-	+ 5d	+ 14d	+ 2d	± 5d	± 5d	± 5d	± 5d	+3d	± 5d	± 5d	± 5d	± 5d		+ 5d	± 5d	± 5d	± 42d	± 5d	± 5d
Questionnaires		X						X					X		X			X		X
Training on 780G system		X	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed		X		As needed	As needed	As needed	
Training on 780 Therapy +SBL		X						Seq. A Only							X					
Start Manual Mode + SBL		X						Seq. A Only							X					
Training on 780 Therapy + Auto Mode				Seq. A Only					Seq. B Only	Seq. B Only, as needed			Seq. A Only			As needed	As needed			
Training on MiniMed 780G BLE 2.0 and DS5 sensor																		Arm A2 only	As needed	
Start Auto Mode				Seq. A Only					Seq. B Only				Seq. A Only			X				
CareLink subject account set up		X													X					
CareLink training		X													X					

Visit	1	2	3	3A	4	5	6	7	8	8A	9	10	11	1A	2A	3A	12	13	14	15
Visit Name	Consent & Screening	Start Manual Mode	End of Run-in & Randomization	Auto Mode Start	Follow-up	Follow-up	Follow-up	End of Period 1	Start of Period 2	Auto Mode Start	Follow-up	Follow-up	End of Study Phase	Consent & Screening	Start Manual Mode + SBL	Follow up & Auto Mode start	Start Continuation Phase - Period 1	End of Continuation phase Period 1 & randomization	Start of Period 2	End of continuation phase period 2 - End of Study
Visit Type	Office	O/R	O/R	O/R	O/R	O/R	O/R	Office	O/R	O/R	O/R	O/R	Office	Office	O/R	O/R	O/R	O	O/R	Office
Target date	-	V1 + 0-3d	V2 + 14d	V3 + 0-3d	V3 + 14d	V3 + 28d	V3 + 56d	V3 + 84d	V7 + 14d	V7 + 28d	V7 + 42d	V7 + 70d	V7 + 98d		V1a + 0-3d	V2 + 7d	V11/1A + 42d	V11/1A + 126d	V13 + 42d	V13 +84d
Window	-	+ 5d	+ 14d	+ 2d	± 5d	± 5d	± 5d	± 5d	+3d	± 5d	± 5d	± 5d	± 5d		+ 5d	± 5d	± 5d	± 42d	± 5d	± 5d
CareLink Upload			X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]			X[1]	X[1]	X[1]	X[1]	X[1]
Sensor site location		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Review Pump therapy / Adjust settings			As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed			As needed	As needed	As needed	As needed	
AEs and DDs	Reported upon awareness																			
Study Deviations	Reported upon awareness																			
Device Accountability	X[3]	X	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed		X	As needed	As needed	As needed	As needed	X
Distribution supplies	X[3]	X	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed		X		As needed	As needed	As needed	
Return supplies																				X

[1] *Upload can be done by subject or by site staff*

[2] *For subjects entering the continuation phase only*

[3] *For subjects where visit 2 is managed remotely and eligibility criteria are met*

9.1.1 Pump Settings and Sensor Site

Preferred Guardian 4/DS5 sensor site insertion for studied population should be arm or buttocks unless there is a justification, and the rationale will be collected in eCRF.

During the study phase the following pump settings are recommended for subjects using the MiniMed 780G system in Auto Mode. All pump settings will be adjusted based on subject's needs, per investigator judgment.

Table 6. Pump Settings for subjects starting within study phase

Initial Setting (VISIT 3A/8*)		Week 2 (VISIT 4/8A*)			Week 4 (VISIT 5/9*)			From Week 8 (VISIT 6/10*) to EOS		
Target Setting	**AIT Setting**	**Option**	**Target Setting**	**AIT Setting**	**Option**	**Target Setting**	**AIT Setting**	**Option**	**Target Setting**	**AIT Setting**
120 mg/dL (6.7 mmol/L)	2 hours	***Option 1:*** TIR > 70% No Hypo Concerns	120 mg/dL (6.7 mmol/L)	2 hours	***Option 1:*** TIR > 70% & No Hypo Concerns	120 mg/dL (6.7 mmol/L)	2 hours	*To continue with the same settings*		
					Option 2: TIR < 70% & No Hypo Concerns	110 mg/dL (6.1 mmol/L)	2 hours	*To continue with the same settings*		
					Option 3: Hypo Concern	120 mg/dL (6.7 mmol/L)	3 hours	***Option 1:*** No Hypo Concerns:	120 mg/dL (6.7 mmol/L)	2 hours
								Option 2: Hypo Concerns:	*To continue with the same settings*	
		Option 2: TIR < 70% No Hypo Concerns	110 mg/dL (6.1 mmol/L)	2 hours	***Option 1:*** TIR > 70% & No Hypo Concerns	110 mg/dL (6.1 mmol/L)	2 hours	*To continue with the same settings*		
					Option 2: TIR < 70% & No Hypo Concerns	100 mg/dL (5.5 mmol/L)	2 hours	*To continue with the same settings*		

<table>
<tr><th colspan="2">Initial Setting (VISIT 3A/8*)</th><th colspan="3">Week 2 (VISIT 4/8A*)</th><th colspan="3">Week 4 (VISIT 5/9*)</th><th colspan="3">From Week 8 (VISIT 6/10*) to EOS</th></tr>
<tr><th>Target Setting</th><th>AIT Setting</th><th>Option</th><th>Target Setting</th><th>AIT Setting</th><th>Option</th><th>Target Setting</th><th>AIT Setting</th><th>Option</th><th>Target Setting</th><th>AIT Setting</th></tr>
<tr><td rowspan="6"></td><td rowspan="6"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td><u>Option 3:</u>
Hypo Concern</td><td>120 mg/dL
(6.7 mmol/L)</td><td>2 hours</td><td colspan="3">To continue with the same settings</td></tr>
<tr><td rowspan="5"><u>Option 3:</u>
Hypo Concern</td><td rowspan="5">120 mg/dL
(6.7 mmol/L)</td><td rowspan="5">3 hours</td><td rowspan="2"><u>Option 1:</u>
TIR > 70% &
No Hypo Concerns</td><td rowspan="2">120 mg/dL
(6.7 mmol/L)</td><td rowspan="2">3 hours</td><td colspan="3">To continue with the same settings</td></tr>
<tr><td><u>Option 1:</u>
No Hypo Concerns:</td><td>120 mg/dL
(6.7 mmol/L)</td><td>2 hours</td></tr>
<tr><td><u>Option 2:</u>
TIR < 70% &
No Hypo Concerns</td><td>120 mg/dL
(6.7 mmol/L)</td><td>2 hours</td><td><u>Option 1 :</u>
Hypo Concerns:</td><td colspan="2">To continue with the same settings</td></tr>
<tr><td rowspan="2"><u>Option 3:</u>
Hypo Concern</td><td rowspan="2">120 mg/dL
(6.7 mmol/L)</td><td rowspan="2">4 hours</td><td><u>Option 1:</u>
No Hypo Concerns:</td><td>120 mg/dL
(6.7 mmol/L)</td><td>2 hours</td></tr>
<tr><td><u>Option 2:</u>
Hypo Concerns:</td><td colspan="2">To continue with the same settings</td></tr>
</table>

** Visits 8; 9 and 10 are for Subjects randomized in Sequence B Period 2.*

For subjects starting in the continuation phase, it is recommended to start using the MiniMed 780G / MiniMed 780G BLE 2.0 system in Auto Mode with a glycemic target of 120 mg/dL (6.7 mmol/L) and 2 hours Active Insulin Time and adjust similarly to the above recommendations. All pump settings will be adjusted based on subject's needs, per investigator judgment.

9.1.2 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:

- MiniMed 780G system training
- DS5 Sensor training
- CareLink upload/training
- Review adverse events or device deficiencies, if any.

9.1.3 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 or sponsor (during a normal study visit or an unscheduled visit). This visit can be conducted onsite or remotely.

The subjects will continue to be treated following the routine practice of each center.

Early Termination procedures:

- Collect blood sample for HbA1c (Study Phase: Local Lab, Continuation: Central Lab), if possible.
- Collect questionnaires, if possible.
- Review adverse events or device deficiencies, if any.
- Collect all study supplies back from subjects.
- CareLink upload

9.1.4 Study Exit

After the study has been completed (at Visit 15 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 Samples collected during the study for study assessments (i.e. blood collected for HbA1c testing) will be destroyed according to the internal procedure of each Local Lab.

9.2 Data Collection

All data collection and study procedure requirements are described at the subject visits in **Section 9**.

9.3 Subject Consent

Informed Consent will be obtained in accordance with ISO14155:2020.

Prior to entry into the study, the EC (Ethics Committee) and Medtronic approved ICF form will be presented to each subject's parent(s)/legal guardian(s) to review and sign, as applicable. The subject's parent(s)/legal

guardian(s) will be given ample time and offered the opportunity to review these documents away from the investigational center.

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

The following will be provided to or explained to the subject's parent(s)/legal guardian(s) and by the investigator or designee: the purpose and duration of the study, the requirements expected to be adhered to by the subject during the study and the potential risks/potential benefits associated with participation in the study. Every attempt will be made to answer the subject's and their parent's, or legal guardian's questions during the informed consent process. The language used shall be as non-technical as possible and must be understandable to the subject's parent(s)/legal guardian(s).

Neither the investigator, nor the investigation center staff shall coerce or unduly influence a subject or their parent or legal guardian to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

Subject's parent(s)/legal guardian(s) will complete the IC form.

The consenting process must be documented in the subject's source documents. The subject's parent(s)/legal guardian(s) will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed. When the parent(s)/legal guardian(s) decide to allow subject to participate in the study, the ICF must be signed and personally dated by the subject's parent(s)/legal guardian(s) and investigator or authorized designee, as required by the ICF. A patient contact card will be provided to the subject's parent(s)/legal guardian(s).

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's parent(s) or legal guardian(s) in a timely manner.

Medtronic will revise the written ICF form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. After approval by the EC, a copy of this information must be provided to the participating subject's parent(s)/legal guardian(s), and the informed consent process as described above needs to be repeated.

Subjects and their parent or legal guardian will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), regulatory authorities and/or the EC, may have access to the clinic records that reveal their identity and health care information.

The investigational center must report the following informed consent violations to their EC (if applicable) and sponsor:

- Failure to obtain informed consent from subject's parent(s) or legal guardian(s)
- Failure to obtain informed consent prior to performing one or more study procedures.

- Failure to maintain ICFs forms on file for all subject's parent(s) or legal guardian(s) who have provided informed consent.
- Use of an ICF form that has not received approval from the EC.
- Use of an incorrect version of the ICF form.

9.3.1 Reconsent for the updated Continuation phase

When applicable, the subject/subject's parent(s) or legal guardian(s) will be reconsented with an amended ICF based on this protocol update, to continue participating into the amended continuation phase. In case the reconsent occurs during the Study Phase and the subject/subject's parent(s) or legal guardian(s)does not agree with this change, the initial signed ICF will remain applicable until the end of the study phase.

9.4 Randomization and Treatment Assignment

Both randomizations will be performed via the electronic CRF.

The randomizations will follow a block randomization with blocks of different sizes and the order of the block sizes will be selected randomly and the 1:1 allocation will be performed within each block. Investigators will be blinded to the number and size of the blocks.

Block randomizations were chosen to preserve a 1:1 randomization ratio as much as possible, while minimizing the likelihood of predicting treatment allocation to the next participant.

For first randomization, confounding is addressed by the random allocation and the cross-over nature of the design that allows within subject comparison, for second randomization confounding is addressed by the random allocation, with the aim that any confounding variable should be equally distributed in the study groups to give balanced comparisons.

9.4.1 Study Phase

At the end of the run-in phase (Visit 3) eligible subjects will be randomized in a 1:1 ratio to one of the following sequences composed of two periods of 12 weeks each:

Sequence A:

- Period 1: MiniMed 780G system in Auto Mode (Treatment)
- Period 2: MiniMed 780G system in Manual Mode with SBL activated (Control)

Sequence B:

- Period 1: MiniMed 780G system in Manual Mode with SBL activated (Control)
- Period 2: MiniMed 780G system in Auto Mode (Treatment)

9.4.2 Continuation Phase

At the end of the continuation phase period 1 (Visit 13) all subjects completing the study phase or newly eligible subjects will be randomized in a 1:1 ratio to one of the following arms and followed up for a period of 12 weeks:

- **Arm A2**: subjects will start using the MiniMed 780G BLE 2.0 system with the DS5 sensor in Auto Mode for 12 weeks
- **Arm B2**: subjects will continue to use MiniMed 780G system with Guardian 4 Sensor in Auto Mode for 12 weeks

9.5 Glucose and Glycemia Measurements

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

9.5.1 Daily Blood Glucose

Values will be assessed during the study by all subjects using the Accu-Chek Guide Link study meter, as needed. The control solution test will be performed following the manufacturer's user guide. Subjects will be trained on the use of the Accu-Chek Guide Link study meter per the manufacturer's instructions.

9.5.2 Sensor Glucose Values

SG data will be collected by subject's study pump and, if needed, calibrated by each subject's Accu-Chek Guide Link study meter.

9.5.3 HbA1c

HbA1c is collected at Visit 1, Visit 7, Visit 11, Visit 13 and Visit 15; if subjects have completed run-in phase and are in the study phase and exit early, a HbA1c will be collected as described in Early Termination Visit. HbA1c will be collected at the Local Lab for Visit 1, Visit 7, Visit 11. HbA1c will be collected at the Central Lab for Visit 13 and 15.

All HbA1c blood specimens from the Continuation phase will be sent to and tested by a National Glycohemoglobin Standardization Program (NGSP) certified Central Laboratory. The blood sample will be destroyed according to the Central laboratory procedure after analysis.

9.6 Recording Data

Data entered by the investigational center staff will be captured on eCRFs using the Electronic Data Capture (EDC) system. Original eCRFs will not be considered as source data and supporting documentation will be required.

Electronic device data will be collected from the study pump using CareLink Personal/CareLink system 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. Electronic device data could also be collected by the MiniMed Clinical app and the CareLink Clinical app.

The investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Medtronic will provide detailed instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the EDC system; otherwise, irresolvable data-related issues will be routed to the sponsor for review and final disposition. An audit trail is maintained in the EDC system to capture any corrections or changes of the eCRFs. System backups for data stored in the EDC system will be consistent with Medtronic 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.

9.7 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. Failure to do so could result in one or all of the following:

- Investigational center disqualification
- Notification to the regulatory authorities/EC depending on the severity of the deviation and reporting requirements

Deviations will not be issued for the following situations:

- If subject's parent/legal guardian do not upload devices, unless the site staff did not train the subject's parent/legal guardian on upload procedures.
- Recommended settings for the use of MiniMed 780G pump in Auto Mode are not being followed.
- Suggested site for sensor insertion not being followed.
- If subjects miss or delay protocol visits, unless the site staff did not plan the visit according to the protocol schedule.

The investigator should not implement any deviation from, or changes to, the CIP without agreement by the sponsor and prior review and documented approval/favorable opinion from the regulatory authority (if applicable) or EC (if applicable), except where necessary to eliminate an immediate hazard(s) to trial subjects. The use of waivers from the CIP are prohibited in this study.

9.7.1 Documenting Requirements for Study Deviations

9.7.1.1 Unplanned CIP Deviations

The investigator may encounter the need to deviate from the CIP when necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's

control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

Deviations from the CIP, regardless of the reason should be documented as soon as possible, after the deviation occurs or is identified. This documentation should include deviation date, description of the deviation, the reason for deviation, and the corrective action. Refer to **Table 8** for reporting timelines for emergency deviations.

CIP deviations should be reported as follows:

a) To the EC (if applicable) for notification/acknowledgement;
b) To the sponsor and, if required;
c) To the applicable regulatory authority (reported by sponsor).

9.7.2 Reporting Requirements for Study Deviations

All study deviations must be reported 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.

The following examples are deviations that could impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study. These deviations are significant and require immediate sponsor notification upon investigator awareness:

- Failure to obtain informed consent/assent, i.e., there is no documentation of consenting
- Informed consent/assent obtained after initiation of study procedures
- Continuation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the EC and RA
- Failure to inform EC and sponsor of reportable AEs (see **Section 11**)
- Investigational study device dispensed without obtaining informed consent/assent

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to Medtronic as well as the EC, if applicable per local regulations, within five (5) working days.

Reporting of all other study deviations should comply with:

- EC/IRB policies and/or
- local laws and/or
- regulatory authority requirements

They must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports and **Table 8** for specific deviation reporting requirements and timeframes for reporting to Medtronic, EC, and regulatory authority (if applicable).

9.7.3 Analyzing Deviations

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

9.8 Subject Exit, Withdrawal or Discontinuation

Subjects and/or their parent/legal guardian 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 the investigator or sponsor (during a normal study visit or an unscheduled visit) (described in **Section 9.1**). 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. All study devices and supplies must be returned (as applicable) and documented both in source documents and on an eCRF. Following study exit, withdrawal or discontinuation subjects will receive standard medical care from their own providers.

A subject will be withdrawn from the study if:

- In the opinion of the investigator, the subject's health or safety would be compromised by continuing in the study (e.g., infection at skin site, severe skin reaction to adhesive).
- In the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study.
- During the course of the study, subject is taking oral, injectable, or IV glucocorticoids
- During the course of the study, subject begins participation in another investigational study (drug or device).

Documentation of the reason(s) leading to subject withdrawal will be kept in the subject's source documentation.

9.8.1 End of Subject Participation in Study/ Completion of Study

After the study has been completed (at Visit 15 or in case of early termination), subjects will be exited from the study. Subjects will continue to work with their physician after study exit per normal standard of care. The clinical investigation is considered completed once the last subject has exited the study.

9.8.2 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 potential residual risks and mitigations associated with the devices used during this study are listed in **Table 7**. Risks associated with the commercially available devices used in the study are listed in the associated device labeling/user guides/instructions for use or IBs.

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 CIP and constantly monitored. There is no additional risks associated with the new devices of the continuation phase.

Table 7. Risks, Prevention and Mitigation

Risks with Infusion Sets	**Prevention and Mitigation**
Risks with infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or infusion site failure including DKA • Hyperglycemia secondary to site falling off including DKA • Anxiety associated with insertion	Prevention and mitigation include: • Follow the provided user guides for insertions and care of infusion sets. • If an infusion site becomes irritated or inflamed, the infusion set will be removed and another placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.
Risks with Insulin Administration and Pumps	**Prevention and Mitigation**
Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software, infusion set and reservoir) as well as the risk of use error during use of the system. DDs or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences: • Hypoglycemia • Hyperglycemia	Prevention and mitigation include: • Follow the provided user guides & instructions for insulin pump management which includes information on infusion set change. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.

• Diabetic ketoacidosis • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Subject removes the reservoir from the pump but forgets to disconnect the infusion set from the body which results in hypoglycemia or severe hypoglycemia • Dislodged cannula leading to hyperglycemia • A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered • Insulin deterioration leading to hyperglycemia • Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia • Remove a reservoir, without suspending and reconnecting after a while resulting in a hypoglycemia • Patient not filling pump reservoir when needed leading to hyperglycemia • Magnetic resonance imaging resulting in pump transmitter malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from the use of the SmartGuard feature where SG values may be used to calculate insulin bolus amounts • Hypoglycemia or hyperglycemia from computer hacking	• Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct to have glucose and glucagon on hand for hypoglycemia. • Instruct to change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. • Parent(s)/guardian(s) should be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems.
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. • Parent(s)/guardian(s) should be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems. • Parent/caregivers should also be present during meal and exercise challenges. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.

	• Instruct to check their meter glucose if their high symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Alternative method of managing glucose levels will be available (insulin and syringe for example).
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. • Parent(s)/guardian(s) should be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems. • Parent/caregivers should also be present during meal and exercise challenges. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate). • Instruct to have glucose on hand for hypoglycemia.
Risk with Sensors	**Prevention and Mitigation**
Risks with sensors may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted	Prevention and mitigation include: • Follow the provided user guides for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor will be removed and another placed in a new location. • Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate.

• Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation • Anxiety • Incorrect SG reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia	• Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed.
Risks with Transmitter	**Prevention and Mitigation**
Risks with transmitter may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Allergic reaction • Soreness or tenderness • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation	Prevention and mitigation include: • Follow the provided user guides. • Train on the proper use of the transmitters.
Risks with Serter	**Prevention and Mitigation**
Risks with serters may include: • Improper insertion may lead to device performance issue	Prevention and mitigation include: • Follow the provided user guides for insertions and care of device. • Train on the proper use of the serter and skin preparation prior to insertion.
Risk with Closed Loop Therapy	**Prevention and Mitigation**

Risks with 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 and 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 SmartGuard may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Hypoglycemia related to patient taking insulin via injection while in Closed Loop (SmartGuard)
• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop (SmartGuard)
• Insulin over-delivery due to potential interference from acetaminophen, which may include false elevation of SG readings potentially resulting in an over-delivery of insulin which may cause hypoglycemia. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject
• Cyber security hacking into pump
	Prevention and mitigation include:
	• Follow the provided user guides for insulin pump management.
	• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.
	• Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions.
	• Instruct to check their meter glucose if there are any concerns that the SG value is not accurate.
	• Instruct if there are no sensor values, no treatments decision will be made until a BG is confirmed.
	• Instruct to have glucose on hand for hypoglycemia.
	• Instruct to avoid the use of products containing acetaminophen
	• If acetaminophen is taken, subjects will be instructed to use additional BG meter readings to verify their glucose levels.
	• If acetaminophen is taken, while the SmartGuard feature is active, subjects will be instructed to use the temp target feature (when used, Auto Correction is not available).
	• Instruct subjects that in case of prolonged use of acetaminophen, the temp target feature can be used repeatedly and in succession.
	• Pump has cybersecurity encryptions to prevent hacking.

Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their high symptoms do not match their

• Acidosis	sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct if there are no sensor values, no treatments decision will be made until a BG is confirmed.
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. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed • Instruct to have glucose on hand for hypoglycemia.

10.2 Risk Minimization

Refer to "Prevention and Mitigation" column in the table under **Section 10.1**.

10.3 Potential Benefits

The objective of this study is to evaluate the safety and performance of the MiniMed 780G system, it is anticipated that the system will allow improved glycemic control in the selected population of young patients in MDI or CSII with or without CGM.

Currently MiniMed 780G pump use is approved for subject older than 7 years old so the study will give the opportunity for subjects, ages 2-6 to have access to this system used both in Manual and Auto Mode during the study.

The information gathered in this study will help to extend labeling for MiniMed 780G system and the data collected in the study might help the patients and physicians determine the best treatment options in the future.

10.4 Risk-Benefit Rationale

The main benefit of this study is that paediatric subjects (2-6 years old) may experience improved glucose control, due to the fact that the participants will be followed with higher frequency of visits, which will allow closer medical follow-up when compared to standard of care.

Parents/legal guardians of the subject may also increase their understanding of the disorder.

Risks related to the pump delivering too much or not enough insulin are minimized through a variety of safety checks that are an integral part of the MiniMed 780G closed loop algorithm.

11 Adverse Events

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. The study personnel will elicit reports of AEs from the subject at each visit (including phone calls) starting at the time of signing the informed consent documenting the medical diagnosis, date of event start and end, causality (relationship to device or procedure), treatment, outcome, assessment of seriousness, and description that includes the details of the event.

11.2 Definitions and Classification of Adverse Events

All adverse events (including non-subject AEs) will be collected and classified by using the ISO 14155:2020 definitions, as defined below. 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.

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 himself or herself, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative.

These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[4]

Diabetic Ketoacidosis/DKA diagnostic criteria: BG greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L, arterial pH less than (<) 7.3, bicarbonate less than (<) 15 mEq/L, moderate ketonuria or ketonemia and requiring treatment within a health care facility.[5]

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 (<) 15 mEq/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)

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

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

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE) (ISO 14155:2020)

Adverse event related to the use of an investigational medical device.

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

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

Note 3 to entry: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE) (ISO 14155:2020)

Adverse event that led to any of the following

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

c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: 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.

Serious Adverse Device Effect (SADE) (ISO 14155:2020)

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)

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

Note 1 to entry: Anticipated serious adverse device effect (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)
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 to entry: 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.

11.3 Recording of Adverse Events

The investigator or designee will record ALL AEs and DDs while the subject is enrolled in the clinical study (Refer to **Section 13** for DD reporting).

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 (e.g., needle (blood draw) insertion pain).

Examples of device or procedure related AEs include:

- ***Device*** related (ADE): insertion site infection
- Serious adverse ***device effect***: cellulitis at device insertion site requiring hospitalization
- ***Procedure*** related AE: bruising at needle (blood draw) insertion site

An outside standard of care CIP procedure related AE in this study is associated with a study procedure that is required per the study protocol and is in addition to the standard of care for the device (see Study Design under **Section 9**).

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 as this is not considered an untoward event, but rather an expected occurrence. Any glycemic excursion that meets the protocol definition of severe hypoglycemia 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.

Baseline 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.

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 EOS participation; however, there will be no eCRF entry for the ongoing follow-up.

11.4 Notification of Adverse Events

Sponsor Notification:

The investigational center staff must report all AEs to Medtronic in a timely manner. All severe hypoglycemia, DKA, SAE, SADE, and DD with SADE potential should be reported immediately to Medtronic (but not later than 72 hours). For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the de-identified known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

Source documents that support the event (e.g., clinic notes, hospital admission and discharge records, lab reports, EMT reports, ER/Urgent Care) should be provided to the sponsor via Medtronic's secure upload application. All source documents/medical records should be redacted of patient identifiers (full name, address, etc.) prior to providing to the sponsor. Each source page should be identified with the subject ID.

Table 8. Investigator Reports to Sponsor

Event Type To Report	Timeframe for Reporting
▪ 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 (see **Section 13**)	Immediately, but no later than **72 hours** after investigational site study personnel's awareness of the event (or sooner if required by local regulation)
▪ Adverse Event (AE) ▪ Device Deficiency (DD) (see **Section 13**)	In a timely manner from the investigator's / site's first knowledge of the event

Sponsor Reports:

Regulatory reporting of AEs and DDs will according to local regulatory requirements.

In countries following EU MDR 2017/745, AEs will be reported according to EU MDR 2017/745 Art. 80(2) and Medical Device Coordination Group (MDCG) 2020-10/1 guidance and additional local requirements if applicable.

In accordance with EU MDR Art. 80(2) the following events are considered reportable:

a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points a) and b).

Table 9. Sponsor Adverse Events Reporting Requirements to National Competent Authority

Events To Report in EU/EEA	Reporting Requirements and Timeframe
▪ Any device and/or procedure related Serious Adverse Events (SAE) and/or Device Deficiency (DD) that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP)	Immediately, but no later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event
▪ Any device and/or procedure related SAE and DD that may have led to an SADE (occurred in the study under same CIP*) – including updates	Immediately, but not later than 7 calendar days after awareness
Events To Report in UK	**Reporting Requirements and Timeframe**

▪ Any SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP)	Immediately, but no later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event
▪ Any SAE and DD that may have led to an SADE (occurred in the study under same CIP*)– including updates	Immediately, but not later than 7 calendar days after awareness by the sponsor of the new reportable event or of new information in relation with an already reported event
▪ All SAEs	Quarterly report according to CA 'letter of no objection'. Quarterly after CA approval date

In addition, it is the responsibility of the investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's EC.

11.5 Adverse Event and Device Deficiency Classification

All AEs and DDs will be reviewed by sponsor and will be classified according to the responsibilities as outlined below in **Table 10**.

Upon sponsor's receipt of an event, a Safety representative will review the AE/DD for completeness and accuracy and when necessary, will request clarification and/or additional information from the Investigator.

It is the responsibility of the investigator and sponsor to abide by any additional AE reporting requirements stipulated by the EC and RA responsible for oversight of the study.

Table 10. Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Procedure, Outside Standard of Care CIP procedure
	Sponsor	Device, Procedure, Outside Standard of Care CIP procedure
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, USADE, and DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

11.6 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. The eCRF may be used as original source data for the assessment of causality and severity.

This review would include the subjects' (or parent/legal guardian) description of the event, study device uploads and medical records (if applicable) from the treating facility. These records will be made available to sponsor.

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

- **Not related:** relationship to the device, comparator, or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device or the procedures related to the application of the investigational device;
  - 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, when applicable;

  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.

- **Possible:** the relationship with the use of the investigational device, comparator, or the relationship with procedures, 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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

- **Probable**: the relationship with the use of the investigational device, comparator, or the relationship with procedures, seems relevant and/or the event cannot reasonably be explained by another cause.

- **Causal relationship:** the event is associated with the investigational device, comparator, 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.

11.7 Anticipated or Unanticipated

If an AE is determined to be related to the study device the sponsor will then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; Investigator's Brochure (IB) or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; IB or user guide.

12 Data Review Committees

12.1 Clinical Events Committee

A 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 AEs as required per protocol, which include reports of:

- Serious adverse event
- Serious adverse device effect
- Unanticipated serious adverse device effect (USADE)
- Severe hypoglycemia

- Diabetic ketoacidosis

The CEC will assess events to determine agreement or disagreement with the investigator classification of an event.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to Ecs and regulatory authorities, if required.

The CEC may review applicable information for device related AEs which may include:

- Whether or not the event was unanticipated
- Review of sensor data from CareLink Personal/CareLink system software report (when applicable)
- Review of pump data from CareLink Personal/CareLink system software report (when applicable)
- Misuse of the device by the user

Review of events may require the following information. Final disposition may be delayed based on obtaining this information:

- Monitoring by sponsor at investigational center
- Device return and failure analysis
- CareLink Personal/CareLink system software upload and review of software reports
- Subject clarification to investigational center regarding details about the event
- Source documents that support event: Paramedic records; ER records; Lab records; Hospital admission and discharge summary

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, will be convened to review study progress and safety. The board will convene periodically. The DMC Charter is available under a separate cover.

The DMC will perform 2 main functions:

First: DMC will track and trend the overall safety of the study.

Event rate, defined as number of events per 100 patient years will be reviewed by the DMC with respect to the following:

- Event rate of all SAE

- Event rate of severe hypoglycemia
- Event rate of DKA
- Event rate of device related AE

Second: Based on their meeting, DMC will recommend a decision to the sponsor regarding the following:

- Whether or not enrollment should be halted.
- Whether or not the entire study will need to be stopped including for those subjects who have received study devices already.

12.3 Central Lab

This information may be subject to change during the course of the study. Periodic updates to study contact information will be sent to study sites as needed.

Table 11. Core Laboratory Information

Contact Information	Role
ACM Global Laboratories [redacted]	Analysis of HbA1c samples collected during the Continuation Phase

13 Device Deficiencies

The subject's parent/legal guardian will be instructed to contact the investigational center staff for questions or concerns regarding study devices.

All device deficiencies will be collected and classified by using the ISO 14155:2020 definition, as defined below. All DDs reported directly to the investigational center staff by a subject and those experienced by the investigational center staff will be reported on the appropriate eCRF. In addition, an eCRF should also be completed by the investigational center staff for each reported DD that did not lead to an Adverse Event. A DD that results in an AE should be captured on an AE CRF only.

Subjects participating in the study are expected to have mild irritation from device wear at times. Only discomfort occurring at a threshold resulting in early removal of the device should be reported as a DD or adverse event.

Device Deficiency (ISO 14155:2020)

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

Each DD will be assessed for SADE potential defined as:
A DD 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

To return a study device as part of a DD, the subject is to contact the investigational center staff, and the investigational center staff should then follow the study procedures for returning products with DDs. For a list of study devices that needs to be return to the sponsor, please consult your study materials.

It is the responsibility of the investigator to follow their EC reporting requirements.

14 Statistical Design and Methods

14.1 General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected on eCRFs and electronically by uploading the various devices. Data and analysis will be summarized in a Clinical Study Report. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report. Both the study and continuation phases of the study are used for confirmatory analysis.

14.2 Subject Disposition

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

14.3 Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, medical diagnosis, height, weight, BMI, and baseline HbA1c will be summarized by descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

14.4 Analysis Populations and Handling of Missing Data, Error

- Intention to Treat (ITT) Population
  The ITT population will include all randomized subjects. These subjects will be assessed and analyzed as members of the intended period, irrespective of their compliance to the planned course of treatment or deviations from protocol. For the primary and secondary endpoints, efficacy analyses will be performed in the Intent to Treat (ITT) basis.
- Per Protocol (PP) Population

The PP population will include all randomized subjects, excluding any subject with at least one of the following deviations:

- Auto Mode use during the active study phase is less than 75%
- Sensor use during the active study phase is less than 70%
- Subject did not complete the study phase
- Subject did not meet screening criteria but continued the study
- Subject did not meet randomization criteria but continued the study

Efficacy analysis of the primary endpoint will also be performed in the Per Protocol set.

- Safety Population

  The Safety Population will include all subjects with signed inform consent and safety data will be presented by phase (run-in phase, study phase and continuation phase). Safety reporting will be done separately for the run-in phase, the study phase and continuation phase.

The treatment interventions will be compared with the use of a repeated measures mixed model that uses available data and accounts for possible missing at random data. Data entry errors will be resolved before data analysis. No imputations will be done for missing data.

14.5 Endpoints and Hypotheses

14.5.1 Analysis of Primary Endpoint – Study Phase

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

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

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

The non-inferiority absolute margin of 7.5% TIR was chosen in consensus with physicians as the maximum acceptable decrease of TIR in comparison with the current approved therapy. In addition, the non-inferiority margin of 7.5 % TIR is equivalent to a less than 0.3 % change in HbA1c which is considered non clinically significant [3]. This is in line with the recommendations from the International Consensus on Time in Range (quoted 'an increase in TIR of 10% (2.4 h per day) corresponded to a decrease in A1C of approximately 0.5% (5.0 mmol/mol)") [3].

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

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

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

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

Pass/Fail Criteria:
The study pass/fail criteria is based on statistical hypothesis of the primary endpoint. The study will be considered as success when the evaluation criteria meets the predefined threshold for both ITT and PP sets.

14.5.2 Analysis of Primary Endpoint – Continuation Phase

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

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

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

The choice of the non-inferiority margin of 0.4% reduction in HbA1c was based on well-established historical evidence and accepted for diabetes clinical trials according to FDA guidance[6].
[3]

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

14.5.3 Analysis of Secondary Endpoints – Study Phase and Continuation Phase

A fixed-sequence testing method will be applied to address the multiple comparison. If the primary endpoint analysis is significant, the procedure tests hierarchically the ordered hypotheses in sequence as the order in 4.2.2., at level α=0.025 (one-sided) until one of the hypotheses is non-rejected.

Analysis on each secondary endpoint will be performed using the same methodology in primary endpoint on the ITT population.

14.5.4 Analysis of Exploratory Endpoints

Descriptive summary statistics will be presented for all exploratory endpoints.

14.5.5 Safety Data and Device Deficiencies, Adverse Event and Device Data Summary

All safety summaries and analyses will be presented for the Safety Population. Total number of Severe hypoglycemic events, diabetic ketoacidosis events, serious adverse events, serious adverse device effects, unanticipated serious adverse device effects and device deficiencies will be reported for run-in, study phase and continuation phase, categorized by treatment. The listing of these events will also be reported.

[redacted]

[redacted]

14.6.1 Expected Drop-out Rates

The following drop-out assumptions have been considered, based on experience with previous studies. At screening: 10%; After run-in: 5%; During study phase/continuation phase: 10%.

Incorporating the expected drop-out rates, a total of up to 100 participants will be enrolled to have approximately 72 participants randomized and completing the study phase and approximately 64 subjects completing the continuation phase.

14.7 Interim Analysis

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

No treatment effect evaluation will be performed at the time of interim analysis. If the assumption on HbA1c standard deviation is not met, the sample size for continuation phase only will be increased accordingly.

14.8 Final Report

The primary study results from the study phase will be summarized and presented in the 6-month final report. The study results from the continuation phase will be summarized and presented in the final report.

15 Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as Good Clinical Practice (GCP). GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject's parent/legal guardian before initiating the study.

The CIP342 study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

AE and DD handling in the CIP342 is ISO 14155:2020 compliant for all participating geographies.

The principles of the Declaration of Helsinki (DoH) have been implemented through the IC process, EC and RA approvals, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Following ISO14155:2020, children with legally incompetent and illiterate parent(s)/legal guardian(s) will not be included in this clinical study.

Ultimately, all study sites in all geographies will follow and comply with:

- Principles of DoH
- The CTA

- The procedures described within this CIP
- Local EC Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to ISO14155:2020, DoH version 2013, and in member states of the EU/EEA Regulation (EU) 2017/745 on Medical Devices (MDR).

The study will be publicly registered prior to in accordance with the DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of any subsequent amendments to this CIP, the ICF, 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 and geography specific Regulatory Authorities.

The investigational center will not initiate any subject activities until EC and geography specific Regulatory Authorities approvals 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.

15.2 Role of the Sponsor's Representatives

Sponsor's representatives may provide Study specific training to the site personnel conducting study activities. Sponsor representatives may also provide technical support at investigational centers. Sponsor representatives may provide technical support as required for the study under supervision of the PI, including:

1) Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
2) Technical support will be provided during study phase.
3) Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at investigational centers.
4) Technical support to conduct device interrogations.

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.
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.

15.3 Investigator's Responsibilities

Per ISO14155:2020, an investigator means "individual member of the investigation site team designated and supervised by the PI at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation related decisions."

Each investigational center shall designate a primary investigator who will have overall responsibility for the conduct of the investigation at the investigational center.

The primary investigators (and co-investigators if applicable) are responsible for conducting the study in accordance with this CIP, CTA, ISO14155:2020, applicable regulations, and any conditions of approval imposed by the reviewing EC or regulatory authority requirements. The investigator's responsibilities include but are not limited to:

- Conduct of investigation in accordance to International guidelines for clinical trials on medical devices ISO 14155:2020, to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify regulatory authority's expectations concerning the investigator's responsibility:
    1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    2) 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
- 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 14155:2020
- Supervising the use of investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized to receive it.
- 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:
    - attribution, legibility, and timeliness of source data
    - all relevant correspondence with another investigator, an EC, the sponsor, a monitor, or regulatory authority, including required reports

  - records of receipt, use or disposition of study devices
  - records of each subject's case history and exposure to the device, including information reported in the eCRFs and in all other required reports
  - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
  - any other records the regulatory authority requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation
- Preparation and submission to Medtronic and, when required, regulatory authority and the reviewing EC, the following complete, accurate, and timely reports:
  - any reportable AEs (see **Section 11**) occurring during an investigation
  - progress reports on the investigation as required by the regulatory authority and EC
  - 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 authority and EC about any aspect of the 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 subject's parent(s)/legal guardian(s), 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.

16 Study Administration

16.1 Training of Clinical Staff

Training of the investigational center staff on the conduct of the study and system being studied will be initiated before the CIP is implemented, depending on their role listing on the Delegation of Authority Log, as per Training Plan. Training may contain both lecture and hands-on experience.

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

16.2 Monitoring

Monitoring visits may 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 ICF

have been obtained from each subject's parent(s)/legal guardian at the point of enrollment and that AEs discussed in **Section 11** were reported via completion of the AE eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

16.2.1 Accessibility of Investigational Center Staff and Study Materials

The PI(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel, monitor, regulatory authority personnel, and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Access to subject's medical files for source data verification will need to be granted prior to any monitoring visits.

16.2.2 Audits and Investigational Center Inspections

In addition to regular monitoring visits, the sponsor may conduct 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. 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 sponsor 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 review, and regulatory inspections.

16.2.3 Investigational Center Disqualification

Sponsor and/or the EC retain the right to disqualify an investigational center and remove all study materials at any time. Specific instances that may precipitate investigational center disqualification include but are not limited to:

- Unsatisfactory subject enrollment with regards to quantity.
- Persistent non-compliance to protocol procedures on the part of an investigator/investigational center
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
- The incidence and/or severity of adverse experiences in this or other studies indicating a potential health hazard caused by the device.
- Unsatisfactory accountability of investigational devices.

A written statement fully documenting the reasons for such a termination will be provided to sponsor, the EC, investigational center(s) and other regulatory authorities, as required.

16.3 Data Management

16.3.1 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 the 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 File. The EDC 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 to the use of the eCRFs. Access to final eCRFs for study conduct will be granted after training is performed and prior to patient's enrollment.

16.3.2 CareLink Personal/CareLink System Software

During the course of the study, subject's BG values may be assessed from the Accu-Chek Guide Link study meter. The SG values may be assessed from the study pump. The study pump will be uploaded in CareLink Personal/CareLink system software by the investigator or designated investigational center staff and subject's parent/legal guardian at home. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). The data in the different databases are linked to each other via the subject's ID.

16.3.3 Questionnaires

The questionnaires will be provided in local language in the countries. Subject's parent/legal guardian will be provided a link to complete the questionnaires online or a paper copy. Refer to CIP342 Questionnaire Guide. If the online link cannot be accessed due to technical problems, subject's parent/legal guardian will complete the questionnaire using a paper format. The investigator, or designated investigational center staff, will then enter the subject's parent/legal guardian responses from the paper questionnaires to online once it becomes available. If paper format is used, the investigator or designated investigational center staff should maintain the original paper source in the subject's source file.

16.3.4 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 might 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.

16.3.5 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 the reportable AEs (see **Section 11**). After data entry, eCRFs should be submitted (i.e., saved) so that monitors can proceed with data verification without delay.

16.3.6 Data Review and Processing

Data management will be done according to sponsor 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.

16.4 Direct Access to Source Data/Documents

The subject's clinic file, CareLink Personal/CareLink system software data, laboratory reports and source documents 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 or copies of electronic source documents, completed worksheet if applicable, for the purposes of monitoring, audit, or inspection.

16.5 Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. 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 subject's parent/legal guardian that the above-named representatives will review their study-related records without violating the confidentiality of the subject's parent/legal guardian. All laboratory specimens, evaluation forms, reports, and other records that leave the investigational center will be identified only by the subject ID code in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only. 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.

16.6 Liability and Subject Compensation

Travel fees to the site may be reimbursed for study specific visits if required by local regulations.

16.6.1 Insurance

Medtronic International Trading Sarl 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 local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC or regulatory authority.

16.7 CIP Amendments

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

Sponsor can decide to review the CIP based on new information, or for other reasons, and will submit any amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authority for their approval or as notification, and to the investigators to obtain approval from their EC. The investigator will only implement the amendment after the sponsor has obtained regulatory authority approval (if applicable) and the amendment has been approved by the EC. Administrative amendments to the CIP will be submitted to the EC/IRB for notification.

16.8 Investigational Center Compensation

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

16.9 Records and Reports

16.9.1 Investigator Records

At a minimum, the following records must be kept by the investigator:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- IB/report of prior investigations and/or user guide
- Medtronic and EC-approved Subject ICF
- EC and regulatory authority approval or notification
- Fully signed clinical study agreements (i.e., including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject Screening log and/or subject ID log
- Signed, dated and fully executed Subject ICF
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and DDs
- Device accountability records
- CIP Deviation/ CIP Non-Compliance, if any
- Current signed and dated CV of PI (and key study team members if required per local requirements)
- Study reports

16.10 Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. 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. These records are to be retained in a secure storage facility maintained by the investigational center until 2 years (or longer if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The investigator should not dispose of these records without the approval of the sponsor.

16.11 Suspension or Early Termination

Sponsor or a 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 or because of a business decision). If the clinical study is terminated prematurely or suspended, sponsor shall promptly inform the investigators and regulatory authorities (if applicable) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study subject's parent/legal guardian as applicable by local laws and regulations.

16.11.1 Early Investigational Center Suspension or Termination

Sponsor, EC or a regulatory authority may decide to suspend or prematurely terminate an investigational center (e.g., in case of expiring approval of the reviewing EC, non-compliance to the CIP, or lack of enrollment). Suspended clinical studies cannot be resumed without permission from EC and regulatory authority (if applicable). If an investigational center is suspended or prematurely terminated, sponsor shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC 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, if applicable.

16.11.2 Subject Follow-Up In Case of Termination

In case of early investigational center suspension or termination, all subject's parent/legal guardian should be contacted to plan an early termination visit at the investigational center. 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 investigational center. Following suspension or early termination, subjects will receive standard medical care from their own health care providers.

16.12 Study Close-Out

At the time of a study close-out, after last patient last visit, the investigators will be notified by sponsor. Appropriate notification/report to EC and regulatory authority will be provided if required per local laws and regulations.

16.13 Publication and Use of Information

Publications from this CIP will be handled according to SOPs and as indicated in the CTA. A separate Publication Plan will describe the publication strategy and processes for publications of the study.

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- 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.

Decisions regarding authorship and contributor-ship will be made by a publication planning committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

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 study will be publicly registered on http://www.clinicaltrials.gov prior to subject enrollment. Study results, when available, will be posted in this database.

17 References

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2. Carlson AL, Sherr JL, Shulman DI, et al. Safety and Glycemic Outcomes During the MiniMed Advanced Hybrid Closed-Loop System Pivotal Trial in Adolescents and Adults with Type 1 Diabetes. *Diabetes Technol Ther.* 2022;24(3):178-189.
3. Arrieta A, Battelino T, Scaramuzza AE, et al. Comparison of MiniMed 780G system performance in users aged below and above 15 years: Evidence from 12,870 real-world users. *Diabetes Obes Metab.* 2022.
4. Cryer PE. Defining and reporting hypoglycemia in diabetes: A report from the American diabetes association workgroup on hypoglycemia. *Diabetes Care.* 2005;28(5):1245-1249.
5. Hyperglycemic Crises in Diabetes. *Diabetes Care.* 2004;27(SUPPL. 1):S94-S102.
6. Food and Drug Administration Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. In: Maryland F, ed2016.
7. Tuomaala AK. Glycemic outcomes and safety with MiniMed 780G system in children with type 1 diabetes aged 2 - 6 years. *Diabetes Technology & Therapeutics.* 2022;24(S1):A-1-A-237.

18 Appendices

18.1 Names and addresses

18.1.1 Investigational Centers and EC

The names and addresses of investigators, coordinating clinical investigator if appointed, 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.

18.1.2 Sponsor Contact Information

The names and addresses of sponsor representatives, including 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.

18.1.3 Vendors Contact Information

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

18.2 Labeling of Devices

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

18.3 Sample Consent Materials

Samples of the following consent forms/materials will be provided under separate cover.

18.4 Sample CRF

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

18.5 Questionnaires

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

18.6 Sample Investigator Agreement

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

18.7 List of Consumables and Accessories

A list of all compatible consumables and accessories will be kept under a separate cover upon request to the Sponsor.

19 Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
A	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	[redacted], Sr. Medical Writer

B1) Synopsis and Section 8.3 Inclusion criteria: Inclusion criteria#5 Novorapid™ added together with Novolog throughout the document	1) Novorapid is the brand name used in Europe for Insulin Aspart	1) None	ICF	[redacted], Sr. CRS
2) Synopsis and Section 8.4 Exclusion Criteria: Exclusion criteria #1: added "untreated" to coeliac disease	2) Omitted in previous version by mistake	2) None		
3) Synopsis and Section 8.4 Exclusion criteria: Exclusion criteria #2: comma removed after GLP-1	3) Typographic mistake in the previous version	3) None		
4) Section 5.3 Study Oversight and subsequent section 5.3.1 Steering Committee modified. Removal of the sentence 'and external physicians with an expertise in endocrinology and the management of diabetes including insulin pumps and CGM'	4) No external Steering Committee was finally convene, as DMC and CEC are responsible for study oversight duties.	4) None		
5) Section 6.28 CareLink personal software and Section 6.29 CareLink System software: reference to "Microsoft® Internet Explorer" browser delated	5) Obsolete browser	5) None		
6) Section 9.1 – Visit 1: deleted the word "severe" from severe DKA, page 32	6) Typographic mistake in the previous version	6) None		
7) Table 6 Pump setting correction f typos	7) Typographic mistake in the previous version	7) None		
8) Section 14.4 Analysis Populations and Handling of Missing Data, Error: PP population definition was changed as following:" The PP population will include all randomized subjects, excluding any subject with at least one of the following deviations:	8) Requested from MHRA to define study deviation for PP exclusion	8) None		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	Auto Mode use during the active study phase is less than 75% Sensor use during the active study phase is less than 70% Subject did not complete the study phase Subject did not meet screening criteria but continued the study Subject did not meet randomization criteria but continued the study 9) Section 14. 5.1 Analysis primary endpoint, the following addition were made: A. Rational on 7.5% for choosing 7,5 % non-inferiority margin B: Removal of the phrase: "If the p value of the coefficient of randomization sequence is >0.1, randomization sequence will be removed from the model" 10) Update to template version E	9) MHRA requested rational for choosing 7,5% non-inferiority margin and to request randomization sequence will be included in the model to evaluate the primary endpoint. 10) New template version released on 26MAY2022	9) None 10) None		
C	1) Protocol first page: EUDAMED Number added 2) Glossary updated with new acronym: BLE, NGSP 3) Synopsis and section 6 Product updated to include details about the 2 new investigational devices for the Continuation Phase: MiniMed 780G BLE2.0 Insulin Pump and Disposable Sensor 5	1) Not available at the time of the previous Protocol update 2) To be exhaustive with this protocol update 3) Added devices to the study for the continuation phase which subsequently requires	1) None 2) None 3) None	ICF, CRF	[redacted] Pr. CRS

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	• Table 2, 3 and 4 updated • Figure 5 added • Section 6.2.7 DS5 Sensor added	changes throughout the protocol			
	4) Section 6.2: paragraph from the CIP342 Clinical Investigation Plan Addendum Slovenia Version 1.0 2023 01 23 incorporated. This updated Protocol version obsoletes Addendum for Slovenia	4) Slovenian CIP Addendum created based on Slovenia CA request. Incorporated into the main CIP for other countries to benefit from it	4) None		
	5) Synopsis and Section 5 Study Design: • updated to include 2 new investigational devices for the Continuation Phase: MiniMed 780G BLE2.0 Insulin Pump and Disposable Sensor 5 • Extension of Period 1 duration to accommodate subjects enrolled for the continuation phase only. It is changed from 12 weeks to 18 weeks +/- 6 weeks • Randomization added at V13 to assign one of the 2 treatments	5) The new sensor DS5 is the last generation one, combining with the transmitter. The applicable being simpler, subject burden is decreased. This sensor requires the updated version of the 780G insulin pump, the BLE2.0 version. Duration of continuation phase extended based on added devices	5) None		
	6) Study design graph updated (Synopsis Figure 1, Synopsis Figure 2, Figure 3)	6) Enrolment could be opened for the Continuation phase only to secure statistical analysis of the Continuation Phase endpoints.	6) None		
	7) Synopsis Study visit schedule	7) Per updated Study Design	7) None		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	updated to include subjects enrolling for the continuation phase only 8) Synopsis and Sample Size & Investigational Centers, Section 8.1 Study Population, Section 8.2 Subject Enrollment: • Specification about completed subjects needed for both study phases • Interim analysis added to evaluation sample size and open enrollment for the continuation phase only 9) Synopsis Duration and Section 5.1 updated to reflect study design changes, extending the study duration subjects joining for the Continuation phase only 10) Synopsis and section 8.3 Exclusion criteria Exclusion criteria #6 updated to correct Control IQ name and be specific about Omnipod 5 11) Synopsis Statistical Analysis for Endpoints and Hypothesis, Section 4 and Section 14: • Endpoints divided for each study phase • Study Phase endpoints clarified • Continuation Phase primary and secondary endpoints added 12) Section 3.1 Background • Paragraph added about the 2 new investigational devices used to the Continuation Phase	8) Per updated Study Design 9) Per updated Study Design 10) Typographic mistake and clarification about OmniPod 5 being an advanced hybrid closed loop therapy 11) Per updated Study Design 12) Per updated Study Design	8) None 9) None 10) None 11) Continuation Phase primary and secondary endpoints added 12) None		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	13) Table 1 AHCL Clinical Studies updated with most recent information on status and Studies	13) To reflect and update status at the time of the revision	13) None		
	14) Section 5.3 Study Oversight and subsequent section 5.3.1 Steering Committee deleted	14) The internal overview procedures ensure sufficient oversight and guidance for the conduct of the trial as well as evidence dissemination and ensure that appropriate stakeholders are contacted. This obsoletes the need of an internal Steering Committee.	14) None		
	15) Section 8.5 Randomization Criteria and Section 8.5.2 Continuation Phase added	15) Per updated endpoints	15) None		
	16) Section 9 Study Procedures and subsequent sections	16) Per updated Study Design	16) None		

	17) Section 9.1 Schedule of Events
	• Figure 10 Visit schedule scheme updated
	• Visit 1A, 2A and 3A added for the subjects enrolling for the Continuation Phase only
	• Visit 12 window start from visit 1A added on top of Visit 11
	• Visit 13
	  ○ window start from visit 1A added on top of Visit 11
	  ○ duration extended from 12 weeks to 18 weeks +/- 6 weeks
		17) Per updated Study Design	17) None		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	○ procedures added (questionnaires collection, HbA1c sample analyzed at Central Lab, randomization, training on new devices based on randomization) • Visit 14 ○ window start from visit 13 ○ retraining added about new devices (780G BLE 2.0 insulin pump and DS5) • Visit 15 ○ window start from visit 13 ○ HbA1c samples analyzed at Central Lab in place of local lab 18) Table 5. Visit Details and Activities updated accordingly 19) Section 9.1.1 Pump Settings and Sensor Site 20) Sentence added to guide subjects enrolling for the Continuation Phase only 21) Section 9.1.2 Unscheduled Visit updated with DS5 sensor training 22) Section 9.1.3 Early Termination Visit updated to specify analysis location between local and central lab 23) Section 9.3.1 Reconsent for the updated Continuation Phase	18) Per updated Study Design 19) Per updated study visits 20) Per updated Study Design 21) Per updated Study Design 22) Per updated Study Design 23) Per updated Study Design	18) None 19) None 20) None 21) None 22) None 23) None		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	24) Paragraph added to offer the possibility for the subject to stay until the end of the study phase in case of no reconsent	24) Per updated Study Design	24) None		
	25) Section 9.4 Randomization and Treatment Assignment updated to include second randomization added at V13	25) To be in line with updated endpoints of the Continuation Phase	25) None		
	26) Section 9.4.2 Continuation phase added	26) Per updated Study Design	26) None		
	27) Section 9.5.3 HbA1c updated to reflect HbA1c samples analyzed at the Central Lab under National Glycohemoglobin Standardization Program (NGSP)	27) Per updated Study Design	27) None		
	28) Section 10 Risks and Benefits updated about the 2 new investigational device, sentence added: There is no additional risks associated with the new devices of the continuation phase.	28) Per updated Study Design	28) None		
	29) Section 11.4 Notification of Adverse Events	29) Per updated Study Design	29) None		
	30) Table 9 updated (previously Table 10) to reflect report requirements	30) Per updated Study Design	30) None		
	31) Section 12.3 Central Lab added and Table 11 added	31) Per updated Study Design	31) None		
	32) Administrative changes throughout the document	32) Updates made as needed to formatting throughout document	32) None		
D	1) Updated Table 4 to clarify return of unused DS5	1) Correction	1) None	Not applicable	[redacted], Sr. Medical Writer

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	2) Updated Section 8.1 to add "approximately" 3) Updated Table 5 to add clarification about remote management and make footnotes uniformed 4) Updated Section 9.3.1 to add "amended" 5) Updated Section 14.4 for clarity around analysis 6) Updated Section 14.5.1 to add rationale around non-inferiority margin and correct margins 7) Updates to formatting/spelling mistakes throughout	2) To include sites that are enrolling less than 5 3) Correction 4) Correction 5) Per MHRA request 6) Per MHRA request 7) Corrections	2) None 3) None 4) None 5) Yes 6) Yes 7) None		[redacted] Sr. CRS
E	1) updated Study Product Name to add DS5 2) updated Objective (Synopsis and Section 4.1) to align with Continuation Phase objective 3) updated Exclusion criteria (Synopsis and Section 8.4) 4) Updated Section 8.5.2 to correct a typo 5) Updated section 9.1 to move reconsent procedure from V11 to V13	1) Correction 2) Per FIMEA request 3) Correction 4) Correction 5) Correction	1) None 2) None 3) None 4) None 5) None	Not applicable	[redacted] Pr. CRS