



SMILE

Study of MiniMed™ 640G Insulin Pump with SmartGuard™
in prevention of **Low Glucose Events**
in adults with Type 1 diabetes

Clinical Investigation Plan

Version 1.0

15FEB2016

CEP 311

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A SYNOPSIS

Title

SMILE - Study of MiniMed™ 640G Insulin Pump with SmartGuard™ in prevention of Low Glucose Events in adults with Type 1 diabetes (CEP311).

Purpose

The aim of the study is to evaluate the efficacy of sensor augmented pump (SAP) therapy with MiniMed™ 640G and SmartGuard™ in preventing hypoglycemic events in comparison with continuous subcutaneous insulin infusion (CSII) therapy in type 1 diabetes adults with an increased risk of hypoglycemia.

Design

A pre-market, multi-center, prospective, open label, adaptive, randomized controlled study.

Medical device/product

The following CE-marked products will be provided during the course of the study:

- MiniMed™ 640G Insulin Pump (MMT-1711,mmol/L) or (MMT-1712,mg/dL).
Subjects already using a MiniMed™ 640G pump will not be provided with a pump for the purpose of this study and will continue using their own pump.
- CareLink™ USB 2 (MMT-7306)
- CareLink™ Clinical Therapy Management Software version 5.1 (MMT-7334) or subsequent versions
- MiniMed™ Quick-set™, MiniMed™ Mio™, MiniMed™ Silhouette™, MiniMed™ Sure-T™ and MiniMed™ Mio™ 30 infusion sets (detailed list in appendix L.4).
- MiniMed™ Reservoirs: 1.8 mL (180-unit, MMT-326A) or 3.0 mL (300-unit, MMT-332A)
- Enlite™ One-Press sarter (MMT-7512)
- CONTOUR™ NEXT LINK 2.4 meter by Ascencia (MTT-1151,mmol/L) or (MMT-1152,mg/dL) referred to as the study meter throughout this protocol
Subjects already using a CONTOUR™ Next Link 2.4 meter will not be provided with a meter for the purpose of this study and will continue using their own meter.
- CONTOUR™ NEXT Strips by Ascencia
- CONTOUR™ NEXT Control Solution by Ascencia
- GST3C transmitter accessories:
 - Charger (MMT-7715)
 - Watertight Tester (MMT-7726)
 - USB cable and Wall-powered adapter (MMT-7747)

The following investigational products will be provided during the course of the study:

- Enlite™ 3 sensor (MMT-7020)
- GST3C transmitter (MMT-7811)
- GST3C transmitter accessories:
 - GST3C Dock (T8381)
 - GST3C Download Utility (9029393)

The following CE-marked products are not licensed in Canada and will be considered investigational in Canada:

- MiniMed™ 640G Insulin Pump (MMT-1711, mmol/L) or (MMT-1712, mg/dL).
- CONTOUR™ NEXT LINK 2.4 meter by Ascencia (MTT-1151, mmol/L) or (MMT-1152, mg/dL).

Objectives and endpoints

Primary Objective:

The primary study objective is to demonstrate a reduction in the mean number of hypoglycemic events when using the MiniMed 640G system with the SmartGuard algorithm:

The between group difference in the incidence of hypoglycemic events below or equal 55 mg/dL (3.0 mmol/L) during 6 months of SAP therapy with SmartGuard, as compared to patients on CSII therapy alone over the same period of time, in a population of T1 diabetic patients with an increased risk of hypoglycemia, will be evaluated. A reduction in the mean number of hypoglycemic events below the threshold of 55 mg/dL (3.0 mmol/L) is estimated to be of clinical value.

The evaluation will be made by comparing subject sensor data collected in both groups.

Secondary objectives:

Secondary objectives will aim at evaluating the difference in glycemic parameters and HbA1c.

Primary endpoint:

Mean number of sensor glucose hypoglycaemic events below or equal to 55 mg/dL (3.0 mmol/L) per patient/week. The mean number of sensor glucose hypoglycaemic events will be calculated in each study arm and a between group comparison will be performed. Sensor glucose data for the primary endpoint will consist of 6 weeks of sensor readings in both arms in the randomization phase (as illustrated in Figure 1 (2 weeks (Visit 10 to 11) + 2 weeks (Visit 12 to 13) + 2 weeks (Visit 14 to 15))).

A hypoglycemic event is defined as sensor glucose values of 55 mg/dL (3.0 mmol/L) or less for more than 20 consecutive minutes. When the time between two successive events is less than 30 minutes, they will be combined and counted as one event.

Secondary endpoints:

- Mean number of sensor glucose hypoglycemic events ≤ 40 mg/dL (2.2 mmol/L), ≤ 55 mg/dL (3.0 mmol/L) and ≤ 70 mg/dL (3.9 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Mean Time spent and AUC of sensor glucose values below or equal 40 mg/dL (2.2 mmol/L), 55 mg/dL (3.0 mmol/L) and 70 mg/dL (3.9 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Mean Time spent and AUC of sensor glucose values above 180 mg/dL (10.0 mmol/L), 240 mg/dL (13.3 mmol/L), and 300 mg/dL (16.7 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Mean Time spent of sensor glucose values within range and including 70-140 mg/dL (3.9 -7.8 mmol/L) and 70-180 mg/dL (3.9-10.0 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Mean sensor glucose values surrounding SmartGuard triggered insulin suspensions lasting <30 , ≥ 30 to <90 , and ≥ 90 to 120 minutes. Mean sensor glucose values 60 min before and up to 360 min after suspend before low is activated categorized by suspensions lasting less than 30, ≥ 30 to <90 , ≥ 90 to 120 minutes, and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Proportion of Suspend before low events that reached the pre-set Low Limit calculated, as per the individualised Low Limit settings at any given time point.
- Excursion amplitudes of the glucose values measured by mean amplitude of glycaemic excursions (MAGE), 24-hour standard deviation (SD) of glucose values.
- Mean HbA1c change from baseline to 6 months and stratified by baseline HbA1c level $\leq 7.5\%$ and $>7.5\%$.

Tertiary endpoints / descriptive analyses:

These will include and are not limited to the following (and also described in the Statistical Analysis Plan):

- Safety endpoints: Number of severe hypoglycemic events, diabetic ketoacidosis events, (Serious) Adverse Events, (Serious) Adverse Device Effects and Device Deficiencies (see F.6 for definitions).
- Hypoglycemia-related number and mean duration of hospitalizations, number and mean duration ICU (intensive care unit) care, number of emergency room admissions, number of events requiring ambulance assistance and number of lost days from school or work.
- Mean HbA1c level and mean number of sensor hypoglycemia events per week will be reported by age group, duration of diabetes, duration of pump therapy at time of screening, type of insulin analog used in study
- Mean number of SMBG
- Mean Clarke, Gold, HFS and DTSQ questionnaire score.
- Mean weight and mean insulin total daily delivery dose.

Subject population

Adults (aged 24 to 75 years) diagnosed with Type 1 Diabetes Mellitus with disease duration of 10 years or more before screening and currently on CSII therapy for at least 6 months will be included in this study. Subjects can be naïve or experienced with the MiniMed 640G insulin pump, but should not have been on CGM therapy for at least 3 months prior to screening.

Sample size calculations have shown that 136 subjects (68 in each arm) need to complete the study. Taking into account the anticipated drop-out of 10% at screening, 15% at run-in and 15% during the 6 month follow-up period, it is calculated that 210 subjects need to be screened, in order to have 189 subjects starting the run-in phase, and 160 randomized subjects.

This study is an adaptive design. Adjustment to the required number of patients will be re-assessed by an independent DSMB at interim analysis.

Up to 25 study centers across Europe, Canada and potentially other geographic regions will be selected at study start, based on each investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures, and their potential to randomize an average of 9 subjects within the 6 month enrollment period. The number of investigational sites or period of enrollment may be increased to accommodate a quicker or larger enrollment.

Overall study duration from first subject enrollment until the last subject exits the study is expected to be 18 months, including an estimated period of 6 months to activate all sites, a 6 month enrollment period, and a 6 month follow-up period for each subject.

Treatment

All enrolled subjects will start a run-in phase, receive training and start CSII therapy with the MiniMed 640G insulin pump and usage of blinded Continuous Glucose Monitoring (CGM). Eligible subjects that meet the randomization criteria assessed after the run-in phase will be randomized into the treatment phase of 6 months:

- Treatment Arm: training and start of Sensor Augmented Pump therapy with Suspend before Low feature of SmartGuard turned ON.
- Control Arm: continuation of CSII therapy alone with blinded CGM usage for a total of 6 weeks during the treatment phase.

Inclusion criteria

Subjects will be considered for enrollment in the study, if they meet all of the following criteria, assessed after subject has signed informed consent:

1. Age 24-75 years old at time of screening.
2. Diagnosed with Type 1 diabetes ≥ 10 years prior to screening.
3. On CSII therapy for ≥ 6 months prior to screening.
4. Not on Real Time Continuous Glucose Monitoring for ≥ 3 months prior to screening.
5. HbA1c value $\geq 5.8\%$ and $\leq 10.0\%$ as assessed by local lab ≤ 15 days prior to screening or performed at screening.
6. A documented Severe Hypoglycemia event ≤ 12 months prior to screening, OR
Clarke score ≥ 4 assessed at time of screening, OR
Gold score ≥ 4 assessed at time of screening.
7. Subject is willing to sign and date informed consent, comply with all study procedures and wear all study devices as required during the study.

Exclusion criteria

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

1. Untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis, per investigator judgment.
2. Renal failure defined by creatinine clearance < 30 ml/min, as assessed by local lab test ≤ 3 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations.
3. Hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices, per investigator judgment.
4. Current pregnancy or intention to conceive.
5. Any unresolved adverse skin condition in the area of sensor placement (e.g. psoriasis, rash, Staphylococcus infection).
6. Alcohol or drug abuse, other than nicotine, per investigator judgment.
7. Any other disease or condition that may preclude the patient from participating in the study, per investigator judgment.
8. Legally incompetent, illiterate or vulnerable person.

Randomization criteria

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

1. Subject has worn two weeks the sensor with transmitter during the run-in period.
2. Subject has shown acceptable tolerance of Enlite 3 sensor wear, per investigator judgment.
3. Subject performed ≥ 4 finger stick blood glucose measurements daily, as determined by CareLink Clinical data upload as the mean number of SMBG/day over the past 14 days (SMBG number / day ≥ 3.5 rounds up to 4).
4. Subject showed ability to comprehend the pump training and study procedures, per investigator judgment.

Clinical Procedures

Figure 1: Study design overview

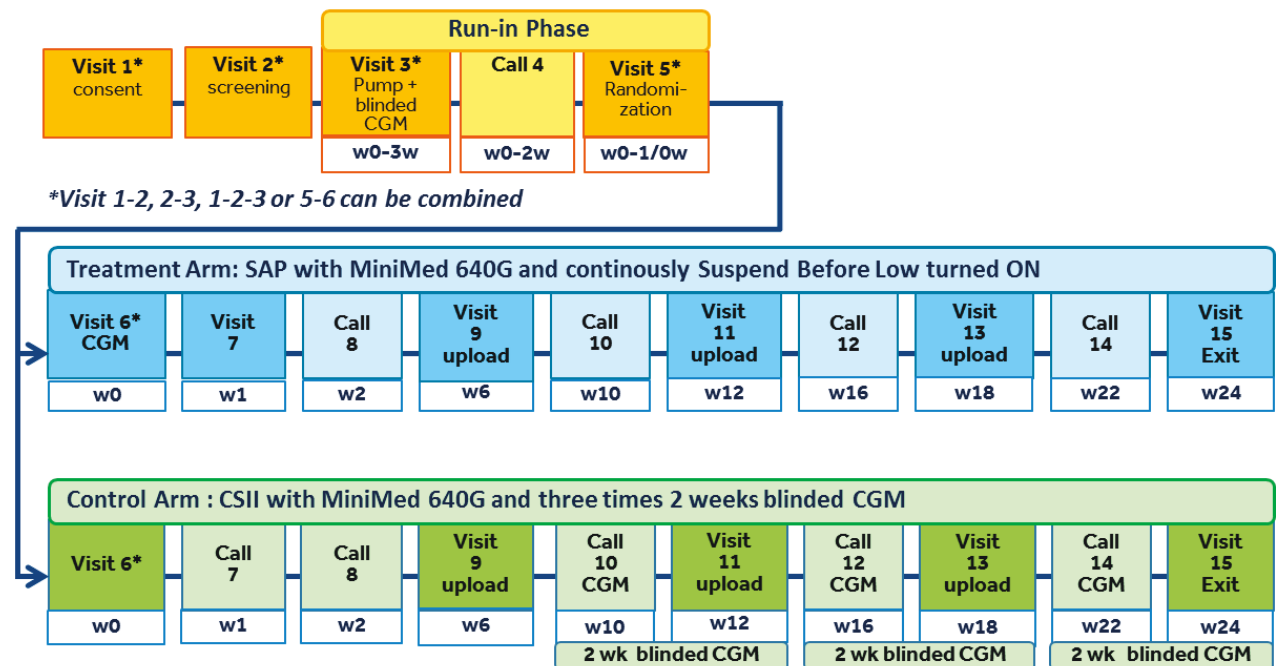


Table 1 Study procedures and data collection

Procedures and Data collection	Enrollment ¹	Screening ¹	Start Run-in ¹	Call	End Run-in/ Randomization ²	Start Treatment ²	1w call/visit	2w call	6 w Visit	10w call	12w visit	16w call	18w visit	22w call	End of Study	Early Termination ⁶
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Target week	w0	w0	w0-3w	w0-2w	w0-1w	w0	w1	w2	w6	w10	w12	w16	w18	w22	w24	
Target day	d0	d0	V2	V3+7d	V4+7d	V5	V6+ d7	V6+ d14	V6+ d42	V6+ d70	V10+ d14	V6+ d112	V12+ d14	V6+ d154	V14+ d14	
Window	-	-	+7d	+3d	+7d	+14d	±3d	±3d	±7d	±7d	+7d	±7d	+7d	±7d	+7d	
Informed consent	X															
Eligibility criteria		X														
Randomization criteria					X											
Demographics		X														
Medical history		X														
A1c (local lab)		O ³									X				X	X
Creatinine test (local)		O ³														
Device Accountability			X		X	X			X		X		X		X	X
MiniMed640G training			X													
CGM training						T ⁴										
Blinded CGM training			X						C ⁵							
Blinded CGM placement			X	X						C		C		C		
Blinded CGM upload					X						C		C		C	C
CareLink Clinical upload					X	X	T		X		X		X		X	X
Distribution supplies			X		X	X			X		X		X			
Clarke questionnaire		X									X				X	X
Gold Questionnaire		X									X				X	X
HFS questionnaire		X									X				X	X
DTSQs questionnaire		X												X		X
DTSQc questionnaire														X		X
AEs and Deficiencies																
Study deviations																

¹ Visit 1-2, 2-3, 1-2-3 can be combined; ² Visit 5-6 can be combined; ³ O = Optional. Only for subjects who did not have a recent test (see Visit 2: Screening for details); ⁴ T = Treatment arm; ⁵ C = Control arm; ⁶ Early Termination visit should be performed at any time if patient withdraws after randomization (Visit 5) and before the end of the study (Visit 15).

B GENERAL INFORMATION

B.1 Introduction

Managing type 1 diabetes requires constant vigilance and attention to diet, exercise, and insulin regimens, and depends on consistently delivering the right amount of insulin at the right time. Medtronic's insulin delivery systems have been helping type 1 diabetes patients with their diabetes management for more than 30 years. The insulin pump system is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. Technological advances in insulin pump delivery systems and key clinical trials have established the value of this therapy in helping patients with their daily diabetes management.

First improvement was real-time continuous glucose monitoring (CGM) data, used in conjunction with insulin pump therapy, allowing patients to safely reduce their HbA1c values in comparison with multiple daily injection (MDI) therapy [1] and continuous subcutaneous insulin injections (CSII) alone [2] by using CGM data to guide them in their insulin dosing regimen. Thereafter a feature was introduced, called Low Glucose Suspend (LGS), allowing the pump to automatically suspend insulin delivery when a pre-set sensor glucose threshold was reached. When this LGS feature is enabled in a Paradigm® Veo™ pump and a sensor glucose value at or below the pre-specified value is detected, the pump will stop insulin delivery for up to 2 hours, if not restarted earlier by the user. The benefits of sensor-augmented pump (SAP) therapy using this feature has been proven in several clinical trials, showing reduction in the incidence, severity and duration of hypoglycemic events [3, 4, 5]. In addition, also data analyses based on routine real world use of pumps with the LGS feature confirm significant reductions in hypoglycemia [6, 7]. The most recent advancement in SAP therapy is SmartGuard™. Medtronic's SmartGuard technology is implemented in the recently commercialized MiniMed™ 640G system and consists of the algorithms called, suspend on low, and suspend before low. The suspend on low is similar to the LGS algorithm in the Paradigm Veo pump and the Suspend before low feature, also called Predictive Low Glucose Management (PLGM), is the newest sensor algorithm that can suspend insulin delivery when the sensor glucose value is predicted to reach or fall below a pre-set low glucose limit within 30 minutes. In addition, the Suspend before low algorithm allows for automatic resumption of basal insulin delivery after 30-120 minutes, if the system predicts patient's recovery from hypoglycemia. During the suspension, insulin delivery can be manually resumed by the user at any time, and settings and alerts are customizable within multiple time blocks depending on the patient's needs in the MiniMed™ 640G system.

Suspending insulin delivery in response to predicted hypoglycemia has been tested in several in-clinic studies employing various investigational configurations of pumps, sensors, induction protocols, and algorithms [8, 9, 10]. One of these studies involving increases in basal insulin delivery rates, noted overnight hypoglycemia in 9 of 10 participants in the control arm, compared to 2 of 10 participants in the predictive pump suspension arm [9]. Another report noted that exercise induced hypoglycemia was prevented with the predictive suspension feature in 80% of the successful experiments [10]. Furthermore, this data was confirmed in a user evaluation study of the MiniMed 640G system (four weeks follow-up period, 40 Type 1 patients) demonstrating that, following 83% of suspend before low activations (out of 2300 suspend before low activations) the pre-set low limit threshold was not reached [11].

Hypoglycemia is an important barrier in achieving tight glycaemic control. Even mild events of hypoglycemia have been shown to disrupt sleep, impair memory, and cause inflammatory reactions, with impacts on driving, work and daily living. Approximately one-third of patients with type 1 diabetes have evidence of impaired hypoglycemia awareness [12, 13, 14], further increasing their risk of severe hypoglycemia. However, avoidance of hypoglycemia in these patients has been shown to restore awareness in small scale proof of concept studies [15, 16]. Till now, most studies of CSII and CGM

therapy have excluded these patients, and therefore, there are few studies to demonstrate if these technologies can provide an improvement specifically in this population.

The SMILE study will specifically recruit subjects with impaired awareness of hypoglycaemia and aim to investigate if this technology can reduce the incidence of hypoglycemia in this group of high risk patients.

Despite the available clinical evidence, as described above, SAP therapy is not widely adopted, partly because CGM is not yet reimbursed in many countries. The current clinical evidence on the ability of SAP to reduce the risk of hypoglycemic events [3, 4, 5] could be considered as not robust enough (e.g. short study duration, small number of subjects, not the right comparator, sub-optimal randomization process). Additional clinical evidence on the ability of SAP with SmartGuard technology to reduce the risk of hypoglycemic events can potentially lead to wider adoption and reimbursement of CGM technology to benefit patients' needs.

In-clinic studies on MiniMed 640G with the Suspend before low feature of SmartGuard demonstrated the safety and the efficacy of the investigational configuration of this system after induced hypoglycemia [8] [9] [10]. Additional clinical evidence with the MiniMed 640G system and SmartGuard algorithm are required to evaluate the efficacy in in-home settings for a longer duration and with more 'real life' variables inducing hypoglycemia, in comparison with CSII therapy, as the current standard of care, to support SAP therapy adoption and CGM reimbursement.

Table 2 Clinical evidence SAP therapy with SmartGuard

Study	Design	Primary endpoint	Status
Buckingham	42-night RCT, Investigational PLGM algorithm ON overnight vs OFF N= 81 pediatrics	Test PLGM algorithm overnight Percent time	Published. Diabetes Care 2010;33:1013-1017
PILGRIM	1 day in clinic , Investigational PLGM algorithm, N=22 pediatrics	Test PLGM algorithm after exercise induced hypoglycemia	Published. DTT Jun2014;16(6):338-47
T. Jones	1 day in clinic, N=21 pediatrics	Test algorithm with bolus and exercise induced hypoglycaemia	Published. DTT Feb 2014; 16(Suppl 1): A-1-A-162, IJPE 2015; (Suppl 1):O36.
User Evaluation	4wk Observational SmartGuard ON, N=24 adults +16 pediatrics	User acceptance MiniMed 640G (1.8ml pump)	Publication accepted DTT 2016
SportGuard	2w RCT, SmartGuard ON vs OFF N=98 pediatrics	Event rate events <65 mg/dL (<3.6mmol/L)	Completed
T. Jones	6m RCT, SmartGuard ON vs OFF N ~176 pediatrics	Time spent in events <3.5 mmol/L, 40% reduction	Ongoing
T. Danne	8w RCT, SmartGuard 2w OFF then 6w ON, N ~24 pediatrics	AUC <70 mg/dl (3,9 mmol/L)	Ongoing
S. Lablanche	6m RCT, SmartGuard ON vs OFF, N ~20 adults	Event rate events <65 mg/dL (<3.6mmol/L)	Ongoing

B.2 Device information

The Medtronic MiniMed™ 640G System evaluated in this study includes investigational and CE-marked, commercially available, device components, which will all be used within their intended use.

The following CE-marked products will be provided during the course of the study:

- MiniMed™ 640G Insulin Pump (MMT-1711, mmol/L) or (MMT-1712, mg/dL).
Subjects already using a MiniMed™ 640G pump will not be provided with a pump for the purpose of this study and will continue using their own pump.
- CareLink™ USB 2 (MMT-7306)
- CareLink™ Clinical Therapy Management Software version 5.1 (MMT-7334) or subsequent versions
- MiniMed™ Quick-set™, MiniMed™ Mio™, MiniMed™ Silhouette™, MiniMed™ Sure-T™ and MiniMed™ Mio™ 30 infusion sets (detailed list in appendix L.4).
- MiniMed™ Reservoirs: 1.8 mL (180-unit, MMT-326A) or 3.0 mL (300-unit, MMT-332A)
- Enlite™ One-Press sarter (MMT-7512)
- CONTOUR™ NEXT LINK 2.4 meter by Ascencia (MTT-1151, mmol/L) or (MMT-1152, mg/dL), referred to as the study meter throughout this protocol
Subjects already using a CONTOUR™ Next Link 2.4 meter will not be provided with a meter for the purpose of this study and will continue using their own meter.
- CONTOUR™ NEXT Strips by Ascencia
- CONTOUR™ NEXT Control Solution by Ascencia
- GST3C transmitter accessories:
 - Charger (MMT-7715)
 - Watertight Tester (MMT-7726)
 - USB cable and Wall-powered adapter (MMT-7747)

The following investigational products will be provided during the course of the study:

- Enlite™ 3 sensor (MMT-7020)
- GST3C transmitter (MMT-7811)
- GST3C transmitter accessories:
 - GST3C Dock (T8381)
 - GST3C Download Utility (9029393)

The following CE-marked products are not licensed in Canada, and will be considered investigational in Canada:

- MiniMed™ 640G Insulin Pump MMT-1711 (mmol/L) or MMT-1712 (mg/dL)
- CONTOUR™ NEXT LINK 2.4 meter by Ascencia (MTT-1151, mmol/L) or (MMT-1152, mg/dL).

All devices and consumables for diabetes pump therapy mentioned above and in appendix L.4 will be provided to the subjects for the duration of the study except for the subjects already using a MiniMed™ 640G insulin pump and/or a CONTOUR™ NEXT LINK 2.4 meter, who will continue with their own device(s) for the study.

Any subsequent model of the above mentioned devices is also eligible, as soon as it becomes commercially available in the participating countries.

Usage of CareLink™ Personal and CareLink™ Pro Therapy Management Software is optional per routine practice by the subjects and sites. Usage of other market released infusion sets and consumables (e.g. Lancets) are optional and prescribed per routine practice.

For additional product information on software applications, correct classification and regulatory status, materials used, installations for use, storage and handling, and the necessary medical procedures involved in the use of each device system/product, refer to the Instructions for Use or Investigator Brochure of each product.

The labeling of the Investigational devices and CE marked devices will be provided in accordance with local language requirements.

Investigational devices and consumables will be labeled as required by national regulations, in local language(s) as follow:

- UK: "Investigational Device. To be Used by Qualified Investigators Only"
- Canada: "Investigational Device. To be Used by Qualified Investigators Only" "Instrument de recherche. Réservé uniquement à l'usage de chercheurs compétents"
- Italy: "Esclusivamente per indagini cliniche"
- The Netherlands: "uitsluitend voor klinisch onderzoek"
- France: "Usage réservé aux études cliniques"

Previous training and experience on the MiniMed 640G system is preferred for the participating centers, as assessed during site qualification.

The subject can use any rapid-acting analogue insulin (e.g. Lispro, Aspart or Glulisine) compatible with CSII during the study, which will be prescribed per routine practice.

The site personnel will be requested to upload subjects' MiniMed 640G insulin pump data using the CareLink Clinical Therapy Management Software at each subject's visit.

B.2.1 Medtronic MiniMed 640G Insulin Pump

The device evaluated in this study is the Medtronic MiniMed 640G insulin pump, which is the latest commercialized version of Medtronic's MiniMed insulin pumps (Figure 2). The MiniMed 640G system is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

In addition, the pump system is indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin, and possible low and high blood glucose events. The pump displays continuous glucose values and stores this data so that it can be analyzed to track patterns and improve diabetes management. Pump history can be downloaded to a computer for analysis of historical glucose values.

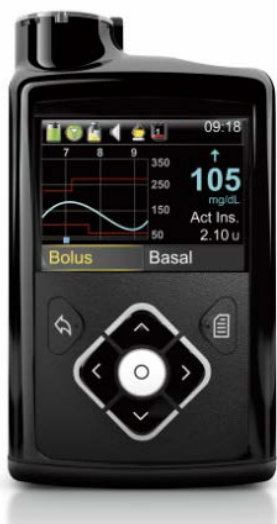
This new pump system has, in comparison to the previous models, an enhanced personalized convenience (e.g. preset bolus, basal pattern options, louder and volume-adjustable alerts) and a more patient-friendly design (e.g. waterproof, color- and auto-brightness display, intuitive screen navigation, ergonomic design).

The MiniMed 640G insulin pump also includes the new SmartGuard technology, which can be programmed with the usage of the Continuous Glucose Monitoring (CGM) components (see section B.2.2). The MiniMed 640G Insulin pump (MMT1711 (mmol/L) or MMT1712 (mg/dL)) is a CE-marked medical device and is commercially available in the countries where the study will be conducted with the exception of Canada, where the device will be investigational.

Contraindications:

Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day; who are unwilling or unable to maintain contact with their healthcare professional; and/or whose vision or hearing does not allow recognition of pump signals and alarms.

Figure 2: Medtronic MiniMed 640G insulin pump



B.2.2 Continuous Glucose Monitoring (CGM)

The MiniMed 640G insulin pump can combine insulin delivery and Continuous Glucose Monitoring (CGM). The CGM system used in this study includes an Enlite 3 sensor measuring glucose levels in the interstitial fluid and the GST3C transmitter, which connects to the sensor and sends glucose readings to the MiniMed 640G insulin pump, where the glucose readings are displayed on the monitor (Figure 3 and Figure 4). Using a Enlite 3 sensor allows users to receive up to 288 sensor glucose readings every 24 hours for a period of 7 days. CGM alert features can help diabetes patients by making them aware of high and low glucose values. The graphs and trend arrows on the pump display show users the direction glucose levels are moving towards.

Furthermore, the MiniMed 640G insulin pump includes SmartGuard technology. With SmartGuard, basal delivery can be suspended to minimize hypoglycemia, if the sensor glucose level is less than 70 mg/dL (3.9 mmol/L) above the preset low limit and predicted to reach 20 mg/dL (1.1 mmol/L) above the low limit within 30 minutes. The suspended basal insulin delivery can be resumed if the patient manually resumes it, or the sensor value is at least 20 mg/dL (1.1 mmol/L) above the preset low limit and predicted to be greater than 40 mg/dL (2.2 mmol/L) above the preset low limit within 30 minutes, or insulin delivery has been suspended for 2 hours.

B.2.3 The Enlite 3 Sensor (MMT-7020) and Enlite One-Press Serter (MMT-7512)

The Enlite 3 sensor, referred to as the “sensor” in this protocol, is an investigational medical device. It may become CE-marked and commercially available during the course of the study.

The Enlite 3 Sensor is intended for use with Medtronic Diabetes glucose sensing systems to continuously monitor glucose levels in persons with diabetes.

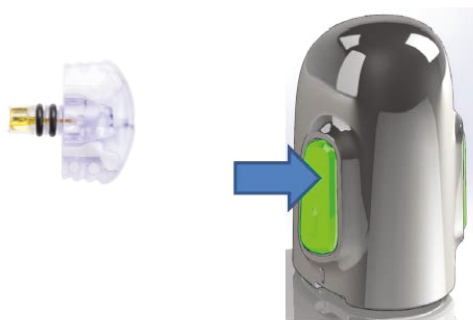
The Enlite 3 Sensor is an electrochemical sensor that contains microelectrodes with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. It is intended to penetrate the skin at a 90-degree angle, similar to the currently market released Enlite sensor (MMT-7008). The sensor is tubeless and as a result has a smaller volume than previous Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The device is affixed to the skin with an adhesive and is attached to a transmitter. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter, 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.

Contraindication: None known.

The Enlite One-Press serter (MMT-7512) is CE-marked in Europe and licensed in Canada

It is used to ensure correct placement of the Enlite 3 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 and multi-use device.

Figure 3: Enlite 3 Sensor and One-Press inserter



B.2.3.1 GST3C Transmitter (MMT-7811) and Charger (MMT-7715)

The GST3C Transmitter is an investigational medical device which is not yet CE-marked nor commercially available at the time this document is finalized (Figure 4). The GST3C transmitter may become CE-marked and commercially available during the course of the study.

The transmitter is indicated for single-patient use as a component of select Medtronic continuous glucose sensing systems and MiniMed sensor-enabled pump systems. Once the sensor has been inserted, the transmitter is connected directly to the sensor where it receives the electronic signal from the sensor electrode, converts the signals into glucose data, and transmits the glucose data to the pump.

The information that the GST3C transmitter collects is intended to supplement, not replace, blood glucose information obtained using standard home glucose monitoring devices (SMBG).

The Charger (MMT-7715) is a CE-marked and commercially available medical device used to recharge the GST3C Transmitter's battery as needed. A fully charged battery provides up to 7 days of GST3C Transmitter use.

Contraindications: Transmitter must not be exposed to MRI equipment, diathermy devices, or other devices that generate strong magnetic fields.

Figure 4: GST3C Transmitter and GST3C Charger



Transmitter

Transmitter + Sensor

Charger

B.2.4 CONTOUR NEXT LINK 2.4 Blood Glucose Meter

The study meter is provided for use in conjunction with the MiniMed 640G insulin pump (Figure 5). The meter determines the subject's capillary blood glucose level and wirelessly transfers the measurements to the MiniMed 640G insulin pump so that the patient can respond to high and low glucose levels. The study meter can be used for CareLink data uploads as well as for remote bolusing. All blood glucose measurements should only be performed using this glucose meter exclusively during the run-in and 6 month treatment phase. The CONTOUR NEXT LINK 2.4 is CE marked by Ascencia.

All potential complaints related to the meter must be reported to Ascencia directly.

Figure 5: CONTOUR NEXT LINK 2.4 meter



B.2.5 Medtronic CareLink™ Therapy Management Software (MMT-7334)

Medtronic CareLink™ Therapy Management Software for Diabetes is a CE-marked medical device. This web-based CareLink system allows device data (e.g. feature settings, insulin delivery and glucose information) to be viewed and easily evaluated by the patient and physician. A computer links to the Medtronic CareLink™ system via the Internet and allows for upload of data from Medtronic MiniMed 640G Systems.

All references to CareLink are meant to imply the clinical support version of Medtronic CareLink™ Therapy Management Software and throughout the protocol will be referred to as 'CareLink Clinical'.

For the purpose of this study, uploads are performed by study site personnel during each subject's site visit. The data contained in CareLink Clinical is accessible to study site personnel in a secured manner, using a standard browser (i.e., Microsoft Internet Explorer on an Internet enabled personal computer) and a unique study username (i.e., 311-XXX-XXX) and password created for each subject.

B.2.6 Medtronic CareLink™ USB 2 (MMT-7306)

The Medtronic CareLink™ USB 2 device enables data from the MiniMed 640G insulin pump to be uploaded into the Medtronic CareLink™ Therapy Management Software. CareLink USB 2 is only compatible with the MiniMed 640G insulin pump and cannot be used with prior Medtronic Paradigm pumps. CareLink™ USB 2 and the study meter are the only devices capable of uploading pump data to CareLink from the MiniMed 640G insulin pump. The Medtronic CareLink™ USB 2 will be provided to each center and is CE marked (Figure 6).

Figure 6: CareLink USB 2



B.3 Comparator information

Subjects in the control arm will be using CSII therapy with the MiniMed 640G insulin pump without CGM, which represents the most common use of CSII therapy across Europe. The goal is to demonstrate the added value and benefit of adding CGM with the Suspend before low feature of SmartGuard to the MiniMed 640G pump therapy.

The GST3C device (MMT-7811) will be used as a blinded continuous glucose recording system for study purposes during the run-in phase for all subjects, and during the treatment phase in the control arm for a total period of 6 weeks, to collect sensor glucose data.

B.3.1 GST3C System for blinded continuous glucose monitoring

The GST3C system consists of the following components:

- GST3C transmitter (MMT-7811) used in a blinded recording mode – *Investigational*
- Enlite 3 Sensor (MMT-7020) - *Investigational*
- GST3C Dock (T8381) - *Investigational*
- GST3C Download Utility Software for GST3C Transmitter (9029393) – *Investigational*
- Charger (MMT-7715)
- USB cable and Wall-powered adapter (MMT-7747)
- Watertight Tester (MMT-7726)

B.3.1.1 GST3C Transmitter, GST3C charger and Enlite 3 Sensor - Investigational

The GST3C transmitter attached to the Enlite 3 sensor will be used as a blinded continuous glucose recording system for the control arm recording and storing sensor glucose data. The GST3C transmitter will not be linked to the Minimed 640G pump, and therefore sensor data will not be transmitted to the pump. The sensor data the GST3C transmitter contains will be downloaded with the GST3C Download Utility software to a site computer. The recorded and transferred sensor data are blinded and not available to subjects and healthcare professionals. Therefore, this data cannot be used for therapy adjustment during the study, and will only be used for comparison with the treatment arm during study data analysis.

Contraindications: GST3C Transmitter must not be exposed to MRI equipment, diathermy devices, or other devices that generate strong magnetic fields.

B.3.1.2 Dock for GST3C Transmitters (T8381) - Investigational

The Dock for the GST3C Transmitter (T8381), referred to as GST3C Dock in this protocol, is an investigational device serving two functions:

1. It creates a communication link between the GST3C Transmitter and a computer to be used for uploading the data stored on the devices and clearing the data. In this function, a cable connects the GST3C Dock to a USB port on the computer.
2. It charges the internal battery of the GST3C Transmitter while it is docked in the Charger that is either connected to a computer (while the computer is on) or to a wall-powered adapter. The wall-powered adaptor configuration will only charge the recorder and will not provide the upload functionality.

When the GST3C Transmitter is removed from the sensor, a Watertight Tester (MMT-7726) is attached and then it is disinfected (see Figure 7). Once the Watertight Tester is removed, the GST3C Transmitter is connected to the GST3C Dock. The GST3C Dock is connected to the computer using a USB cable. The user can upload data from the GST3C Transmitter via the GST3C Download Utility. For the purposes of this study, uploads of the GST3C Transmitter are performed by the investigational study staff.

Contraindications: Not known

B.3.1.3 GST3C Download Utility (9029393) - Investigational

The GST3C Download Utility for use with the GST3C Transmitter is an investigational computer-based program used to set time, upload data and clear data for the GST3C Transmitter. Communication between the GST3C Transmitter and the computer is done via the GST3C Dock.

The data contained in the GST3C Download Utility is transferred to a secured database by site personnel, using a standard browser, i.e., Microsoft Internet Explorer on an Internet enabled computer and a unique username and password for each site. The GST3C Download Utility provides encrypted data that can't be used during the study for therapy adjustments.

Contraindications: Not known

B.3.1.4 USB cable and Wall-powered adapter (MMT-7747) for GST3C Dock

The USB cable and Wall-powered adapter (MMT-7747) is commercially available.

The small end of the Universal Serial Bus (USB) cable connects to the GST3C Dock. The other end of the cable connects to a USB port on a computer, so that the user can upload data using the GST3C Download Utility and charge the GST3C Transmitter. The USB cable can also be connected to a wall-powered adapter.

The wall-powered adapter lets the user charge the GST3C Transmitter by connecting the GST3C Dock to a regular socket, instead of a computer. It comes with 4 interchangeable power plugs. The appropriate power plug needs to be connected to the wall-powered adapter.

Contraindications: Not known

B.3.1.5 Watertight Tester (MMT-7726) – CE-marked

The Watertight Tester (MMT-7726) is a CE-marked and commercially available device that operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation (see Figure 7). It is used as a tester at initiation of the GST3C Transmitter.

Contraindications: Not known

Figure 7: Watertight Tester



Table 3 describes the total number of devices and consumables to be used on average by one subject for during the 6 months treatment phase:

Table 3: Number of devices per subject

Item	Units per Subject (Treatment Arm)	Units per Subject (Control Arm)
640G pump (3.0 mL)	1	1
Reservoir	100	100
Infusion Set	100	100
Infusion Set Serter (if applicable)	1	1
AA Alkaline Battery	28	28
CONTOUR NEXT LINK 2.4 meter	1	1
CONTOUR NEXT Strips	1700	1700
Enlite 3	44	16
Enlite One-press Serter	1	1
GST3C Transmitter	2	2

C STUDY PLAN

C.1 Study objectives

The purpose of the study is to evaluate the efficacy of sensor augmented pump (SAP) therapy with MiniMed 640G and SmartGuard technology in preventing hypoglycemia events in comparison with continuous subcutaneous insulin infusion (CSII) therapy alone in Type 1 diabetes adults with an increased risk of hypoglycemia.

As previously described in Section B.2, the new MiniMed 640G system includes a Suspend before low feature of SmartGuard, which is intended to reduce the frequency and duration of hypoglycemic events by suspending insulin delivery before hypoglycemia occurs.

Regarding safety, all adverse events will be collected and an Clinical Events Committee (CEC) will be in charge of assessing all SAEs, SADEs, UADEs, Severe Hypoglycemia and Severe Hyperglycemia events, DKA and deaths (see section F.6.6).

As subject participation will be up to a maximum of 6 months, the determination of potential long-term effects is not planned in this study.

C.1.1 Primary objective

The primary study objective is to demonstrate a reduction in the mean number of hypoglycemic events when using the MiniMed 640G system with the Suspend before low feature of SmartGuard in a group of high risk patients with impaired awareness of hypoglycaemia. The between group difference in the incidence of hypoglycemic events below or equal 55 mg/dL (3.0 mmol/L) during 6 months of SAP therapy with SmartGuard, as compared to patients on CSII therapy alone over the same period of time, in a population of T1 diabetic patients with an increased risk of hypoglycemia, will be evaluated. A reduction in the mean number of hypoglycemic events below 55 mg/dL (3.0 mmol/L) is thought to be of clinical value. The evaluation will be made by comparing subject sensor data collected in both groups.

C.1.2 Secondary objectives

Secondary objectives will aim at evaluating the difference in glycemic parameters and HbA1c.

C.1.2.1 Difference in glycemic parameters

To evaluate the difference in glycemic parameters after 6 months between arms (see section C.2.2).

C.1.2.2 Between group HbA1c difference

To evaluate the change from baseline and the difference in HbA1c after 6 months between arms (see section (see section C.2.2)).

C.2 Clinical endpoints

C.2.1 Primary endpoint

The primary endpoint is defined as the mean number of sensor glucose hypoglycaemic events below or equal to 55 mg/dL (3.0 mmol/L) per patient/week. The mean number of sensor glucose hypoglycaemic events will be calculated in each study arm and a between group comparison will be performed. Sensor glucose data for the primary endpoint will consist of 6 weeks of sensor readings in both arms in the randomization phase (as illustrated in Figure 1 (2 weeks (from Call 10 to Visit 11) + 2 weeks (from Call 12 to Visit13) + 2 weeks (from Call 14 to Visit 15))).

The average of the mean number of sensor glucose hypoglycaemic events will be calculated in each study arm and a between group comparison will be performed.

A hypoglycaemic event is defined as sensor glucose values of 55 mg/dL (3.0 mmol/L) or less for more than 20 consecutive minutes. When the time between two successive events is less than 30 minutes, they will be combined and counted as one event.

Sensor glucose data will be collected during the 6 months of the study follow-up using the GST3C Transmitter + Enlite 3 sensor, used continuously in the treatment arm. A blinded CGM system with the GST3C transmitter + Enlite 3 sensor will be used for subjects in the control arm to collect sensor glucose data for 14 days at 10, 16 and 22 weeks.

C.2.2 Secondary endpoints

C.2.2.1 Frequency of hypoglycemic events

- Mean number of sensor glucose hypoglycemic events ≤ 40 mg/dL (2.2 mmol/L), ≤ 55 mg/dL (3.0 mmol/L) and ≤ 70 mg/dL (3.9mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00). Sensor glucose hypoglycemic events are defined as sensor glucose values equal or less than the predefined threshold that occur for more than 20 consecutive minutes. When the time between two successive events is less than 30 minutes, they will be combined and counted as one event.

C.2.2.2 Time spent and AUC in hypoglycemia

- Mean Time spent and AUC of sensor glucose values below 40 mg/dL (2.2 mmol/L), 55 mg/dL (3.0mmol/L) and 70 mg/dL (3.9mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).

C.2.2.3 Time spent and AUC in hyperglycemia

- Mean Time spent and AUC of sensor glucose values above 180 mg/dL (10.0 mmol/L), 240 mg/dL (13.3 mmol/L), and 300 mg/dL (16.7 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).

C.2.2.4 Time spent and AUC in euglycemia

- Mean Time spent of sensor glucose values within range and including 70-140 mg/dL (3.9 -7.8 mmol/L) and 70-180 mg/dL (3.9-10.0 mmol/L) and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).

C.2.2.5 HbA1c

- Mean HbA1c change from baseline to 6 months and stratified by baseline HbA1c level $\leq 7.5\%$ and $>7.5\%$.

C.2.2.6 Sensor glucose values surrounding SmartGuard events

- Mean sensor glucose values surrounding SmartGuard triggered insulin suspensions lasting <30 , ≥ 30 to <90 , and ≥ 90 to 120 minutes. Mean sensor glucose values 60 min before and up to 360 min after suspend before low is activated categorized by suspensions lasting less than 30, ≥ 30 to <90 , ≥ 90 to 120 minutes, and categorized by starting at daytime (08:01 to 21:59) and night-time (22:00 to 08:00).
- Proportion of Suspend before low events that reached the pre-set Low Limit calculated, as per the individualised Low Limit settings at any given time point.

C.2.2.7 Change in glycemic variability

- Excursion amplitudes of the glucose values measured by mean amplitude of glycaemic excursions (MAGE), 24-hour standard deviation (SD) of glucose values.

C.2.3 Tertiary endpoints / descriptive analysis:

These will include and are not limited to the following (and described in the Statistical Analysis Plan):

- Safety endpoints: Number of severe hypoglycemic events, diabetic ketoacidosis events, (Serious) Adverse Events, (Serious) Adverse Device Effects and Device Deficiencies (see F.6 for definitions).
- Hypoglycemia-related number and mean duration of hospitalizations, number and mean duration of ICU care, number of emergency room admissions, number of events requiring ambulance assistance and number of lost days from school or work.
- HbA1c level and mean number of sensor glucose hypoglycemic events per week will be reported by age groups, duration of diabetes, duration of pump therapy at time of screening, type of insulin analog used in study
- Mean number of SMBG
- Mean Clarke, Gold, HFS and DTSQ questionnaires scores.
- Mean Weight and mean insulin total daily delivery dose.

C.3 Study Hypothesis

The primary study hypothesis is described as follow:

Mean number of sensor glucose hypoglycaemic events below or equal to 55 mg/dL (3.0 mmol/L) per patient/week (MNSHE) will be calculated in the TREATMENT arm (SAP with MiniMed 640G and SmartGuard) and the CONTROL arm (CSII with MiniMed 640G) and will be compared using the next hypotheses:

Null-hypothesis: $H_0: \text{MNSHE}_{\text{TREATMENT}} = \text{MNSHE}_{\text{CONTROL}}$

Alternative hypothesis: $H_A: \text{MNSHE}_{\text{TREATMENT}} \neq \text{MNSHE}_{\text{CONTROL}}$

The null-hypothesis will be rejected in favor of the alternative hypothesis if the p-value of the two-sided two-sample t-test is less than 0.05. Once the null hypothesis is rejected a nested superiority test in favor of the treatment group will be performed while maintaining the overall type 1 error.

C.4 Study population

Adults (aged 24-75 years) diagnosed with Type 1 Diabetes Mellitus with disease duration of 10 years or more before screening and currently on CSII therapy for at least 6 months will be enrolled. Subjects present an increased risk of hypoglycemia. Subjects can be naïve or experienced with the MiniMed 640G insulin pump, but should not have been on CGM therapy for at least 3 months prior to screening.

Sample size calculations have shown that 136 subjects (68 in each arm) need to complete the study (section C.7). Taking into account an anticipated drop-out rate of 10% at screening, 15% at run-in and 15% during the 6 month follow-up period, it is calculated that 210 subjects need to be screened, in order to have 189 subjects starting the run-in phase, and 160 randomized subjects.

Up to 25 study centers across Europe, Canada and potentially other geographic regions will be selected at study start, based on each investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures, and their potential to randomize an average of 9 subjects within the 6 month enrollment period. The number of investigational sites and period of enrollment may be increased to accommodate a quicker and/or larger enrollment.

C.5 Study design

This is an international, multi-center, prospective, open-label, adaptive, randomized, controlled, pre-market clinical investigation with parallel groups. The study is designed to compare CGM-based hypoglycemic events in a treatment group to a control group. Groups are defined as:

- Treatment group: CSII with MiniMed 640G with CGM and Suspend before Low feature of SmartGuard turned ON (T)
- Control group: CSII with MiniMed 640G alone (C)

This study has an adaptive design. Due to the uncertainty about the hypoglycemic event rate and the magnitude of the true effect of treatment, the sample size will be re-estimated by Data Safety Monitoring Board (DSMB) in an interim assessment after a total of 60 subjects (30 treatment and 30 control group) have been randomized and followed up for 6 months. An interim analysis for sample size re-estimation will be based on the conditional power approach by Li et al. [17] and a method of by Chen et al. [18] as extended by Mehta and Pocock [19].

The interim analysis will be performed by a statistician unaffiliated with the sponsor or study statistician and member of the DSMB. Detailed instructions will be given to this statistician concerning the analysis, because it involves both the primary safety and efficacy endpoints.

The DSMB will share no data or results of analyses with the sponsor or sponsor's statistician, and present one of following messages to the sponsor after the interim analysis:

- Study has reached the futility boundary and it is recommended to be terminated for futility.
- Continue the study to its conclusion without modification of sample size or inclusion criteria.
- Increase the numbers of patients in each treatment group.
- Revise the inclusion criteria.

The statistician will prepare and save a report of the interim analysis. This report will be sent to the sponsor on completion of the study.

C.6 Randomization

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

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

Randomization will be performed via the electronic CRF.

In case technical issues occur with the electronic CRF (i.e. Internet access, system maintenance), a randomization list will be generated for each site by the statistician and the statistician will be able to communicate the randomization arm to the study team and site staff.

C.7 Sample size

The sample size calculation was performed based on assumptions from the results from the *ASPIRE study* [3]. In particular, the mean number of sensor glucose hypoglycemic events below or equal to 55 mg/dL (3.0 mmol/L) per patient/week is expected to be 2 in the arm with CSII with MiniMed 640G alone (control group) and standard deviation of 1.56.

Assuming $\alpha=0.05$, power=80% and 40% reduction in the mean number of sensor glucose hypoglycaemic events per patient/week in the treatment arm, as compared to the control arm, the required sample size is 136 subjects (68 in each arm).

The drop-out rate during the 6 month follow-up after randomization has been estimated to be 15%. Incorporating this drop-out rate, a total of 160 subjects will be randomized in a 1:1 ratio to either the arm using MiniMed 640G with CGM and SmartGuard or the arm using CSII with MiniMed 640G alone.

The following drop-out assumptions have been taken into account, based on experience with previous studies:

- At screening: 10%
- After run-in: 15%
- During 6 months follow-up: 15%

Based on these assumptions, the following estimations can be made: in total 210 subjects need to be screened, in order to have 189 starting the run-in phase and 160 randomized to start the treatment phase.

Due to the uncertainty about the magnitude of the effect of treatment, the sample size will be re-estimated by the independent DSMB in an interim assessment soon after a total of 60 subjects (30 treatment and 30 control group) have been randomized and followed up for 6 months.

Enrollment period is expected to be 6 months. It may be extended based on the outcome of the interim analyses.

C.8 Number of investigational sites and study duration

The study is planned to be conducted in Europe in the following countries: Netherlands, France, Italy, and the UK, where the MiniMed 640G system is commercially available. The study will also be conducted in Canada, where the MiniMed 640G system is not licensed and therefore will be investigational. Other geographic regions are also being considered. At the time this Clinical Investigation Plan was finalized, not all participating investigation sites were identified. A list of participating investigation sites will be available under a separate cover.

It is estimated that 205 subjects will have to be enrolled in up to 25 study centers, which will be activated over a period of 6 months (see also section C.7).

The recruitment period will be 6 months, but could be extended if needed. At the finalization of this document, recruitment of 11 subjects on average at each site is expected.

It is expected that each site should enroll a minimum of 7 subjects, to ensure each site has sufficient study execution knowledge and to minimize differences in center practice to avoid bias. In addition, limiting the number of sites should reduce time for site activation and recruitment. A maximum of 20 subjects per site is recommended.

The number of investigational sites may be increased to accommodate a quicker enrollment rate.

Overall study duration from first subject enrollment until the last subject exits the study is expected to be 18 months, including an estimated period of 6 months to activate all sites, 6 months enrollment period, and a 6 months follow-up period for each subject.

D SUBJECT SELECTION

D.1 Inclusion criteria at screening

Subjects will be considered for enrollment in the study, if they meet all of the following criteria, assessed after subject has signed informed consent:

1. Age 24-75 years old at time of screening.
2. Diagnosed with Type 1 diabetes ≥ 10 years prior to screening.
3. On CSII therapy for ≥ 6 months prior to screening.
4. Not on Real Time Continuous Glucose Monitoring for ≥ 3 months prior to screening.
5. HbA1c value $\geq 5.8\%$ and $\leq 10.0\%$ as assessed by local lab ≤ 15 days prior to screening or performed at screening.
6. A documented Severe Hypoglycemia event ≤ 12 months prior to screening (see F.6.2 for definition), OR Clarke score ≥ 4 assessed at time of screening, OR Gold score ≥ 4 assessed at time of screening.
7. Subject is willing to sign and date informed consent, comply with all study procedures and wear all study devices as required during the study.

D.2 Exclusion criteria

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

1. Untreated Addison's disease, thyroid disorder, growth hormone deficiency; hypopituitarism, or definite gastroparesis, per investigator judgment.
2. Renal failure defined by creatinine clearance < 30 ml/min, as assessed by local lab test ≤ 3 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations.
3. Hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using CGM, in the opinion of the investigator.
4. Current pregnancy or intention to conceive.
5. Any unresolved adverse skin condition in the area of sensor placement (e.g. psoriasis, rash, Staphylococcus infection).
6. Alcohol or drug abuse, other than nicotine, per investigator judgment.
7. Any other disease or condition that, in the opinion of the Investigator, may preclude the patient from participating in the study.
8. Legally incompetent, illiterate or vulnerable person.

D.3 Randomization criteria

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

1. Subject has worn two weeks the Enlite 3 sensor with blinded GST3C transmitter during the run-in period.
2. Subject has shown acceptable tolerance of Enlite 3 sensor wear, per investigator judgment.
3. CareLink data shows subject performed ≥ 4 finger stick blood glucose measurements daily, as determined by CareLink Clinical data upload as the mean number of SMBG/day over the past 14 days (SMBG number / day ≥ 3.5 round up to 4).
4. Subject showed ability to comprehend the pump training and study procedures, in the opinion of the investigator.

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigation site selection

E.1.1 Investigator selection criteria

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

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

- Medtronic MiniMed 640G System experience is preferred
- Past experience in conducting clinical studies
- Availability for study execution
- Interest in participating in pre-market interventional studies with devices.

E.1.2 Investigation site selection criteria

- The following requirements will be evaluated for each investigation site considered for participation in the clinical study:
- Site staff experience with using the Medtronic MiniMed 640G system is preferred*
- Past experience of site staff in conducting clinical studies
- Adequate resources (including study nurse or coordinator), facilities and administrative support for the total study duration of at least 18 months
- Site has the capacity to recruit enough subjects for the study as defined in section D.1: Expected recruitment of 11 subjects on average, with a minimum of 7 subjects and a maximum of 20 subjects in a 6 month enrollment period.
- Preferable experience with the use of CareLink Diabetes software systems (CareLink Personal or CareLink Pro)
- Computer with Internet access for EDC system and CareLink Diabetes software systems (ensuring authorized access in case of firewall)

*For sites not having experience with Medtronic MiniMed 640G System (e.g. Canadian sites will have limited experience as the MiniMed 640G is not yet commercialized in Canada), an intensified training of the site staff will be performed before enrollment starts and at start of the follow-up period.

E.1.3 Clinical Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

E.1.4 Curriculum Vitae

An up to date signed and dated Curriculum Vitae from all key members of the investigation site team participating in this clinical study as listed on the Delegated task List shall be obtained, preferably in English, evidencing the required qualifications, including the year and where obtained, and including their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the investigation site.

If the CV is not in English, a summary of the Curriculum Vitae template will be provided by Medtronic.

E.2 Ethics

E.2.1 EC/IRB approval

Prior to enrolling subjects in this clinical study, each investigation site's EC/IRB will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent form, including any other written information to be provided to the subjects and, if applicable. EC/IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC/IRB roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB. Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigation site has started enrollment. If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

E.2.2 Informed consent process

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

Well in advance of the consent discussion, the patient should receive the EC/IRB approved Patient Information and Informed Consent Form (PIC). During the consent discussion the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

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

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

When the patient decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the patient, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the patient with a copy of the Patient Information and the signed and dated Informed Consent Form.

A patient contact card will be made available to the patient.

E.2.3 Revisions in Patient Information and Informed Consent Form

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

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

E.2.4 Regulatory submission

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

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

Other documents that are referred to in this Clinical Investigation Plan are listed below and will be made available upon request:

- Monitoring Plan
- Data Management Plan
- Statistical Analysis Plan
- Patient Information and Informed Consent Form
- Case Report Forms
- Instructions for Use of study devices

E.3 Regulatory compliance

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki, the international standard ISO 14155:2011 ('Clinical Investigation of medical devices for human subjects'), laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

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

Following Declaration of Helsinki and ISO14155:2011, legally incompetent and illiterate persons, or vulnerable populations will not be included in this clinical study.

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements and EC/IRB approval.

E.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide relevant clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities, as a minimum, investigator responsibilities, ISO 14155:2011, the CIP, the PIC, use of data collection tools, and applicable local regulations must be reviewed.

Previous training and experience on the MiniMed 640G system is preferred for the participating centers, as assessed during site qualification, with the exception of Canada where it will be investigational.

Study-specific training will be documented prior to site activation.

E.5 Clinical study materials and clinical study-specific equipment

Medtronic will provide study documentation (e.g. Investigator Site File, eCRF access, Study Worksheets, etc.) and study devices to the site personnel.

The site personnel are responsible to send an acknowledgment of receipt to the sponsor after receiving the study devices (via email or fax).

Computer and Internet access are required and are a pre-requisite for site participation (see section E.1.2)

E.6 Study device/product traceability

E.6.1 Supply of devices/products

All serialized devices will be provided as free-of-charge loaners to each subject for the duration of the study, except for the subjects already using a MiniMed 640G insulin pump and/or a CONTOUR NEXT LINK 2.4 meter, who will continue using their own device(s) for the study.

Consumable products will be granted free-of-charge to all subjects for the duration of the study. All devices/products will be shipped to the investigational sites using the commercial supply chain infrastructure when practical. All shipments, no matter the origin, will include an invoice.

Medtronic will only allow shipment of study devices/products to the investigational sites or investigator after the Clinical Study Manager has declared the investigational site ready to start the clinical study.

An initial batch of devices/products will be shipped to each site, after site activation. Based on the number of subjects who have been enrolled at the site, additional devices/products will be shipped as needed; quantities will be discussed with the site staff to adapt to site recruitment.

E.6.2 Storage & handling of study devices/products

The devices/products, as listed in section B.2 will be provided free of charge by the sponsor. Full tracking must be performed as soon as the device/product is received by the investigator/investigation site.

The study devices/products must be stored in a secured area. The method of storage shall prevent the use of study devices/products for other applications than mentioned in this Clinical Investigation Plan. In addition, all information for the use, storage and handling of the investigational device/product as indicated in the Investigator's Brochure or Instructions for use must be taken into account.

Standard Medtronic practice is not to re-package, re-label or sticker commercially-released devices/products used in clinical studies. Investigational devices and consumables will be labeled for investigational use only or as required by national regulations, in local language (as described in section B.2).

The GST3C Download utility, as investigational software will be installed on the sites computer to download the subject data.

E.6.3 Device/product return procedures

Non-functioning devices/products must be returned to Medtronic as soon as possible for investigation.

At the end of the study, all serialized devices must be returned to the Medtronic warehouse. The site Monitor/Clinical Research Specialist will ensure all applicable products are returned to Medtronic. All unused consumables (expired and non-expired) may be destroyed at study site or returned to Medtronic, as required by national regulation. The destruction or return shall be documented respectively on study specific Products Destruction form or Products Return form signed by the responsible person at the site.

E.6.4 Device/product disposition requirements

Devices/products provided by Medtronic will be traced during the clinical study by assigning specific lot numbers, batch numbers, or serial numbers to each device/product. Devices/products reception by the Site will be confirmed on the shipping documents. Devices/products returned from the Site to Medtronic will be documented on a study specific Products Return form.

Devices/products provided to the subjects will be traced on the Subject Products Tracking log in the eCRF which must be approved by the principal investigator at the end of the study.

Investigational software will be traced during the clinical study. Dates of installation and uninstallation on the investigational site computer will be documented in the initiation and close-out visits reports; dates of data download and subject ID will be documented in the electronic CRFs.

F STUDY METHODS

F.1 Point of enrollment

A subject is considered enrolled in the clinical study at the time at which he/she signs the Informed Consent Form.

A subject will be assigned a unique study subject ID via the eCRF, which is a 9-digit code (311-xxx-xxx).

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

F.2 Procedure aspects

The SMILE study is comprised of a run-in phase and a treatment phase. Subjects must successfully complete the run-in phase by demonstrating appropriate self-management and compliance with blinded Continuous Glucose Monitoring prior to being randomized for the treatment period, in which subjects will either be using the MiniMed 640G Pump with the SmartGuard feature programmed turned ON (Treatment Arm = T) or will use the MiniMed 640G Pump without CGM (Control Arm = C).

After the study has been completed, the subjects will continue to be treated following the routine practice of each center.

F.2.1 Pump and CGM Trainings

A training will be provided to all participating subjects, including topics such as initial pump and threshold settings, alarms and alerts, Bolus Wizard usage, blinded CGM and calibration requirements.

Sensor compliance:

Compliance for sensor usage is expected to be at least above 70%. This will be verified at each study visit for subjects in treatment arm. Deviations will need to be reported if compliance is not respected.

SmartGuard (Suspend before Low) settings:

The low limit threshold of Suspend before Low need to be programmed at for all subjects at start CGM (Visit 6) at: **60 or 65 mg/dL (3.4 or 3.6 mmol/L) for 24 hours.**

Adjustments to this low limit and 24 hour time segment are allowed upon **Visit 7** based on the subject's needs per investigator's judgment within the following range: **55 to 70 mg/dL (3.2 to 4.0 mmol/L)**

If changes are made to low limit threshold and selected time segments, the rationale for the changes will be described in the eCRF.

The SmartGuard set-up training materials are available as separate documents.

SMBG:

The study staff will review the number of SMBG at each visit, and remind subjects to perform a minimum of 4 SMBG per day throughout the study.

Bolus Wizard:

The study staff will train all subjects on and carb counting and use of Bolus Wizard, if additional training is needed. A maximum use of the Bolus Wizard is strongly recommended and will be reviewed at each study visit. The study staff will remind subjects to regularly use the Bolus Wizard throughout the study.

F.2.2 Glucose targets

During the course of the study, the following glucose targets (Table 4) from the American Diabetes Association guidelines [20], should be used for all subjects. Insulin titration will be performed to achieve these targets.

F.2.2.1 HbA1c at local lab

During the study, HbA1c will be collected at the local laboratory of the subject, as per routine practice at baseline, 3 months- and 6 months follow-up. If possible, the subject should use the same laboratory for the collection and analysis of all HbA1c samples throughout the study.

Maintenance or calibration certificates of the local laboratories (as they can vary and are numerous) will not be required, as HbA1c is a secondary endpoint and renal failure, assessed by creatinine clearance test, is not a study endpoint.

Table 4 Summary of glycemic recommendations for non-pregnant adults with diabetes

HbA1C	< 7.0%
Preprandial capillary plasma glucose	80–130 mg/dL (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	180 mg/dL (10.0 mmol/L)

† Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

F.2.3 GST3C blinded recorder Training

The GST3C blinded recorder training is available as a separate document.

F.2.4 Patient Questionnaires

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

- Clarke Questionnaire
- Gold Questionnaire
- Hypoglycemia Fear Survey (HFS)
- Diabetes Treatment Satisfaction Questionnaire (DTSQ)

F.2.4.1 Clarke Questionnaire

The Clarke method [21] comprises eight questions characterizing the participant's exposure to events of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to, hypoglycemia. A score of four or more implies impaired awareness of hypoglycemia.

All subjects will be asked to complete the Clarke questionnaire (paper version) at screening (Visit 2), at visit 11 (3 months of follow-up) and at visit 15 (6 months of follow-up), which is also the end of study. In case the subject withdraws early from the study, it is important to ensure that he/she is asked to complete the Clarke Questionnaire at the time of study exit. Data collected from the paper questionnaire will be copied by the site staff into the electronic database.

F.2.4.2 Gold Questionnaire

The Gold questionnaire is a 7-point visual analogue scale that is validated to characterize the participant's impaired awareness of hypoglycemia as confirmed by a score of ≥ 4 in the Gold score. All subjects will be asked to complete the Gold question (paper version) at screening (Visit 2), at visit 11 (3 months of follow-up) and at visit 15 (6 months of follow-up), which is also the end of study. In case the subject withdraws early from the study, it is important to ensure that he/she is asked to complete the Gold Questionnaire at the time of study exit. Data collected from the paper questionnaire will be entered by the site staff into the electronic database.

F.2.4.3 Hypoglycemia Fear Survey (HFS)

Hypoglycemia can lead to various aversive symptomatic, affective, cognitive, physiological, and social consequences, which in turn can lead to the development of possible phobic avoidance behaviors associated with hypoglycemia. The hypoglycemia fear survey (HFS) is a psychometric instrument designed to quantify this fear [22]. The instrument has internal consistency and test-retest stability, and varies with elevated glycosylated hemoglobin. The HFS has in most translations two subscales, the behavior subscale and the worry subscale and has a recollection period of 6 months.

All subjects will be asked to complete the HFS at screening (Visit 2); at visit 11 (3 months of follow-up) and at visit 15 (6 months of follow-up), which is also the end of study. In case the subject withdraws from the study early, it is important to ensure that he/she is asked to complete the HFS at the time of study exit. Data collected from the paper questionnaire will be copied by the site staff into the electronic database.

F.2.4.4 Diabetes Treatment Satisfaction Questionnaire (status version and change version) :

The DTSQ has been specifically designed to measure satisfaction with diabetes treatment regimen in people with diabetes [23]. The DTSQ [status version (DTSQs)] is an eight-item questionnaire, in which six questions assess treatment satisfaction and the other two assess perceived frequency of hyper- and hypoglycemia [23, 24, 25]

Each item is scored from 6 (very satisfied) to 0 (very dissatisfied) such that the Treatment Satisfaction scale can range from 36 (very satisfied) to 0 (very dissatisfied) and the perceived frequency of hyper- and hypoglycemia scores range from 6 (most of the time) to 0 (none of the time).

The DTSQs has been extensively used and is sensitive to changes in response to a variety of interventions, including the start of insulin or the switch between insulin regimens [20, 21, 22].

Although the DTSQs has proved highly sensitive to change, in many studies where patients are very satisfied with treatment used at baseline, the DTSQs cannot show improvements when they switch to a new treatment, even though they might be even more satisfied with the new treatment. To overcome this limitation of the DTSQs, a change version (DTSQc) has also been developed, which asks participants to rate how their current treatment compared with their previous treatment [26, 27]

This instrument contains the same 8 items as the DTSQs version. The difference lies in the wording of the response options and instructions, which, in the DTSQc, direct the respondent to compare their experience of treatment before the study began.

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

[28]. A major advantage of the DTSQs and DTSQc is that it has been developed to be suitable for people with type 1 or type 2 diabetes using a wide range of treatments, including various methods of insulin delivery, oral medications and diet alone, and is, therefore, appropriate for use before and after patients switch between very different treatment regimens.

All subjects will be asked to complete the DTSQs questionnaire at: Screening (Visit 2) and at Visit 14 (22 weeks of follow-up), which is before the last blinded CGM period in the Control Arm.

All subjects will be asked to complete the DTSQc questionnaire at: Visit 14 (22 weeks of follow-up).

In case the subject withdraws from the study before Visit 15, it is important to ensure that he/she is asked to complete: the DTSQs and DTSQc questionnaire at the time of study exit.

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

F.3 Details of Procedures and Data Collection requirements per visit

A calendar will be provided to the study staff to facilitate planning of each study visit according to the protocol schedule and authorized time windows.

The flowchart below (Figure 8) gives an overview of the study and Table 5 shows the study procedures and data collection requirements.

All subject visits including target dates and visit windows are displayed in Table 5, indicating the main procedures performed and study data to be collected per visit.

Figure 8: Study design overview

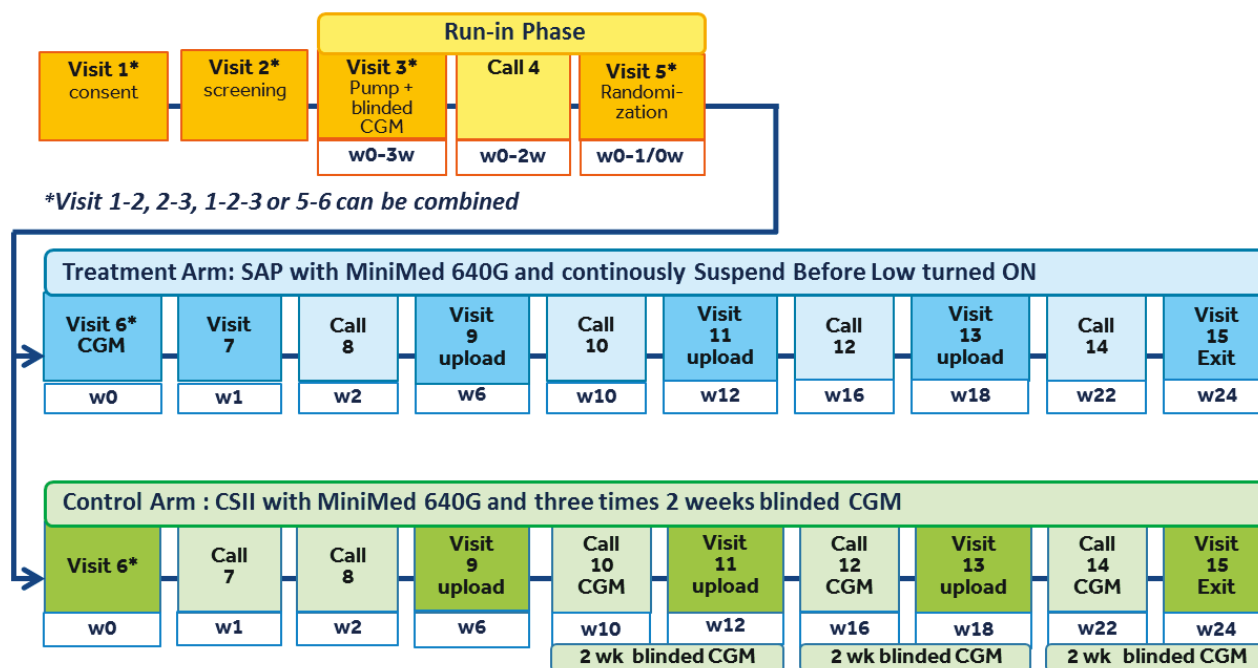


Table 5: Study procedures and Data collection

Procedures and Data collection	Enrollment ¹	Screening ¹	Start Run-in ¹	Call	End Run-in/ Randomization ²	Start Treatment ²	1w call/visit	2w call	6w Visit	10w call	12w visit	16w call	18w visit	22w call	End of Study	Early Termination ⁶
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Target week	w0	w0	w0 -3w	w0 -2w	w0 -1w	w0	w1	w2	w6	w10	w12	w16	w18	w22	w24	
Target day	d0	d0	V2	V3+ 7d	V4+ 7d	V5	V6+ d7	V6+ d14	V6+ d42	V6+ d70	V10+ d14	V6+ d112	V12+ d14	V6+ d154	V14+ d14	
Window	-	-	+7d	+3d	+7d	+14d	±3d	±3d	±7d	±7d	+7d	±7d	+7d	±7d	+7d	
Informed consent	X															
Eligibility criteria		X														
Randomization criteria					X											
Demographics		X														
Medical history		X														
A1c (local lab)		O ³									X				X	X
Creatinine test (local)		O ³														
Device Accountability			X		X	X			X		X		X		X	X
MiniMed640G training			X													
CGM training						T ⁴										
Blinded CGM training			X						C ⁵							
Blinded CGM placement			X	X						C		C		C		
Blinded CGM upload					X						C		C		C	C
CareLink Clinical upload					X	X	T		X		X		X		X	X
Distribution supplies			X		X	X			X		X		X			
Clarke questionnaire		X									X				X	X
Gold Questionnaire		X									X				X	X
HFS questionnaire		X									X				X	X
DTSQs questionnaire		X												X		X
DTSQc questionnaire														X		X
AEs and Deficiencies																
Study deviations																

¹ Visit 1-2, 2-3, 1-2-3 can be combined; ² Visits 5-6 can be combined; ³ O = Optional. Only for subjects who did not have a recent test (see Visit 2: Screening for details); ⁴ T = Treatment arm; ⁵ C = Control arm; ⁶ Early Termination visit should be performed at any time if patient withdraws after randomization (Visit 5) and before the end of the study (Visit 15).

F.3.1 Visit 1: Enrollment

Note: If convenient, visits 1-2, 2-3 or 1-2-3 can be combined.

Visit 1 Procedures:

- Conduct Informed Consent Process as described in E.2.2.
Subject will be enrolled in the study once Informed Consent is obtained.

Visit 1 Data collection:

- Enrollment eCRF: add date of signature Patient Informed Consent
Note: data collection Visit 1 and Visit 2 are combined on one Enrollment eCRF.

F.3.2 Visit 2: Screening

Visit 2 Procedures:

- The investigator will determine if subject meets eligibility criteria (see D.1 and D.2).
- Collect demographic information (age, gender)
- Measure height and weight
- Perform blood sample collection for HbA1c at local lab.
 - If already performed ≤ 15 days prior to screening, only confirm date of collection by local lab and HbA1c value.
Reminder: HbA1c value for inclusion $\geq 5.8\%$ and $\leq 10.0\%$
- Perform blood sample collection for creatinine clearance at local lab.
 - If already performed ≤ 3 months prior to screening, only confirm date of collection by local lab and creatinine clearance value.
Reminder; creatinine clearance threshold for exclusion < 30 mL/min
- Confirm Subject Medical History: including date of T1DM diagnosis, indication, length of time on pump therapy, previous pump model, mean daily insulin dose, insulin molecule, mean number SMBGs/day (based on subject's record or CareLink data if available), and diabetes-related complications.
- Collect information regarding:
 - Level of education
 - Subject to complete Clarke Questionnaire
 - Subject to complete Gold Questionnaire
 - Subject to complete HFS
 - Subject to complete DTSQs
 - Report any Adverse Events, if applicable

Visit 2 Data collection:

- Enrollment eCRF:
 - Eligibility: validation of inclusion- and exclusion criteria
 - Demographics: age, gender, height, weight, level of education, HbA1c, creatinine clearance
 - Medical History: year of T1DM diagnosis, current pump model, indication and time on pump therapy, mean daily insulin dose and insulin type, mean number SMBGs/day, number and diabetes-related complications.
- Clarke eCRF
- Gold eCRF
- HFS eCRF
- DTSQs eCRF
- Adverse Event eCRF, if applicable

F.3.3 Visit 3: Start Run-in [Visit 2 (+7 days max)]

Once eligibility has been confirmed at Visit 2, subject will start a 2 week run-in phase at Visit 3.

The objective of the 2 week run-in phase is to train the subjects on the MiniMed 640G insulin pump, assess subjects' compliance and ability to comprehend the study procedures and tolerance of wearing the sensor and transmitter continuously.

Visit 3 Procedures:

- Subject will receive training on:
 - MiniMed 640G pump therapy, according to the training guidelines (the training may be performed over several days).
 - Performing at least 4 finger stick blood glucose measurements per day.
 - Regular Bolus Wizard use and carb counting, if needed.
 - Use of the Enlite 3 and GST3C transmitter in a blinded manner.
- Report any Adverse Event or Device Deficiency, if applicable
- Study staff needs to create a CareLink Clinical account for the subject, with a unique Subject ID Number (311-XXX-XXX) and password.
- Site staff will dispense to subject (for 2 weeks):
 - 1 MiniMed 640G pump (if subject is not using already a MiniMed 640G pump)
 - 1 CONTOUR NEXT LINK 2.4 meter by Ascencia (if subject is not using already this meter)
 - 2 GST3C transmitters (1 is back-up)
 - 1 GST3C charger
 - 1 GST3C watertight tester
 - 4 Enlite sensors (2 are back-up)
 - 1 Enlite One-Pressserter
 - 150 Strips
 - 10 Infusion sets (1 box of 10)
 - 10 Reservoirs (1 box of 10)
 - 4 AA batteries (1 pack)
- Plan next call with subject in 1 week (Visit 4) and 2 weeks (Visit 5).

Visit 3 Data collection:

- Visit 3 eCRF
- Subject Products Tracking Log eCRF to record products allocated to subject.
- Adverse Event or Device Deficiency eCRFs, if applicable.

F.3.4 Visit 4: Call [Visit 3 + 7 days (+3 days max)]

Visit 4 Procedures:

Study staff will call the subject to:

- Evaluate sensor/transmitter tolerance since Visit 3
- Confirm that new transmitter is started adequately with proper sensor insertion.
- Evaluate MiniMed 640G use; remind the subject about SMBG and Bolus Wizard use.
- Ask if any adverse event or device deficiency occurred.
- Confirm with subject next scheduled visit in 1 week (Visit 5).
- Remind subject to bring back all devices and unused consumables for the next visit to the site.

Visit 4 Data collection:

- Visit 4 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable

F.3.5 Visit 5: Randomization [Visit 4 + 7 days (+7 days max)]

Note: If convenient, visits 5 and 6 can be combined.

Visit 5 Procedures:

- Upload data of the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload data of the 2 used GST3C transmitters using the GST3C Download utility. Use correct file name (Subject ID_XXX_DATE).

Note: data from the GST3C upload via the GST3C Download utility remains blinded to the site staff and subjects and therefore, it cannot be used for therapy adjustment.

- Investigator will review randomization criteria per section D.3.
 - If eligible:** subject will be randomized after completion of the Visit 5 eCRF to one of the 2 arms:
 - Treatment arm: MiniMed 640G with CGM and Suspend before low feature turned ON.
 - Control arm: MiniMed 640G alone
 - Site staff will collect from the subject:
 - 2 GST3C transmitters
 - 1 GST3C charger
 - 1 GST3C watertight tester
 - Site staff will dispense to subject for 2 weeks:
 - 150 Strips
 - 10 Infusion Sets (1 box of 10)
 - 10 Reservoirs (1 box of 10)
 - Site staff plans the following visits with subject:
 - Visit 6 within 2 weeks of the Visit 5 Randomization, or Visit 5 will be combined with Visit 6 on the same day.
 - It is strongly recommended to schedule all study visits and calls (Visit 6 to Visit 15) with the subject.

Note: the electronic database can be used to generate the schedule of the remaining study visits in compliance with target dates.

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

Visit 5 Data collection:

- Pump data upload in CareLink Clinical.
- Transmitter data upload using GST3C Download utility.
- Visit 5 eCRF (including arm allocation)
- Subjects Products Tracking Log eCRF to record products allocated to subject.
- Adverse Event or Device Deficiency eCRF, if applicable.

If subject is not eligible:

- Study Exit eCRF: date and reason for withdrawal.

F.3.6 Visit 6: Start Treatment [Visit 5 (+14 days max)]

Visit 6 Procedures Treatment arm:

Start CGM Visit

Subject will come to the site and be trained on CGM use, following section F.2.1.

Site staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review MiniMed 640G use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any.
- Dispense supplies to subjects for 6 weeks:
 - 2 GST3C transmitter (1 is back-up)
 - 10 Enlite 3 Sensors (2 box of 5)
 - 350 Strips
 - 20 Infusion sets (2 box of 10)
 - 20 Reservoirs (2 box of 10)
 - 8 AA batteries (2 pack of 4)
- Plan next visit with subject in 1 week.

Visit 6 Data collection:

- Visit 6 eCRF
- Subjects Products Tracking log eCRF
- CareLink Clinical pump data upload.
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 6 Procedures Control arm:

Follow-Up Visit

Subject will come to the site.

Site staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review MiniMed 640G use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Dispense supplies to subjects for 6 weeks:
 - 350 Strips
 - 20 Infusion sets (2 box of 10)
 - 20 Reservoirs (2 box of 10)
 - 8 AA batteries (2 pack of 4)
- Plan next call with subject in 1 week

Visit 6 Data collection:

- Visit 6 eCRF
- Subjects Products Tracking log eCRF
- CareLink Clinical pump data upload
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.7 Visit 7: 1 week Follow-Up Visit or Call [Visit 6 + 7 days (±3 days max)]

Visit 7 Procedures Treatment Arm:

1 week Follow-up Visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review MiniMed 640G and sensor use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Plan next call with subject in 1 week

Visit 7 Data collection:

- Visit 7 eCRF
- CareLink clinical data upload
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 7 Procedures Control Arm:

1 week Follow-Up Call

Study staff will call the subject:

Study staff will:

- Review MiniMed 640G use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Plan next call with subject in 1 week

Visit 7 Data collection:

- Visit 7 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.8 Visit 8: 2 week Follow-Up Call [Visit 6 + 14 days (±3 days max)]

Visit 8 Procedures Treatment Arm:

2 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G and sensor use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Plan next visit with subject in 4 week

Visit 8 Data collection:

- Visit 8 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 8 Procedures Control Arm:

2 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G use
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Plan next visit with subject in 4 week

Visit 8 Data collection:

- Visit 8 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.9 Visit 9: 6 week Follow-up Visit [Visit 6 + 42 days (±7 days max)]

Visit 9 Procedures Treatment Arm:

6 week Follow-up Visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review subject's sensor compliance [70-100%]. Retrain subject if needed.
- Review subject therapy and make adjustments, per investigator judgment
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Dispense supplies for 6 weeks:
 - 10 Enlite sensors (2 box of 5)
 - 350 Strips
 - 20 Infusion sets (2 box of 10)
 - 20 Reservoirs (2 box of 10)
 - 4 AA batteries (1 pack of 4)
- Plan next call with subject in 4 weeks.

Visit 9 Data collection

- Visit 9 eCRF
- CareLink clinical data upload
- Subjects Products Tracking log eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 9 Procedures Control Arm:

6 week Follow-up Visit

Subject will come to the site

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review subject therapy and make adjustments, per investigator judgment
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any
- Provide a refresher training on sensor insertion, replacement and blinded recording with the GST3C transmitter.
- Dispense supplies for 6 weeks:
 - 2 GST3C transmitter (1 back-up)
 - 1 GST3C charger
 - 1 GST3C watertight tester
 - 1 Enlite One-Pressserter
 - 4 Enlite sensors (2 back-up)
 - 350 Strips
 - 20 Infusion sets (2 box of 10)
 - 20 Reservoirs (2 box of 10)
 - 4 AA batteries (1 pack of 4)
- Plan next call with subject in 4 weeks.

Visit 9 Data collection

- Visit 9 eCRF
- CareLink clinical data upload
- Subjects Products Tracking log eCRF.
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.10 Visit 10: 10 week Follow-Up Call [Visit 6 + 70 days (± 7 days max)]

Visit 10 Procedures Treatment Arm:

10 week Follow-Up Call

Study staff will call the subject to:

- Review MiniMed 640G and sensor use.
- Review SMBG/Bolus Wizard use.
- Review adverse event or device deficiency, if any.
- Plan next visit with subject in 2 weeks.

Visit 10 Data collection:

- Visit 10 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 10 Procedures Control Arm:

10 week Follow-Up Call

Study staff will call the subject to:

- Review MiniMed 640G use.
- Review SMBG/Bolus Wizard use.
- Ensure blinded GST3C transmitter recording is started adequately with proper sensor insertion, and will be continued until next clinic visit.
- Remind subject to replace the sensor after maximum 7 days of wear.
- Review adverse event or device deficiency, if any.
- Plan next visit with subject in 2 weeks.

Visit 10 Data collection

- Visit 10 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.11 Visit 11: 12 week Follow-up Visit [Visit 10 + 14 days (+7 days max)]

Visit 11 Procedures Treatment Arm:

12 week Follow-up Visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review subject's sensor compliance [70-100%]. Retrain subject if needed.
- Collect blood sample for HbA1c.
- Review subject therapy and make adjustments, per investigator judgment.
- Review SMBG/Bolus Wizard use
- Review adverse event or device deficiency, if any.
- Ask subject to complete 3 questionnaires (Clarke, Gold, HFS)
- Dispense supplies for 6 weeks:
 - 10 Enlite 3 sensors
 - 350 Strips (7 boxes of 50)
 - 20 Infusion Sets (2 boxes of 10)
 - 20 Reservoirs (2 boxes of 10)
 - 8 AA batteries (2 pack of 4)
- Plan next call with subject in 4 weeks

Visit 11 Procedures Control Arm:

12 week Follow-up Visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload the GST3C transmitter using GST3C Download utility. Use correct file name (Subject ID_XXX_DATE).
- Collect blood sample for HbA1c.
- Review subject therapy and make adjustments, per investigator judgment.
- Review SMBG/Bolus Wizard use.
- Review adverse event or device deficiency, if any.
- Ask subject to complete 3 questionnaires (Clarke, Gold, HFS)
- Dispense supplies for 6 weeks:
 - 4 Enlite sensors (2 back-up)
 - 350 Strips (7 boxes of 50)
 - 20 Infusion Sets (2 boxes of 10)
 - 20 Reservoirs (2 boxes of 10)
 - 8 AA batteries (2 pack of 4)
- Plan next call for subject in 4 weeks.

Visit 11 Data collection

- Visit 11 eCRF with HbA1c value
- Clarke eCRF
- Gold eCRF
- HFS eCRF
- Subjects Products Tracking log eCRF.
- Adverse Event or Device Deficiency eCRF, if applicable.
- Pump data upload in CareLink Clinical.

Visit 11 Data collection

- Visit 11 eCRF with HbA1c value
- Clarke eCRF
- Gold eCRF
- HFS eCRF
- Subjects Products Tracking log eCRF.
- Adverse Event or Device Deficiency eCRF, if applicable.
- Pump data upload in CareLink Clinical.
- Transmitter data upload using GST3C Download utility.

F.3.12 Visit 12: 16 week Follow-Up Call [Visit 6 + 112 days (± 7 days max)]

Visit 12 Procedures Treatment Arm:

16 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G and sensor use.
- Review SMBG/Bolus Wizard use.
- Review adverse event or device deficiency, if any.
- Plan next visit with subject in 2 weeks

Visit 12 Data collection

- Visit 12 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 12 Procedures Control Arm:

16 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G use.
- Review SMBG/Bolus Wizard use.
- Ensure blinded GST3C transmitter recording is started adequately with proper sensor insertion, and will be continued until next clinic visit.
- Remind subject to replace the sensor after maximum 7 days of wear.
- Review adverse event or device deficiency, if any.
- Plan next visit with subject in 2 weeks

Visit 12 Data collection

- Visit 12 eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.13 Visit 13: 18 week Follow-up Visit [Visit 12 + 14 days (+7 days max)]

Visit 13 Procedures Treatment Arm:

18 week Follow-up visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review subject's sensor compliance [70-100%]. Retrain subject if needed.
- Review subject therapy and make adjustments, per investigator judgment.
- Review SMBG/Bolus Wizard use .
- Review adverse event or device deficiency, if any.
- Dispense supplies for 6 weeks:
 - 10 Enlite 3 sensors (2 boxes of 5)
 - 350 Strips (7 boxes of 50)
 - 20 Infusion Sets (2 boxes of 10)
 - 20 Reservoirs (2 boxes of 10)
 - 4 AA batteries (1 pack of 4)
- Provide subject DTSQs and DTSQc questionnaires to be completed at home in 4 weeks (Call14).
- Plan next call with subject in 4 weeks.

Visit 13 Data collection

- Visit 13 eCRF
- Subjects Products Tracking log eCRF.
- Adverse Event or Device Deficiency eCRF, if applicable.
- Pump data upload in CareLink Clinical

Visit 13 Procedures Control Arm:

18 week Follow-up visit

Subject will come to the site

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload the GST3C transmitters using GST3C Download utility. Use correct file name (Subject ID_XXX_DATE).
- Review subject therapy and make adjustments, per investigator judgment.
- Review SMBG/Bolus Wizard use.
- Review adverse event or device deficiency, if any.
- Dispense supplies for 6 weeks:
 - 4 Enlite 3 sensors (2 back-up)
 - 350 Strips (7 boxes of 50)
 - 20 Infusion Sets (2 boxes of 10)
 - 20 Reservoirs (2 boxes of 10)
 - 4 AA batteries (1 pack of 4)
- Provide subject DTSQs and DTSQc questionnaires to be completed at home in 4 weeks (Call14).
- Plan next call with subject in 4 weeks.

Visit 13 Data collection

- Visit 13 eCRF
- Subjects Products Tracking log eCRF.
- Adverse Event or Device Deficiency eCRF, if applicable.
- Pump data upload in CareLink Clinical
- Transmitter data upload using GST3C Download utility.

F.3.14 Visit 14: 22 week Follow-Up Call [Visit 6 + 154 days (±7 days max)]

Visit 14 Procedures Treatment Arm:

22 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G and sensor use.
- Review SMBG/Bolus Wizard use.
- Review adverse event or device deficiency, if any
- Remind subject to complete DTSQs and DTSQc questionnaires and to return them at next clinic visit.
- Plan End of Study visit in 2 weeks
- Remind subject to bring back all study materials at End of Study visit.

Visit 14 Procedures Control Arm:

22 week Follow-Up Call

Study staff will call the subject

- Review MiniMed 640G use
- Review SMBG/Bolus Wizard use
- Ensure blinded GST3C transmitter recording is started adequately with proper sensor insertion, and will be continued until next clinic visit.
- Remind subject to replace the sensor after maximum 7 days of wear.
- Review adverse event or device deficiency, if any
- Remind subject to complete DTSQs and DTSQc questionnaires and to return them at next clinic visit
- Plan End of Study visit in 2 weeks.
- Remind subject to bring back all study materials at next clinic visit.

Visit 14 Data collection

- Visit 14 eCRF
- DTSQs completion by subject at home
- DTSQc completion by subject at home
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 14 Data collection

- Visit 14 eCRF
- DTSQs completion by subject at home
- DTSQc completion by subject at home
- Adverse Event or Device Deficiency eCRF, if applicable

F.3.15 Visit 15: 24 week End of study Visit [Visit 14 + 14 days (+ 7 days max)]

Visit 15 Procedures Treatment Arm:

End of study visit

Subject will come to the site.

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Review subject's sensor compliance [70-100%]. Retrain subject if needed.
- Review adverse event or device deficiency, if any.
- Collect blood sample for HbA1c at local lab.
- Ask subject to complete Clarke questionnaire.
- Ask subject to complete Gold questionnaire.
- Ask Subject to complete HFS questionnaire.
- Collect DTSQs and DTSQc paper questionnaires completed by subject at Visit 14 at home.
- Retrieve all study related devices and material.
- After the study end, subjects will continue to be followed per routine practice, according to their doctor advice.

Visit 15 Data collection

- Visit 15 eCRF with HbA1c value
- Study Exit eCRF
- Pump data upload in CareLink Clinical.
- Clarke eCRF
- Gold eCRF
- HFS eCRF
- DTSQs eCRF
- DTSQc eCRF
- Subjects Products Tracking log eCRF with all return dates of study products.
- Adverse Event or Device Deficiency eCRF, if applicable.

Visit 15 Procedures Control Arm:

End of study visit

Subject will come to the site

Study staff will:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload the GST3C transmitters using GST3C Download utility. Use correct file name (Subject ID_XXX_DATE).
- Review adverse event or device deficiency, if any.
- Collect blood sample for HbA1c at local lab.
- Ask subject to complete Clarke questionnaire.
- Ask subject to complete Gold questionnaire
- Ask Subject to complete HFS questionnaire.
- Collect DTSQs and DTSQc paper questionnaires completed by subject at Visit 14 at home.
- Retrieve all study related devices and material.
- After the study end, subjects will continue to be followed per routine practice, according to their doctor advice.

Visit 15 Data collection

- Visit 15 eCRF with HbA1c value
- Study Exit eCRF
- Pump data upload in CareLink Clinical.
- Transmitter data upload using GST3C Download utility.
- Clarke eCRF Gold eCRF
- HFS eCRF
- DTSQs eCRF
- DTSQc eCRF Subjects Products Tracking log eCRF with all return dates of study products.
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.16 *Unscheduled visit:*

In case additional data need to be reported, unscheduled visit can be used (*i.e. in case of early termination outside of a normal protocol visit*)

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

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload GST3C transmitters using GST3C Download utility, if applicable (Control Arm only). Use correct Subject ID (Subject ID_XXX_DATE).
- Review adverse event or device deficiency, if any.

Unscheduled visit Data collection

- Unscheduled visit eCRF
- Pump data upload in CareLink Clinical.
- Transmitter data upload using GST3C Download utility (control arm only)
- Subjects Products Tracking log eCRF
- Adverse Event or Device Deficiency eCRF, if applicable.

F.3.17 *Early Termination visit:*

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

Early Termination Procedures:

- Upload the MiniMed 640G into CareLink Clinical. Use correct Subject ID (311-XXX-XXX).
- Upload GST3C transmitters using GST3C Download utility, if applicable. Use correct Subject ID (Subject ID_XXXX_DATE).
- Collect blood sample for HbA1c at local lab, if applicable
- Ask subject to complete Clarke questionnaire, if applicable
- Ask subject to complete Gold questionnaire, if applicable. Ask Subject to complete HFS questionnaire, if applicable
- Ask subject to complete DTSQs and DTSQc questionnaires, if applicable
- Review adverse event or device deficiency, if any
- Retrieve all study related devices and material .

Early Termination Data collection:

- Unscheduled Visit eCRF, if withdrawal occurred in between scheduled study visits.
- Study Exit eCRF: with date and reason for withdrawal; last available HbA1c value, if applicable,
- Subjects Products Tracking log eCRF to record all returned devices and dates.
- Pump data upload in CareLink Clinical.
- Transmitter data upload using GST3C Download utility, if applicable
- Clarke eCRF, if available.
- Gold eCRF, if available
- HFS eCRF, if available.
- DTSQs eCRF, if available.
- DTSQc eCRF, if available.
- Adverse Event or Device Deficiency eCRF, if applicable.

F.4 Role of the sponsor's representatives

Sponsor's representatives may provide technical support following routine practice in the participating countries (i.e. pump or CGM training) and for study specific activities (i.e. data uploads, IT support). In the applicable participating sites where sponsor is involved in subject device trainings, the sponsor's representatives providing technical support will be listed on the sponsor technical support list.

F.5 Source documents

The patient's hospital/clinic file, CareLink data, HbA1c laboratory reports, data collected on the paper questionnaires are handled as source data.

The investigator will mark the clinical records to indicate that the subject is enrolled in this clinical study.

In addition, the site personnel will receive paper worksheets that detail all required data collection to be performed during the patient visits and copied in the CRFs. The objective of these paper worksheets is to remind the center of all study-related procedures to be performed and items to be recorded, before data is actually entered into the study database. Worksheets can serve as source document for study specific data.

Collected data of each subject will need to be recorded on electronic Case Report Forms (eCRFs), which access will be provided via Internet based electronic data collection (EDC) software.

For monitoring purposes, audit or inspection, Medtronic clinical representatives or delegates, monitors, auditors and inspectors will be granted access by the site to all source documents including electronic source documents, if applicable. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

F.6 Adverse events

F.6.1 Definitions

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2011.

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.

Adverse Event (AE): (ISO14155:2011 3.2)

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

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

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

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

Adverse Device Effect (ADE): (ISO14155:2011 3.1)

Adverse event related to the use of an investigational medical device

NOTE 1: 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: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): (ISO 14155:2011 3.37)

An adverse event that

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function, 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) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: 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 14155:2011 3.36)

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Unanticipated Serious Adverse Device Effect (USADE): (ISO 14155:2011 3.42)

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

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device deficiency: (ISO 14155:2011 3.15)

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

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

F.6.2 Definitions of Diabetes related events

Since it is inherent to the disease of diabetes that patients may daily experience variations in their blood sugar levels above and below the normal range, hypoglycemia and hyperglycemic events should not be defined and reported as an adverse event. Only *Severe Hypoglycemic*, *Severe Hyperglycemia*, and *Diabetic Ketoacidosis* need to be reported in this study. See the definitions of these events in the following paragraphs.

Severe Hypoglycemia is an event *requiring* assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat his or her self, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative.

These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. (*Adapted from American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005*)

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

Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than 250 mg/dL (or greater than 13.9 mmol/L), arterial pH less than 7.3, bicarbonate less than 15mEq/l, Anion gap greater than 12, moderate ketonuria or ketonemia and requiring treatment within a health care facility. (*American Diabetes Association-Diabetes Care, Volume 27, Supplement 1, January 2004; S94-S102*)

DKA will be recorded as an adverse event in the presence of all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Serum ketones or large/moderate urine ketones
- Arterial blood pH less than 7.30 or serum bicarbonate less than 15mEq/l
- Treatment provided in a health care facility

F.6.3 Recording and reporting of Adverse Events

In this study *all adverse events* will be collected (including at minimum the following information: date of the adverse event, date of first awareness by investigator, action taken, outcome status and resolution, and assessment of both the seriousness and the relationship to the investigational device and procedure).

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

In the event the database is not functioning for any reason, the site will inform the Medtronic MCO Safety Specialist (see Sponsor list for contact details) and the site staff will manually complete the AE CRF and email the form, as soon as possible and/or within reporting guidelines outlined in this document (see Table 6), to Medtronic Safety team at the following email address for all geographies: rs.mstsafetydiabetes@medtronic.com. In the event the internet is not functioning, the site will inform the Medtronic Study Manager via phone (see Sponsor list for contact details).

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

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

F.6.4 Recording and reporting of Device Deficiencies

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

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

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

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

Device deficiencies that did not lead to an Adverse Event, but could have led to an SADE require immediate reporting (see Table 6).

- a) if either suitable action had not been taken,
- b) if intervention had not been made, or
- c) if circumstances had been less fortunate,

Initial reporting will be done on the eCRF completing as much information as is available. The Device Deficiency eCRF must be validated and saved "complete", for submission to Medtronic.

In case technical issue occurs with the electronic CRF (i.e. Internet access, system maintenance...), initial reporting for Device Deficiencies that require immediate reporting (see Table 6), may be done via email: rs.mstsafetydiabetes@medtronic.com. In the event the internet is not functioning, the site will inform Medtronic Study Manager via phone (see Sponsor list for contact details).

F.6.5 Adverse Event and Device Deficiency review process

The potential adverse events (risks) and their mitigations associated with the use of these devices are identified in the Instructions for Use (IFU) for the CE-marked commercially available devices/consumables and in the Investigator Brochure (IB) for the pre-market devices/consumables (also see Section J.2 of this CIP).

All Adverse Events and Device Deficiencies will be reviewed by Medtronic MCO Safety Specialist or designee. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements (see Table 6 Adverse Event Reporting Requirements). The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global regulatory requirements.

The Medtronic MCO Safety Specialist or designee will immediately report any Adverse Events/Device Deficiencies that are associated with the device to the Medtronic Diabetes Complaint Handling Unit. The Diabetes Complaint Handling Unit will ensure prompt review, and appropriate reporting.

Table 6 Adverse Event Reporting Requirements	
Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other AEs	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submit to:	
Medtronic	Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.

F.6.6 Clinical events Committee

An independent Clinical events Committee (CEC) consisting of external physicians with an expertise in endocrinology and the management of diabetes, including insulin pumps and CGM will be convened. The CEC will review all reports of:

- Serious Adverse Event (SAE)
- Serious Adverse Device Effect (SADE)
- Unanticipated Adverse Device Effect (UADE)
- Severe Hypoglycemia
- Severe Hyperglycemia
- Diabetic Ketoacidosis (DKA)
- Death

The responsibilities of an CEC committee are:

- Review all reported SAE, SADE, UADE, Severe Hypoglycemia, Severe Hyperglycemia, DKA and deaths, and determines event classification (e.g. seriousness, severity, relatedness to device and procedure, unanticipated/anticipated) on a periodic basis.
- Upon request advise Sponsor about the potential clinical impact of an observed unintended device performance.
- Advise Sponsor in cases of SADEs.

A CEC charter will be established to indicate explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate an event.

The CEC will assess these events to determine agreement or disagreement with the Investigator classification of the event. CEC decisions will be documented in meeting minutes. The Sponsor will notify the Investigator of any disagreement in assessment of an event by the CEC.

All other events will be reviewed and classified by the Sponsor's qualified internal safety individual(s) to ensure they should not be adjudicated by the CEC and that the events are appropriately classified by the investigator.

F.6.7 Data Safety Monitoring Board

The purpose of a data monitoring committee is to protect the safety of trial participants, the credibility of the study and the validity of study results. An independent Data Safety Monitoring Board (DSMB) will reassess the study sample size at the moment of the planned interim analysis.

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

- Review the interim analysis of effectiveness and safety measures after 60 subjects(30 treatment and 30 control group) have been randomized and followed up for 6 months.
- Following predefined rules in the DSMB chart, implement the assessment of modifications to the trial design.
The primary planned modification is a sample size re-estimation.
- Monitor baseline comparability.
- Monitoring adverse events: review aggregate subject data.
- Provide recommendations to continue or terminate the trial depending upon these analyses.

F.6.8 Emergency contact details in case of serious AEs

In case of an immediately reportable Adverse Event the investigators can contact the Medtronic study manager. Should the team members change during the course of the study, you may contact the current study manager.

F.7 Subject accountability

Subjects who are unwilling to participate in the follow up visits or complete study procedures should be withdrawn.

If a subject is withdrawn from the clinical study, the reason for withdrawal shall be recorded in the eCRF and in the subject's hospital/clinic record. If discontinuation is because of safety, the subject shall be asked to be followed to collect safety data outside the clinical study.

In case follow-up visits are missed, a study deviation should be completed on the eCRF to document this.

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 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.

F.8 Study deviations and CIP changes

A study deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan or to early terminate the investigation, in accordance with Medtronic SOPs.

F.8.1 Request for approval of study deviations

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

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

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

F.8.2 Reporting requirements for study deviations

All deviations will be reported on the *Deviation* eCRF by the Investigation site staff. The description of the deviation and justification must be documented and submitted to Medtronic via the eCRF. Once a deviation has been identified, it should be reported to Medtronic promptly. Deviations may be identified through numerous sources, including but not limited to: telephone conversations, site monitoring, patient record, or data review.

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

F.8.3 Amendments to the Clinical Investigation Plan (CIP)

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

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

G QUALITY CONTROL PROCEDURES

G.1 Procedures for database management

G.1.1 Data collection

G.1.1.1 Electronic Case Report Forms (CRFs):

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the patient medical file.

Only authorized persons can complete electronic CRFs (eCRF). eCRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in the eCRFs. If a person is only authorized to complete eCRFs or to make changes to an already signed eCRF, the investigator shall re-sign this eCRF.

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

Investigation site will be trained for use of the eCRF prior, or at latest during, site initiation visit, on a training database. Access to final CRFs for study conduct will be granted after training is performed and prior to patient's enrollment.

G.1.1.2 Paper Study Worksheets:

All investigation sites 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 will be considered as source documents. Only authorized persons can complete the Worksheets as specified on the Delegated Tasks List (DTL) included in the Investigator Site File.

G.1.1.3 Medtronic CareLink Therapy Management System:

The MiniMed 640G insulin pump data needs to be uploaded in Medtronic's CareLink Clinical database by the investigator or designated person. This system uses Secure Sockets Layers (SSL) 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 subjects ID, which is a 9-digit code (311-xxx-xxx) to prevent patient identification by the sponsor.

G.1.1.4 GST3C Download Utility Software – Investigational:

The Download Utility Software for use with the GST3C Transmitter(s) is an investigational computer-based program used to set time, upload data and clear data for the GST3C Transmitter(s) (described in section B.3.1.3). Communication between the GST3C Transmitter(s) and the computer is done via the GST3C Dock. Once the GST3C data is downloaded, each site uses a specific username and password to access the site's database and upload the device data.

Refer to the Download Utility guidelines for more details.

G.1.1.5 Patient Questionnaires:

The Clarke, Gold, HFS and DTSQ questionnaires will be provided in local language in the countries. The data will initially be collected on paper questionnaires that will be kept at the site.

The investigator, or designated site personnel, will then copy the answers of the subject from the paper questionnaires into the EDC system. It is important that the investigator, or designated site personnel verifies the questionnaires for completeness, because missing answers for some questions would prevent calculations of total scores.

G.1.2 Time windows for completion and submission of Case Report Forms

It is expected that CRFs are completed in a timely manner, approximately within 5 to 10 days of data collection on source documents and/or the worksheets, with the exception of serious adverse events and (unanticipated) serious adverse device effects and Device deficiencies with SADE potential, which need to be recorded immediately after awareness of the site staff on the *Adverse Event* or *Device Deficiency* eCRFs. Most CRFs should be submitted in final form, i.e. saved as complete upon data entry, so that study monitors can proceed with data verification without delay. Exceptions to this rule apply for CRF forms that need to be accessed on multiple occasions before they can be finalized (i.e. *Device/Consumables Accountability* eCRF).

G.1.3 Data review and processing

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request.

Collected data will be reviewed for completeness, correctness and consistency, as per monitoring plan. In case of issues, queries will be sent to the investigator to complete, correct or comment the data.

G.2 Monitoring procedures

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

G.2.1 Accessibility of investigation site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

G.2.2 Audits and investigation site inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. 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 bodies may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

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

G.3 Study suspension or early termination

G.3.1 Early study suspension or termination

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

G.3.2 Early investigation site suspension or termination

Medtronic, EC/IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic 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/IRB and the study subjects.

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 investigation site and immediately inform the sponsor and EC/IRB, if applicable.

G.3.3 Subject follow-up in case of termination

In case of early investigational site suspension or termination, all subjects should be called to plan an early Termination visit (see section F.3) at the site. All efforts will be made to complete and report all study observations at the time of termination. The subject will return the study devices to the site (unless subject is allowed to keep them per country requirement).

G.4 Study close out

In case of a study close-out, the Investigators will be notified by Medtronic. Appropriate notification/report to EC/IRB and Competent Authorities will be provided, if required per local laws and regulations.

After study close-out, the follow-up treatment and medical care of the subjects will continue to be as per routine practice of the site.

H DATA ANALYSIS AND REPORTING

A detailed description of the data analyses and timing will be provided in a separate Statistical Analyses Plan (SAP).

Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

H.1 Analysis of clinical data

A detailed statistical analysis will be outlined in a separate statistical analysis plan (SAP). The SAP will include information on the following items:

- Patient demographics and baseline characteristics will be presented using appropriate summary statistics (mean, standard deviation, median, minimum and maximum for continuous variables; frequency counts and percentages for categorical variables).
- The criteria for selection of subjects as described in section D.
- A Consort diagram will describe the number of subjects that were enrolled, randomized, completed follow-up, early terminated the study, and number of subjects included for analysis.
- Statistical methods to be used including a description of the statistical test (see section C.3) for testing of the null-hypothesis of the primary endpoint and statistical test for secondary endpoints and multiple imputation method for missing data.
- Between groups comparison of secondary and tertiary endpoints
- Subgroups for analysis by baseline HbA1c level $\leq 7.5\%$ and $>7.5\%$ (as a threshold for “well-controlled” patients below this value)

- An interim analysis for sample size re-estimation will use the method described in the SAP when approximately 60 subjects have reached the 6 months of follow-up. The independent DSMB will re-estimate the sample size taking into account the observed treatment effect and the estimated standard deviation. The board will be able to recommend one of the following to the sponsor after the interim analysis:
 - Study has reached the futility boundary and it is recommended to be terminated for futility.
 - Continue the study to its conclusion without modification of sample size or inclusion criteria.
 - Increase the numbers of patients in each treatment group.
 - Revise the inclusion criteria.
- Detailed description of the Intention To Treat (ITT) analysis: Analysis will be performed on the Intent to Treat (ITT) basis. The ITT set will be composed of randomized subjects who underwent at least two week of CGM (blinded CGM in the Control arm and unblinded CGM in the Treatment arm). These subjects will be followed up, assessed and analyzed as members of the intended randomized arm, irrespective of their compliance to the planned course of treatment or deviations from protocol. Imputation of missing data in the ITT analysis will be performed using multiple imputation.
- Additional ad-hoc analysis may be performed and will be described as such in the report of study results.

H.2 Publication Policy

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

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

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

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is in accordance with the International Committee of Medical Journal Editors (ICMJE) published guidelines (JAMA 2013), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

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

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

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

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

I STUDY MANAGEMENT

I.1 Study staff

This study is sponsored by Medtronic International Trading Sàrl and Medtronic of Canada.

A list of sponsor staff involved in the study is available from the sponsor; it will be kept under separate cover and provided upon request.

I.2 Advisory committees

I.2.1 Steering Committee

A steering committee composed of physicians (section L.1.1) and Medtronic representatives has been set up to coordinate the study, as defined in the Steering Committee charter. *The Steering Committee Charter is available under a separate cover.*

I.2.2 Clinical Events Committee (CEC) (section F.6.6)

An independent Clinical Events Committee (CEC) consisting of external physicians with an expertise in endocrinology and diabetes management will review the reported safety events, as defined in the CEC Charter. *This Clinical Steering Committee Charter is available under a separate cover.*

I.2.3 Data Safety Monitoring Board (DSMB) (section F.6.7)

An independent DSMB, consisting of external physicians and at least one statistician, will protect the safety of trial participants, the credibility of the study and the validity of study results, as defined in the DSMB Charter. *This DSMB Charter is available under a separate cover.*

I.3 Records and reports

I.3.1 Investigator Records

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

- Clinical Investigation Plan and, if applicable, any amendments
- Investigator's Brochure and/or Instructions for Use
- Medtronic and EC/IRB approved Patient Informed Consent form
- Regulatory Authority approval or notification
- Fully signed Clinical Investigation Agreement and confidentiality agreement (if not included in the Clinical Investigation Agreement)
- Insurance certificates
- Completed Delegated Task List and Curriculum Vitae
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated and fully executed Patient Informed Consent forms
- Completed worksheets
- Fully executed CRFs and corrections, including Randomization CRFs
- Reports of Adverse Events and Device Deficiencies
- Device accountability records

1.3.2 Investigator reporting responsibilities

Report	Submitted to	Description
Adverse Events	Sponsor, EC/IRB, and local regulatory authority, where applicable	Refer to sections F.6.3, F.6.4, F.6.5 for reporting requirements.
Withdrawal of EC/IRB approval	Sponsor	Investigator will inform Medtronic in case EC/IRB approval is withdrawn.
Final Clinical Study Report	EC/IRB	A copy of the Final Clinical Study Report will be provided to the EC/IRB.
Deviations from Investigational Plan		
Emergency Use	Sponsor, EC/IRB, regulatory authority	Investigator will report deviation as soon as possible to the sponsor and EC/IRB.
Planned deviation	Sponsor, EC/IRB, regulatory authority	Prior any deviation, approval must always be obtained from Medtronic. If the deviation affects scientific soundness of the clinical study or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from the EC/IRB and regulatory authority.
Other Deviations	Sponsor	Deviations that are beyond the control of the investigator (such as subject who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the clinical study or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the investigation site or Medtronic staff.

1.3.3 Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and any amendments, if applicable
- Investigator Brochure and/or Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum Vitae of site staff
- Delegated Task Lists and training records of investigators and investigation site personnel
- EC/IRB approvals/notifications and regulatory approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Insurance certificates,
- Shipping records for investigational devices and clinical-investigation related documents and materials
- Medtronic and EC/IRC approved Patient Informed Consents
- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event and Device Deficiency reports
- Fully executed CRFs and corrections (including randomization CRFs).

1.3.4 Sponsor reporting responsibilities

Report	Submit to	Description
Adverse Events	EC/IRB, Investigators, and regulatory authorities, where applicable	Medtronic will report adverse events as required and in compliance with local regulatory requirements, as applicable. Refer to sections F.6.3, F.6.4, F.6.5 for reporting requirements.
Withdrawal of EC/IRB approval	EC/IRB, Investigators, and regulatory authorities, where applicable	In case of withdrawal of EC/IRB approval Medtronic will suspend the clinical study as described below.
Premature termination or suspension of study	EC/IRB, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to EC/IRB and regulatory authorities.
Final Report	Investigators, and regulatory authorities, where applicable	Medtronic will provide all investigators with a copy of the Final Clinical Study Report of the clinical study. EC/IRBs and regulatory authorities will be informed when required.
Emergency Deviations from Investigational Plan	Regulatory authorities, where applicable	If required, Medtronic will inform regulatory authorities as soon as possible about any emergency deviations that affect scientific soundness of the clinical study or the rights, safety, or welfare of the subject.

1.3.5 Record retention

The investigator must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after market-release in his/her region. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

1.4 Miscellaneous

1.4.1 Insurance

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

1.4.2 Subject compensation and indemnification

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

1.4.3 Subject confidentiality

All records and other information about subjects participating in this clinical study will be treated as confidential.

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (study - site - subject number) will be assigned and used to allow identification of all data reported for each subject.

This will also ensure that the information can be tracked back to the source data.

Study data may 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. The identity of a subject will never be disclosed in the event that study data are published. Only anonymized data will be analyzed and published.

J RISKS AND BENEFITS

J.1 Anticipated Clinical Benefits

The goal of the study is to demonstrate the impact of the SmartGuard feature of the new MiniMed 640G system on the incidence of hypoglycemia. It is anticipated that this new system will allow reducing hypoglycemia in this selected population of patients. Previous studies are supporting this hypothesis: it was shown in the PILGRIM study [10] that hypoglycemic events were decreased by 80% using SmartGuard during physical exercise. In a MiniMed 640G user evaluation [11] 83.1% of the SmartGuard events where the pump stopped delivering insulin, the sensor glucose value never reached the pre-set low limit.

The study will give the opportunity to subjects of the treatment arm to have access to CGM therapy, which may not be reimbursed in all countries.

It is possible that the subjects of control arm do not get any benefit in participating in this study, nevertheless, it gives them the opportunity to use the last generation pump MiniMed 640G, with new features (e.g. new user interface, easier adjustment of insulin doses...).

The information gathered in this study may help the patients and physicians determine the best treatment options in the future. The experience of participating in this study may also help other patients benefit from improved diabetes management learned by patients and investigational staff using the MiniMed 640G System. Furthermore, results from this study may address potential device and clinical issues not identified in previous studies, support the development of new devices and therapies, and may facilitate reimbursement of the device components (and subsequent systems) in countries where they are not currently reimbursed.

J.2 Risks

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

- Hypoglycemia
- Severe Hypoglycemia
- Hyperglycemia
- Diabetic Ketoacidosis

The potential side effects related to the insulin administration and pump use, insulin pump infusion sets and finger sticks are anticipated to be the same as per standard of care for the study participants.

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

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

The history of recall of the investigational devices is described in the Investigator Brochure, if applicable.

J.2.1 *Potential risks associated with the use of the Enlite 3 Sensor*

Serious Adverse Events during past studies involving glucose sensor use were relatively rare. Usually side effects are often limited to reactions to the sensor insertion site, adhesives or tape associated with device placement and device irritation on the skin. These potential risks include the following:

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, Allergic reaction, Fainting 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 and Scarring.

Either the subject or investigational center may remove a sensor if they are concerned with skin irritation or skin discomfort. Also, the possibility of infection is minimized by aseptic technique of sensor insertion and site rotation. Subjects should base their diabetes management on fingerstick readings and not sensor glucose values.

While there is no evidence of an Enlite sensor breaking in a patient's body, if there is suspicion of sensor breakage, subject should contact his healthcare professional for assistance in removing the sensor.

The same risks apply for the subjects in the treatment arm and those in the control arm with the use of the GST3C transmitter device and sensor, with a reduced frequency of use for the control arm.

J.2.2 Potential risks associated with the use of the GST3C Transmitter

The GST3C transmitter is similar to the Guardian 2 Link transmitter which is CE-marked and commercially available.

There are no anticipated risks with the use of the GST3C at this stage.

Contra-indications:

Transmitter must not be exposed to MRI equipment, diathermy devices, or other devices that generate strong magnetic fields. If the transmitter is inadvertently exposed to a strong magnetic field, its use must be discontinued and it must be replaced.

J.2.3 Potential risks associated with the use of other investigational devices

No risks are known or anticipated at this stage with the other investigational study devices:

- GST3C Dock (T8381)
- GST3C Download Utility (9029393)

J.2.4 Potential risks associated with the use of MiniMed 640G Insulin pump:

Potential risks associated with the use of an insulin infusion pump 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. Device deficiencies or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences:

- Hypoglycemia
- Hyperglycemia
- Diabetic ketoacidosis (DKA)
- Severe hypoglycemia with or without associated seizure, coma or death
- Kinked cannula leading to hyper or hypoglycemia
- Infusion set disconnection from pump leading to hypo or hyperglycemia
- Dislodged cannula leading to hypo or hyperglycemia
- A pump error indicating hardware failure may lead to under delivery
- Battery failure – no insulin delivered
- Remove a reservoir, without suspending and reconnecting after a while resulting in a

Hypoglycemia

- 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 computer hacking

Risks associated with hyperglycemia include:

- DKA
- Symptomatic ketosis
- Cardiovascular event
- Dehydration
- Potassium and sodium imbalance
- Shock
- Altered mental status
- Coma
- Acidosis

Risks associated with hypoglycemia include:

- Seizure
- Coma
- Altered mental status
- Loss of consciousness
- Cardiovascular event
- Death
- Risk of rebound hyperglycemia with ketosis

Prevention and mitigation risks include:

- Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management.
- Subjects will be trained prior to study device use and diabetes management principles and told to call with problems.
- Subjects will be required to check SMBG at least 4 times a day and before driving.
- Subjects will be told to have glucose on hand for hypoglycemia
- Subject with persistent hyperglycemia especially if ketones develop will be told they may need to change their infusion set if they suspect catheter occlusion or administer insulin with syringe.

Warning:

Exposure to magnetic fields and radiation: Pump must not be exposed to X-ray, MRI, diathermy treatment, CT scan, or other type of devices that generates radiation. The magnetic fields and radiation in the immediate vicinity of this equipment can make the device non-functional or damage the part of the pump that regulates insulin delivery, possibly resulting in over delivery and severe hypoglycemia.

The pump must not be exposed to a permanent magnet, such as pump cases that have a magnetic clasp. Exposure to a permanent magnet may interfere with the motor inside the pump.

This device complies with Industry Canada licence-exempt RSS standard(s). Operation is subject to the following two conditions: (1) this device may not cause interference, and (2) this device must accept any interference, including interference that may cause undesired operation of the device.

J.2.5 Potential risks associated with the use of SmartGuard Feature

- When SmartGuard is turned ON, the feature may not activate when the blood sugar is low.
- When SmartGuard is turned ON, the feature may falsely activate when the subject's blood sugar is not low.
- When SmartGuard is turned ON, it cannot always reduce the severity and duration of hypoglycemia (for example over-bolusing with insulin).
- Standard mitigations include:
- Subject instruction to test BG via finger stick testing > 4 times a day.
- Subject instruction to adhere to 100% sensor wear.
- Subject instruction to use the bolus wizard when determining meal or correction bolus.

J.2.6 Potential risks associated with the use of CONTOUR NEXT LINK 2.4 meter

The risks are not any different than the risk associated with the commercially available meters in Europe. For use of the meter, refer to the instructions for use.

All these risks must be continuously monitored, assessed and documented by the investigator in the *Adverse Event eCRF*.

J.3 Risk-to-benefit rationale

The results of risk analysis, balancing benefits against risks associated with both the device system itself and procedures involved in its use, is included in the Instructions for Use and Investigator's Brochure.

The present study devices are all used within their intended use.

Provided that patients will use the MiniMed 640G system as it is intended to be used in routine practice, the anticipated risks for a patient to be in the study is not expected to be higher than in routine practice in Europe.

The patients will be followed with higher frequency of visits, which will allow a closer medical follow-up when compared to standard of care.

With the use of continuous glucose monitoring by the patients in treatment group, it is anticipated to see a reduction of hypoglycemia. The risks associated with the use of the sensor as described in section J.2.1 are often limited to skin irritation. Serious Adverse Events that occurred in past studies involving the glucose sensor use were relatively rare. One goal of the run-in phase is to identify patients who would not tolerate sensor wear and therefore, they would not be eligible to be randomized into the study. As CGM is not reimbursed in all the participating countries, it can be a benefit for patients in the treatment arm to have access to this therapy within the course of the study.

K REFERENCES

- [1] Bergenstal, «Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes,» *N Engl J Med*, 2010.
- [2] Battelino, «The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial,» *Diabetologia*, 2012.
- [3] Bergenstal, «Threshold-based insulin-pump interruption for reduction of hypoglycemia,» *N Engl J Med*, 2013.
- [4] Choudhary, «Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk,» *Diabetes Care*, 2011.
- [5] Ly, «Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: A randomized clinical trial,» *JAMA*, 2013.
- [6] Agrawal, «Usage and effectiveness of the low glucose suspend feature of the Medtronic Paradigm Veo insulin pump,» *J Diabetes Sci Technol*, 2011.
- [7] Agrawal, «Retrospective analysis of the real-world use of the threshold suspend feature of sensor-augmented insulin pumps,» *Diabetes Technol Ther*, 2015.
- [8] Buckingham, «Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension,» *Diabetes Care*, 2010.
- [9] DeBock, «Performance of a predictive insulin pump suspension algorithm for prevention of overnight hypoglycaemia,» *Diabetes*, 2014.
- [10] Danne, «The PILGRIM Study: In Silico Modeling of a Predictive Low Glucose Management System and Feasibility in Youth with Type 1 Diabetes During Exercise,» *Diabetes Technol Ther*, 2014.
- [11] Choudhary, «Performance of the predictive low glucose management feature of the MiniMed 640G system in a user evaluation study. ADA Poster,» *Diabetes*, p. 64:A27, 2015.
- [12] Barkai, «Prospective assessment of severe hypoglycaemia in diabetic children and adolescents with impaired and normal awareness of hypoglycaemia,» *Diabetologia*, 1998.
- [13] t. Braak, «Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia,» *Diabetes Care*, 2000.
- [14] Geddes, «Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes,» *Diabet Med*, 2008.
- [15] Fanelli, «Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM.,» *Diabetes*, 1993.
- [16] Cranston, «Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes,» *Lancet*, 1994.
- [17] Li et al., «A sample size adjustment procedure for clinical trials based on conditional power,» *Biostatistics*, 2002.

- [18] Chen et al., «Increasing the sample size when the unblinded interim result is promising.,» *Statistics in Medicine*, 2004.
- [19] Mehta and Pocock, «Adaptive increase in sample size when interim results are promising: A practical guide with examples,» *Statistics in Medicine*, 2011.
- [20] ADA, «Standards of Medical Care in Diabetes,» 2015.
- [21] Clarke, «Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms,» *Diabetes Care*, 1995.
- [22] Cox, «Fear of Hypoglycemia: Quantification, Validation, and Utilization,» *Diabetes Care*, 1987.
- [23] Bradley, «The Diabetes Treatment Satisfaction Questionnaire: DTSQ,» *Handbook of Psychology and Diabetes*, 1994.
- [24] Bradley, «Diabetes Treatment Satisfaction Questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur,» *Diabetes Care*, 1999.
- [25] Bradley, «Measures of psychological wellbeing and treatment satisfaction developed from the responses of people with tablet-treated diabetes,» *Diabet Med*, 1990.
- [26] Howorka, «Dealing with ceiling baseline treatment satisfaction level in patients with diabetes under flexible, functional insulin treatment: assessment of improvements in treatment satisfaction with a new insulin analogue,» *Qual Life Res*, 2000.
- [27] Bradley, «Diabetes Treatment Satisfaction Questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur,» *Diabetes Care*, 1999.
- [28] Bradley, «The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ,» *Health Qual Life Outcomes*, 2007.
- [29] Ly, «Predictive Low Glucose Insulin Suspension With The Medtronic Predictive Low Glucose Management System: Can It Prevent Exercise-induced Hypoglycemia?,» *ATTD Poster*, 2013.

L APPENDICES

L.1 Names and addresses

L.1.1 List of contact persons

Coordinating investigators:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Other contacts

The names and addresses of sponsor team, monitors, investigators and participating investigational centers will be kept under separate cover. These lists 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 lists of the contact persons (Sponsor List ; Monitors List ; Investigators List) are available upon request.

L.2 Case Report Forms

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

L.3 Sample Investigator Agreement

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

L.4 List of consumables

INFUSION SETS EUROPE

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

INFUSION SETS CANADA

MMT-921600	MiniMed™ Mio Pink 18" tubing with 6mm cannula (box of 10)
MMT-941600	MiniMed™ Mio Blue 18" tubing with 6mm cannula (box of 10)
MMT-923600	MiniMed™ Mio Pink 23" tubing with 6mm cannula (box of 10)
MMT-943600	MiniMed™ Mio Blue 23" tubing with 6mm cannula (box of 10)
MMT-965600	MiniMed™ Mio Clear 32" tubing with 6mm cannula (box of 10)
MMT-975600	MiniMed™ Mio Clear 32" tubing with 9mm cannula (box of 10)
MMT-905600	MiniMed™ Mio30 23" tubing with 13mm cannula (box of 10)
MMT-900660	MiniMed™ Mio30 43" tubing with 13mm cannula (box of 10)
MMT-394600	MiniMed™ Quick Set 18" tubing with 6 mm cannula (box of 10)
MMT-399600	MiniMed™ Quick Set 23" tubing with 6 mm cannula (box of 10)
MMT-387600	MiniMed™ Quick Set 32" tubing with 6 mm cannula (box of 10)
MMT-398600	MiniMed™ Quick Set 43" tubing with 6 mm cannula (box of 10)
MMT-397600	MiniMed™ Quick Set 23" tubing with 9 mm cannula (box of 10)
MMT-386600	MiniMed™ Quick Set 32" tubing with 9 mm cannula (box of 10)
MMT-396600	MiniMed™ Quick Set 43" tubing with 9 mm cannula (box of 10)
MMT-368600	MiniMed™ Silhouette 18" tubing with 13mm cannula (box of 10)
MMT-381600	MiniMed™ Silhouette 23" tubing with 13mm cannula (box of 10)
MMT-383600	MiniMed™ Silhouette 32" tubing with 13mm cannula (box of 10)
MMT-382600	MiniMed™ Silhouette 43" tubing with 13mm cannula (box of 10)
MMT-378600	MiniMed™ Silhouette 23" tubing with 17mm cannula (box of 10)
MMT-384600	MiniMed™ Silhouette 32" tubing with 17mm cannula (box of 10)
MMT-377600	MiniMed™ Silhouette 43" tubing with 17mm cannula (box of 10)
MMT-862	MiniMed™ Sure-T 18" tubing with 6mm cannula (box of 10)
MMT-864	MiniMed™ Sure-T 23" tubing with 6mm cannula (box of 10)
MMT-874	MiniMed™ Sure-T 23" tubing with 8mm cannula (box of 10)

INFUSION SET INSERTION DEVICES

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

RESERVOIRS

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

OTHERS

ACC-LR6	AA Battery (Alkaline)
MMT-174	Tape HMS-174 ADH IV3000 1-hand 13L
7005739-006	Standard tape
HMS-180	Skin Tac Adhesive Wipe (box of 50)
MMT-173	Skin preparation wipes

L.5 Sample Questionnaires

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

L.6 Abbreviations

ADE	Adverse Device Effect
AE	Adverse event
CEC	Clinical Events Committee
AUC	Area Under the Curve
BG	Blood Glucose
BP	Blood pressure
CIP	Clinical Investigation Plan
C	Control Arm
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
d	day
DD	Device Deficiency
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
EC	Ethical Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture (Oracle Clinical)
FDA	Food and Drug Administration
FU	Follow up
HFS	Hypoglycemia Fear Survey
IFU	Instruction For Use
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IRB	Institutional Review Board
ISF	Investigator Site File
m	months
MAGE	Mean Amplitude Glucose Excursion
MDD	Medical Device Directive
MDI	Multiple Daily Injection
PIC	Patient Informed Consent
PRO	Patient Reported Outcome
RA	Regulatory Affairs
RAE	Regulatory Affairs Europe
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump
SMBG	Self-Monitoring Blood Glucose
SOP	Standard operating procedure
T	Treatment arm
T1DM	Type 1 Diabetes Mellitus
USADE	Unanticipated Serious Adverse Device Effect
w	week
WECAN	West Europe and Canada
yrs	Years