Medtronic	
Study Title	Safety Evaluation of the Hybrid Closed Loop (HCL) system in pediatric subjects with Type 1 Diabetes
NCT Number	NCT02660827
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Medtronic

Title:	Safety Evaluation of the Hybrid Closed Loop (HCL) system in pediatric subjects with Type 1 Diabetes
Protocol Number:	CEP302DOC/J
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Date of Protocol:	29 January 2019

Synopsis

Title	Safety Evaluation of the Hybrid Closed Loop (HCL) System in pediatric subjects with Type 1 Diabetes
IDE Number	**G150247**
Devices	***Investigational and Commercially available devices used outside their approved intended use:*** **Hybrid Closed Loop (HCL) System:** ○ Medtronic® MiniMed® 670G Insulin Pump (MMT-1780) –Investigational configuration ○ Medtronic® MiniMed® 670G Insulin Pump (MMT-1780) US approved configuration; ▪ Commercially available but used outside intended use in the US; ▪ Investigational in Israel ○ GST3C Transmitter (MMT-7811) – Investigational configuration ○ Guardian Link (3) Transmitter Kit (MMT-7810) US approved configuration; ▪ Commercially available but used outside intended use in the US; ▪ Investigational in Israel ○ Guardian Link (3) Transmitter (MMT-7811) US approved configuration; ▪ Commercially available but used outside intended use in the US; ▪ Investigational in Israel ○ Transmitter Charger (MMT-7715) – Investigational configuration ○ Transmitter Charger (MMT-7715) – US approved configuration which is included in the MMT-7810 Transmitter Kit; ▪ Commercially available but used outside intended use in the US ○ TST Tester (MMT-7726) investigational ○ TST Tester (MMT-7736) included in the MMT-7810 Transmitter Kit US approved configuration; ▪ Commercially available but used outside intended use in the US; ○ Medtronic MiniMed Enlite® 3 Glucose Sensor (MMT-7020) – Investigational configuration ○ Guardian Sensor (3) Glucose Sensor (MMT-7020) – US approved configuration ▪ Commercially available but used outside intended use in the US; ▪ ○ Bayer CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (MMT-1352 in US) – Investigational configuration; ○ CONTOUR ® NEXT LINK 2.4 Blood Glucose Meter by Ascensia (MMT-1352) – US approved configuration; MMT-1152 (Israel) ▪ Commercially available but used outside intended use in the US; ▪ Investigational in Israel ○ One-Press Serter (MMT-7512) included in the MMT-7810 Transmitter Kit; Commercially available but used outside intended use in the US ***Non-Investigational, commercially available or Exempt devices:*** ○ Transmitter Charger (MMT-7715) – US approved configuration which is included in the MMT-7810 Transmitter Kit; ▪ Commercially available in Israel

	○ TST Tester (MMT-7736) included in the MMT-7810 Transmitter Kit US approved configuration; ▪ Commercially available in Israel ○ Guardian Sensor (3) Glucose Sensor (MMT-7020) ▪ Commercially available in Israel ○ One-Press Serter (MMT-7512) included in the MMT-7810 Transmitter Kit ▪ Commercially available in Israel ○ CareLink USB (MMT-7306) ○ Abbott® Precision Xtra™ Meter (US) to be used for blood ketone measurements only (referred to as the Ketone Meter throughout this protocol and utilized in US only) ○ Abbott FreeStyle Optium Blood Glucose and Ketone Monitoring System (OUS) to be used for blood ketone measurements only (referred to as the Ketone Meter throughout this protocol and utilized in Europe, Middle East and Africa (EMEA) region only) ○ Medtronic CareLink® Clinical Therapy Management Software for Diabetes (MMT-7334) -– referred to as CareLink Clinical throughout this protocol – (Class 1 Exempt device in the US, CE marked, not commercially available in Israel)
Europe Classification of devices by Rules according to MDD	Infusion set: MDD, Annex IX, Rule 8, Class IIb Insertion devices: MDD, Annex IX, Rule 12, Class I Reservoirs: MDD, Annex IX, Rule 2, Class IIa Insulin Pump: MDD, Annex IX, Rule 11, Class IIb Transmitter: MDD, Annex X, Rule 10, Class IIa Transmitter Charger: MDD, Annex IX, Rule 1 and 12, Class I Sensor: MDD, Annex IX, Rule 8, Class III Glucose Meter (Bayer): In vitro diagnostic device, Annex II of the DIRECTIVE 98/79/EC, List B Blood Glucose and Ketone Monitoring System (Abbott): In vitro diagnostic device, Annex II of the DIRECTIVE 98/79/EC, List B
Europe Classification for Biocompatibility according to ISO EN 10993-1 Table 1 and 2 (Type of Body contact/duration)	Infusion sets, Pump reservoirs: In compliance with ISO10993-1 and USP requirements for the use of insulin in the infusion sets. Insulin Pump: In compliance with ISO10993-1 Transmitter: In compliance with ISO10993-1 Sensor: In compliance with ISO10993-1
Europe Device Nomenclature: GMDN (Global Medical Device Nomenclature)	Reservoirs: 35838, Ambulant insulin infusion pump reservoir Infusion sets: 35833, Infusion Pump Administration Set Insulin Pump: 35983, Insulin Infusion Pump Transmitter: 44611, Interstitial-Fluid Glucose Monitoring System Sensor: 59016, Subcutaneous Glucose Sensor Transmitter Charger: 44611, Interstitial-Fluid Glucose Monitoring System Serter: 45449, Injector Reset Device
Purpose/ Objective	The purpose of this study is to demonstrate that the hybrid closed loop system and the *Low Management Suspend before Low* feature are safe.

Study Design	This study is a single-arm, multi-center, Home and Hotel Clinical Investigation in pediatric subjects with type 1 diabetes on insulin pump therapy. Once 10 adult subjects in the pivotal closed loop study have completed participation (i.e. performed last study visit), the DSMB will determine whether it is safe for the pediatric subjects in this study to begin enrollment. As part of this review, the DSMB will look at data from ***all*** enrolled subjects in the adult study at this time. Staged enrollment for 2-6 years age group: The younger ages (2-4 years) will not be enrolled until it has been shown that all Safety criteria for the 5-6 year olds have been met as follows: Once the DMC (Data Monitoring Committee) have reviewed data for 10 subjects (5-6 years of age) during the first month of the study period and have determined that study participation is safe, subjects 2-4 years of age will be permitted to enroll. **Run-in Period** A total of up to 200 subjects (age 2-13) will be enrolled at up to 15 investigational centers (14 in the US, 1 in the Europe, Middle East and Africa (EMEA) region) in order to reach 120 subjects who will complete the HCL study. The run-in period will primarily be used to allow subjects to become familiar with the new study devices. During the run-in period, subjects will be using the Study Pump (670G) with the Sensor Augmented Pump function only activated (i.e. SmartGuard Low Management features OFF and Auto Mode OFF). At the end of the CGM run-in period at Run-in Visit 4, subjects 7-13 years of age will be asked to undergo 12 hours (maximum) of *Low Management Suspend before Low* frequent sample testing on the first day of sensor wear. Testing will begin during the day and extend for an overnight stay at the clinic. Subjects 2-6 years of age will not undergo frequent sample testing procedures at this visit. (Please see section 11.4 for further details). Manual Mode: Run-in Pump Settings **before** frequent Sample testing, i.e.: *Low Management Suspend before Low* ○ High and Low Setup limits and alert(s) will be set at investigator discretion ▪ Low Setup Limit may not be set lower than 65mg/dL ▪ For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL ○ SmartGuard −Low Management must be OFF during this period ○ SmartGuard − Auto Mode must be OFF during this period Manual Mode: Run-in Settings Pump **during** frequent Sample testing, i.e. *Low Management Suspend before Low*: ○ Low Setup limit for subjects 7-13 years must be set at 65 mg/dL ○ Subjects 2-6 years of age will not participate in frequent sample testing, but will still complete Visit 4. ○ Alert before low should be ON ○ Resume basal alert should be ON

Prior to wearing study devices, all subjects and their parent(s)/guardian(s)/companion(s) will be trained on the devices as well as diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training regarding the need to have access to oral glucose in case of hypoglycemia and glucagon. Subjects and their parent(s)/guardian(s)/companion(s) will be instructed to monitor blood glucose using self-monitoring of blood glucose (SMBG) 4-6 times a day. As a precaution, subjects and their parent(s)/guardian(s)/companion(s) will be told that they should keep their own insulin pump supplies in a safe place in case they should be asked during the study to revert back to their own pump. Subjects and their parent(s)/guardian(s) will also be instructed that they should always have back up to their study pump on hand such as insulin and syringe in case of study pump issues (i.e. infusion set occlusion with high glucose).

Study Period – At Home

Following the two week run-in period using the Study Pump (670G), all subjects will participate in a 3-month study period. Prior to entry into Auto Mode, subjects will use the pump in Manual Mode during the first 6 days of the study period in order to collect data on insulin utilization and sensor glucose levels which will be used by the closed loop algorithm. After this 6 day period, the subjects will be allowed to enter Auto Mode. When subjects are in Manual Mode, the SmartGuard Low Management feature is recommended (optional) to be set to Suspend Before Low with a limit setting of 70 mg/dL.

Subjects will be required to have a companion 18 years or older with them during the night for the duration of the study period. The companion will need to be under the same roof, but not necessarily in the same bedroom. During the Hotel stay where subjects are monitored closely, the presence of a companion is not necessary.

Subjects less than 11 years of age should call a parent if they are transitioned out of Auto Mode or for any questions about use of Auto Mode. For subjects 11-13 years of age it is at the investigator's or parents' discretion to determine if a parent should be called in the event of an exit from Auto Mode.

A lockable pouch for the pump may be distributed to subjects at the investigator's discretion. Since the pump version used in this study does not include Block Mode, the purpose of the pouch is to prevent subjects from changing pump settings.

Settings:

- Manual Mode:
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
    - Low Setup limit recommended to be set at 70 mg/dL
    - Low Setup Limit may not be set lower than 65mg/dL
    - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
  - It is recommend (optional) to have the SmartGuard Low Management turned ON
  - Alarms that are fixed in Manual Mode:
    - When Sensor glucose at or below 50 mg/dL

- Auto Mode:
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
  - Low Setup limit recommended to be set at 70 mg/dL
    - Low Setup Limit may not be set lower than 65mg/dL

- For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
- The Temp Target is recommended to be used when subject exercises
- Alarms that are fixed in Auto Mode:
  - When Sensor glucose at or below 50 mg/dL
  - When sensor glucose at or above 300 mg/dL for one hour
  - When sensor glucose at or above 250 mg/dL for 3 hours

Study Period - Hotel Study

Subjects 7-13 years of age will participate in a Hotel study (6 days, 5 nights), with the remainder of the study period to be spent at home. The Hotel study may be conducted at either a clinic (GCRC is acceptable), a Hotel or a house as long as staffing, meal and activity requirements are met. Subjects may leave to go to school but must return after school or school activities have finished for the day.

During the hotel stay, subjects will also participate in a daily exercise/activity regimen for a minimum of 4 hours spread throughout the day; exercise/activity may also take place in the evening. See a sample list of activities in Section 11.5.5. With respect to meals, subjects will be allowed to eat as they normally do.

Subjects 2-6 years of age are not required to participate in a hotel study. Instead, they will participate in an out-of-home study for 5 consecutive days, 4-6 hours per day. During that 5 day period, subjects should engage in significant activity/exercise. Such activities could include utilizing gym play areas appropriate for toddlers and young children, swimming, and playground games. Evidence of geographic location and exercise/activity will be documented by daily photograph. In addition, investigational center staff will be present daily for the 4-6 hours of exercise during the 5 day period.

Auto Mode Frequent Sample testing

While in Auto Mode, subjects 7-13 years of age will undergo daytime and/or nighttime Frequent Sample Testing (FST) during the Hotel study with i-STAT® used as a reference value.

Subjects 7-13 years:

Overnight frequent sample testing (10PM to 7AM) in Auto Mode will be every 30 minutes; daytime frequent sample testing (7AM to 10PM) in Auto Mode will be every 60 minutes. The exact times of FST may differ, but the interval for testing should remain as described.

Subjects 2-6 years:

During one of the days of the out-of-home study subjects should undergo frequent sample testing for 4-6 hours using SMBG as a reference method. The frequent sample testing period will be supervised by investigational center staff. Frequency of testing is every 30 minutes.

Note 1: The Auto Mode Frequent Sample Testing may be performed at any time during the hotel study (7-13 years) or the out-of-home study (2-6 years).

Note 2: It is important that calculation of total blood draw be maintained throughout the study so that the total amount of blood volume does not exceed the maximum each subject is allowed. If the maximum is reached, FST will be stopped.

All participating investigational centers will target 3-6 subjects (7-13 years) to undergo a hotel study on Day 7 to Day 14 in Month 1 of the study period. On Days 1-6 of the Study

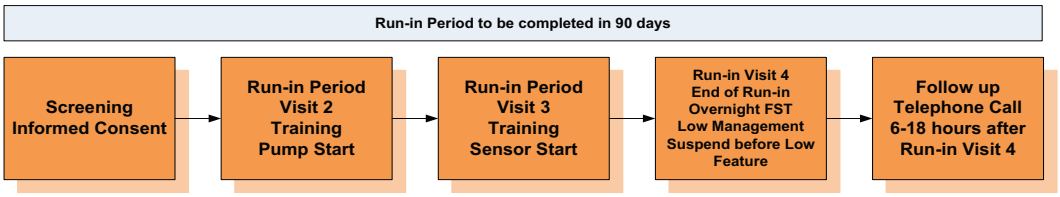
	period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON. Entry into Auto Mode will occur on day 7 whether at home or in hotel. A minimum of 4 subjects are recommended to participate in each of the hotel studies. However, the sponsor has discretion to allow more or less subjects to attend a hotel stay should the site request this. The remaining subjects at each site will be assigned to participate in hotel studies during the last 2 months of the study period: • Month 2 (Day 36-Day 66): 1-2 Hotel Studies N = minimum 20 subjects from all participating research centers will participate in hotel study during month 2. On Days 1-6 of the Study period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON. • Month 3 (Day 67-Day 96): 1-2 Hotel Studies N = minimum 20 subjects from all participating research centers will participate in hotel study during month 2. On Days 1-6 of the Study period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON. Since all subjects 7-13 years of age are expected to participate in a Hotel Study, each site may conduct 3 - 4 Hotel Studies to ensure that all subjects have the opportunity to take part. After the initial hotel study, sites may schedule additional hotel studies per sponsor discretion. **Continued Access Program: Devices and Supplies:** Subjects will be given the opportunity to extend the use of their study devices for a period of up to 3 years after the end of the study period or until product is available commercially for children 2-13 years of age. If subjects choose to participate in this optional continued access program, they will retain the study devices at the end of study period. During the continued access period, subjects will come in for office visits every 3 months. At each of the quarterly visits, subjects will be asked about the occurrence of adverse events and device complaints. They will also be tested for A1C at each of those visits. Continued Access Program - Participation in ancillary studies not outlined in this protocol: Subjects will be permitted to participate in other studies during the continued access period of the study with Sponsor permission, provided that the studies do not include the use of drugs or devices, i.e. devices not used in this study.
Sample Size and Investigational Sites	A total of up to 200 subjects (age 2-13) will be enrolled at up to 15 investigational centers (14 in the US, 1 EMEA) in order to reach 120 subjects who will complete the HCL study. A minimum of 20 subjects 2-6 years of age will be enrolled (N=10 5-6 years of age, N=10 2-4 years of age). There will be 4-20 subjects per site.
Study Duration	The study is anticipated to last no longer than 12 months from investigational center initiation to completion of all data entry and monitoring procedures with an optional 2-3 year period for continued access to study devices and supplies after the end of the study period. It is estimated that all subjects will be enrolled into the study within approximately 6 months of study start. Subjects can expect to participate for approximately 5 months through the study period and an optional 2-3 year program for continued access to study devices and supplies.
Inclusion Criteria	

	Subjects will be considered for enrollment in the study if they meet all of the following criteria: ***General Inclusion Criteria*** 1. Subject is age 2-13 years at time of screening 2. Subject age 7 -13 years has a clinical diagnosis of type 1 diabetes for 1 year or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 3. Subject age 2-6 years has a clinical diagnosis of type 1 diabetes for 3 months or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis ***Study-specific inclusion criteria*** 4. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units 5. Subjects 7-13: Subjects and their parent(s)/guardian(s) are willing to participate in an overnight visit at the end of the run-in period. 6. Subject 7-13 years of age and their parent(s)/guardian(s) are willing to participate in a hotel study for the specified duration of hotel stay. 7. Subject 2-6 years of age and their parent(s)/guardian(s) are willing to participate in an extended visit during the study period to perform Frequent Sample Testing. 8. Subject must have companion 18 years or older who will sleep in the same dwelling place every night during the study period. This requirement may be verified by subject report at screening visit. 9. Subject is willing to perform ≥ 4 finger stick blood glucose measurements daily 10. Subject is willing to perform required sensor calibrations 11. Subject is willing to wear the system continuously throughout the study 12. Subject has a Glycosylated hemoglobin (A1C) value less than 10.0% (as processed by Central Lab) at time of screening visit **Note: All HbA1C blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.** 13. Subject has TSH in the normal range **OR** if the TSH is out of normal reference range the Free T3 is below or within the lab's reference range and Free T4 is within the normal reference range. 14. Subject 7 -13 years of age has had pump therapy for greater than 6 months prior to screening (with or without CGM experience) 15. Subject 2-6 years of age has had pump therapy for greater than 90 days prior to screening (with or without CGM experience) 16. Subjects and their parent(s)/guardian(s) are willing to upload data from the study pump; must have Internet access and a computer system that meets the requirements for uploading the study pump 17. If subject has celiac disease, it has been adequately treated as determined by the investigator 18. Subjects and their parent(s)/guardian(s) are willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount) o Humalog® (insulin lispro injection) o NovoLog® (insulin aspart) 19. Subjects and their parent(s)/guardian(s)/companions must be able to speak and be literate in English as verified by the investigator

Exclusion Criteria	1. Subject has a history of 2 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening: a. Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization) b. Coma c. Seizures 2. Subject is unable to tolerate tape adhesive in the area of sensor placement 3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection) 4. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator. 5. Subject has a cardiovascular condition which the investigator determines should exclude the subject, i.e. ventricular rhythm disturbance, hypertrophic cardiomyopathy 6. Subject is being treated for hyperthyroidism at time of screening 7. Subject has diagnosis of adrenal insufficiency 8. Subject 7-13 years of age has had DKA in the 6 months prior to screening visit. 9. Subject 2-6 years of age has had DKA in the 3 months prior to screening visit 10. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study 11. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks 12. Subject 7-13 years of age has been hospitalized or has visited the ER in the 6 months prior to screening resulting in a **primary diagnosis** of uncontrolled diabetes 13. Subject 2-6 years of age has been hospitalized or has visited the ER in the 3 months prior to screening resulting in a **primary diagnosis** of uncontrolled diabetes 14. Subject is currently abusing illicit drugs 15. Subject is currently abusing marijuana. 16. Subject is currently abusing prescription drugs 17. Subject is currently abusing alcohol 18. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of screening 19. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator 20. Subject has elective surgery planned that requires general anesthesia during the course of the study 21. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation 23. Subject diagnosed with current eating disorder such as anorexia or bulimia 24. Subject has been diagnosed with chronic kidney disease that results in chronic anemia 25. Subject has a hematocrit that is below the normal reference range of lab used. 26. Subject is on dialysis 27. Subject has serum creatinine of >2 mg/dL.
Study Timeline	**Run-in Period Visits: To be completed in 90 days**

- Screen **Visit 1** (Office): Consent and Screening
- Run-in **Visit 2** (Office): Study and device training; Pump Start
- Run-in **Visit 3** (Office): Start of CGM Run-in; Pump Follow-Up; Start CGM with Sensor; (CGM run-in with two week window of wearing SAP) **Note: Run-in Visit 2 and Run-in visit 3 may be combined**
- Run-in **Visit 4** (Office): *Low Management Suspend before Low* Overnight Frequent Sample testing; End of CGM run-in
- Run-in **Visit 4B** (Telephone): Call to subjects 6-18 hours after completion of overnight visit

Run-in visit schedule



Study Period Visits: This period lasts 96 - 110 days

Overview

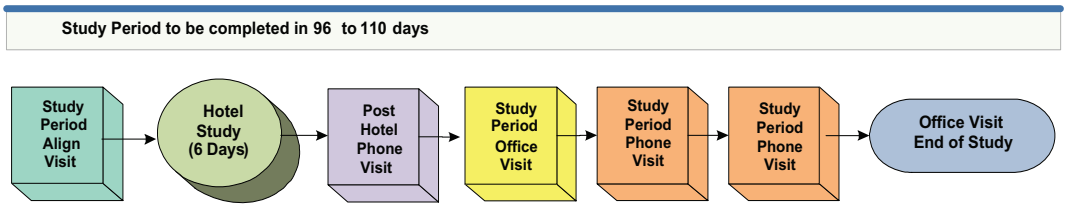
- All enrolled subjects will be asked to participate in 1 of the hotel studies
  - Subjects who cancel or are otherwise unable to participate in the hotel study may be re-scheduled for the next available hotel study
- Each site will target 6 subjects who must come in for the Hotel Study on Day 1 - Day 6 in Month 1 of the study period
  - If site has less than 4 subjects for a Hotel study the sponsor will determine whether or not the Hotel Study should proceed.
- Remaining subjects will be assigned to participate in the hotel study(ies) during Month 2 (Day 36- Day 66) or Month 3 (Day 67- Day 96)
- Telephone Visit windows are counted from the start of the study period (Day 1)
- Sponsor may guide the speed of enrollment during the study

Visit Schedule:

Hotel Visit Month 1 Cohort Schedule

- Office Visit Day 1 - Study Period Alignment Visit
- Hotel Study (Day 7- Day 14)
  - Subjects 2-6 years may do FST during this period of time
- Phone Visit (Day 30 – Day 37)
- Office Visit (Day 44 – Day 51)
- Phone Visit (Day 60 – Day 67)
- Phone Visit (Day 74 – Day 81)
- **End of Study** Period (Office Visit): Day 96 - Day 110

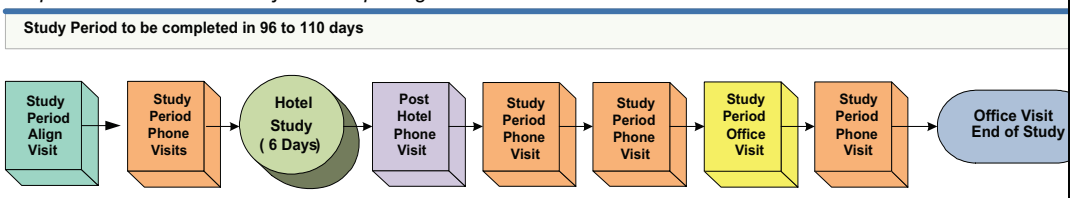
Sample visit schedule for subjects completing the Hotel visit in Month 1:



Hotel Visit Month 2 Cohort Schedule

- Office Visit Day 1 - Study Period Alignment Visit
- Telephone Visit (option of office visit) Day 7
- Telephone Visit (option of office visit) Day 8
- Telephone Visit (option of office visit) Day 9
- Telephone Visit (option of office visit) Day 10
- Telephone Visit (option of office visit) Day 11
- Telephone Visit (option of office visit) Day 12
- Telephone Visit (option of office visit) Day 13
- Hotel Study (Day 36 – Day 66)
  - Subjects 2-6 years may do FST during this period of time
- Post Hotel Phone Visit:
  - This Phone visit is to occur within 5 days from the last day of the Hotel study.
- Phone Visit (Day 36 – Day 43)
  - Phone visit not required if any of these days overlap period of hotel stay
- Phone Visit (Day 50 – Day 57)
  - Phone visit not required if any of these days overlap period of hotel stay
- Office Visit (Day 66 – Day 73)
- Phone Visit (Day 80 – Day 87)
- **End of Study Period** (Office Visit): Day 96 – Day 110

Sample visit schedule for subjects completing the Hotel visit in Month 2:

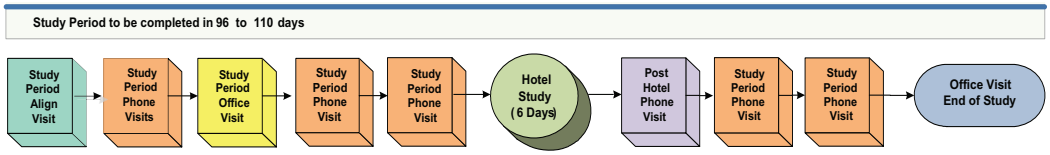


Hotel Visit Month 3 Cohort Schedule

- Office Visit 1 - Study Period Alignment Visit
- Telephone Visit (option of office visit) Day 7
- Telephone Visit (option of office visit) Day 8
- Telephone Visit (option of office visit) Day 9
- Telephone Visit (option of office visit) Day 10
- Telephone Visit (option of office visit) Day 11
- Telephone Visit (option of office visit) Day 12
- Telephone Visit (option of office visit) Day 13

- Office Visit (Day 14 – Day 21)
- Phone Visit (Day 30 – Day 37)
- Phone Visit (Day 44 – Day 51)
- Hotel Study (Day 67 – Day 96)
  - Subjects 2-6 years may do FST during this period of time
- Post Hotel Phone Visit:
  - This Phone visit is to occur within 5 days from the last day of the Hotel study.
  - If the Phone visit after Hotel study occurs within the window period of an interim Phone visit, the corresponding interim Phone visit is not required.
  - If the End of Study visit occurs within 2 days after the Hotel study, the Phone visit after Hotel study is not required. For example: The Hotel study ends on Day 90. The End of Study visit occurs on Day 91.
- Phone Visit (Day 66 – Day 73)
  - Phone visit not required if any of these days overlap period of hotel stay
- Phone Visit (Day 80 – Day 87)
  - Phone visit not required if any of these days overlap period of hotel stay
- **End of Study Period** (Office): Day 96 – Day 110

Sample visit schedule for subjects completing the Hotel visit in Month 3:



Continued Access Program: Devices and Supplies

Visit Schedule
Subjects will come in for quarterly office visits for a period of approximately 3 years.

Office Visit Day 180 Continued Access (Day 150-210)
Office Visit Day 270 Continued Access (Day 240-300)
Office Visit Day 360 Continued Access (Day 330-390)
Office Visit Day 450 Continued Access (Day 420-480)
Office Visit Day 540 Continued Access (Day 510-570)
Office Visit Day 630 Continued Access (Day 600-660)
Office Visit Day 720 Continued Access (Day 690-750)
Office Visit Day 810 Continued Access Period (Day 780-840)
Office Visit Day 900 Continued Access (Day 870-930)
Office Visit Day 990 Continued Access (Day 960-1020)
Office Visit Day 1080 Continued Access (Day 1050-1110)

Safety Monitoring/ Risk Analysis	Safety monitoring/risk analysis details are outlined in Section 13.
Device Deficiencies	Reports of device deficiencies will be collected. For additional information, see Section 21.

Study Stopping Rules for Entire Study	During the study period, the following steps will be taken for: 1. UADE 2. DKA 3. Severe hypoglycemia events that result in subject requiring paramedic assistance, an ER visit or subjects who experience seizure, coma or death: • Site will notify the sponsor on the same day after receiving knowledge of the event. If the event becomes known to the site after hours, then it should be reported to the sponsor the next day. • Sponsor will notify FDA and the country-specific regulatory agency in the EMEA region within 24 hours of knowledge of event and provide updates to those agencies as information becomes available. • Enrollment will be stopped after the above events have been reported • DSMB is to review the event within 48 hours from the time that sponsor is notified. If possible, the investigator should be available to answer questions by DSMB. • DSMB will provide recommendation to sponsor on the following: ○ If enrollment may resume ○ If the entire study has to be stopped, including subjects who have already received study devices
Subject Stopping Rules	1. Any event of DKA will result in withdrawal of subject from study. For stopping rules specific to In Clinic frequent sample testing for *Low Management Suspend before Low,* see section 11.4.6 2. Severe hypoglycemia secondary to subject non-compliance or other individual safety concerns: ○ Subject is not using the bolus wizard ○ Subject is not checking blood glucose using finger sticks ○ Subject is non-compliant with sensor wear ○ Subject is not following protocol procedures ○ Subject experiences a study pump malfunction
Statistical Analysis for Endpoints and Hypothesis	***DURING HOME PERIOD:*** **Descriptive Endpoints** • The mean change in A1C will be presented from baseline to end of study • Change of Total Daily Dose (TDD) of insulin from baseline to end of study • Change of weight from baseline to end of study • Time spent in Auto Mode versus time spent in Manual Mode • Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤ SG ≤ 180 mg/dL, SG > 180, 250 mg/dL, 350 mg/dL • Number of Events, AUC and Time in the hyperglycemic range: sensor glucose (SG) > 180, 250, 350 mg/dL • Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL **Safety Data Summarized** • Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) • Unanticipated Adverse Device Effects (UADE)

- Incidence of Severe Hypoglycemia
- Incidence of DKA

STUDY PERIOD DURING HOTEL

Descriptive Endpoints

During the Run-In Period

Low Management Suspend before Low Evaluation:

- Success rate of prevention of hypoglycemia (i.e. 1 - percent of *Low Management Suspend before Low* experiments that have 2 or more consecutive reference glucose values of <= 65 mg/dL)
- *Low Management Suspend before Low* Performance
- Sensor performance

During the Hotel Period in the Study Period

Auto Mode Evaluation:

- Time in different range (% of i-STAT): BG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤ BG ≤ 180 mg/dL, BG > 180, 250 mg/dL
- Number of Events, AUC and Time in the hyperglycemic range: i-STAT® glucose > 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: i-STAT® glucose < 50, 54, 60, and 70 mg/dL

Exploratory Analysis

Analysis of Primary Endpoint

The primary effectiveness endpoint is change in A1C from baseline to end of 3-month treatment period, defined as A1C measured at the 3-month treatment visit minus A1C measured at the randomization visit. The goal is to show simple superiority in reducing A1C from baseline to end of 3-month study period.

Analysis of Secondary Endpoint

The secondary endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study phase.

- **Secondary Endpoint: % of Time in Euglycemia (70 – 180 mg/dL)**

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

	• **Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)** The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided). • **Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)** The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).
Final Report	**Study Phase Final Report for Subjects 7-13 Years Old** A study phase final report will be generated once the 7-13 year old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 7-13 years old subjects will be summarized and presented in the final report. **Study Phase Final Report for Subjects 2-13 Years Old** An addendum study phase final report will be generated once the 2-6 year old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 2-13 years old subjects will be summarized and presented in the final report. **Continued Access Phase Final Report for Subjects 2-13 Years Old** An addendum continuation phase final report will be generated once the 2-13 year old cohort have completed the continuation phase visits. Safety data will be summarized and presented in the final report.

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List of Abbreviations

Abbreviation	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
ADE	Adverse Device Effect
ASIC	Application Specific Integrated Circuit
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CL	Closed Loop
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EC	Ethics Committee
EIS	Electrochemical Impedance Spectroscopy
ER	Emergency Room
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GCRC	General Clinical Research Center
hCG	Human chorionic gonadotropin
HCL	Hybrid Closed Loop
HFE	Human Factors Engineer
HL	HelpLine
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
IV	Intravenous
LSL	Low Suspend Limit
MedDRA	Medical Dictionary for Regulatory Activities
NDC	National Drug Code
NGSP	National Glycohemoglobin Standardization Program
OC-RDC	Oracle Clinical Remote Data Capture
OLS	Clinical Online Store
PC	Personal Computer
QC	Quality Control
RF	Radio Frequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SG	Sensor Glucose
SGV	Sensor Glucose Value
SMBG	Self-Monitoring of Blood Glucose
SSL	Secure Socket Layer
TDD	Total Daily Dose
TSH	Thyroid-stimulating hormone
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

1. Background and Rationale

Closed loop technology has been shown to reduce both hypoglycemia and hyperglycemia, as well as reduce glycemic variability.

Previous studies have evaluated prototype versions of the Medtronic closed-loop insulin delivery systems in pediatric patients, as well as adolescents and young adults. Researchers at the Yale University School of Medicine studied the performance of both a hybrid closed-loop algorithm and a fully closed loop algorithm using the Medtronic MMT-715 insulin pump, the Medtronic Sof-sensor and MiniLink transmitter and a control algorithm running on a laptop computer [Weinzimer et al, 2008]. Seventeen subjects between the ages of 13 and 20 years old participated in the study with eight subjects undergoing testing with a fully closed-loop algorithm, and the remaining nine subjects being evaluated using the hybrid closed-loop algorithm. This study demonstrated that a fully closed loop artificial pancreas using an external glucose sensor is feasible and effective in adolescents with type 1 diabetes.

The Type 1 Diabetes TrialNet Study Groups used this same system to evaluate inpatient hybrid closed-loop control (HCLC) initiated shortly after the diagnosis of type 1 diabetes [Diabetes Research in Children Network Study Group, 2013]. Forty eight subjects between the ages of 7.8 and 37.7 years old participated in the intensive treatment group and received inpatient HCLC followed by outpatient sensor augmented pump therapy. Forty six of the 48 subjects were less than 18 years old. The study found that inpatient HCLC safely initiated soon after the diagnosis of type 1 diabetes resulted in the rapid decrease in blood glucose levels within 24 hours of initiation and that while using HCLC, about 80% of the glucose levels were in the target range of 71-180 mg/dL, with minimal hypoglycemia.

Researchers at Princess Margaret Hospital for Children and the University of Western Australia in Perth, Australia studied a closed-loop system consisting of the Medtronic Paradigm Veo insulin pump, the Medtronic Enlite sensor, MiniLink transmitter and a fully closed-loop algorithm running on BlackBerry Storm smartphone in eight subjects between the ages of three and 21 years old [O'Grady et al, 2012]. These subjects underwent a total of 145 hours of closed-loop control over 16 nights. During these experiments, the closed-loop algorithm maintained venous plasma glucose in target (between 70 and 144 mg/dL) 78% of the time. This study also demonstrated the feasibility of a portable, automated, closed-loop system for overnight glucose control in adolescents and young adults with type 1 diabetes.

2. Names and Intended Use of Devices

The study will be conducted using the component described in the table below. Instructions for use are provided in the respective device manuals.

Investigational labeling requirements for the User Manuals will include the following statement for the United States: "CAUTION – Investigational device. Limited by Federal Law (USA) to Investigational use".

In accordance with the MDD directive, the investigational devices for EMEA will be labeled "Exclusively for Clinical Investigations". Language requirements for labeling (e.g. device labels and user guides) of

investigational devices will be followed in accordance with local regulations. For the EMEA region site, subjects will be required to sign a statement that they can understand English since the pump software user interface will only have the capability to display in English.

Medtronic MiniMed 670G Investigational System Components

Device Name	Model Number/ Part Number	Regulatory Status in US/OUS
Investigational Devices - Israel		
MiniMed 670G Pump (closed loop algorithm)	MMT-1780	Investigational
MiniMed 670G Pump (closed loop algorithm) – US approved	MMT-1780	Investigational
GST3-C Transmitter	MMT-7811	Investigational
Guardian Link (3) Transmitter – US approved	MMT-7811	Investigational
Guardian Link (3) Transmitter	MMT-7811	Investigational
Guardian Link (3) Transmitter Kit – US approved	MMT-7810	Investigational
Guardian Link (3) Transmitter Kit	MMT-7810	Investigational
Enlite 3 Glucose Sensor	MMT-7020	Investigational
Commercially available devices used outside their approved intended use - US		
Medtronic® MiniMed® 670G Insulin Pump (MMT-1780) - US approved	MMT-1780	US- Commercially available but used outside intended use
Guardian Link (3) Transmitter – US approved	MMT-7811	US- Commercially available but used outside intended use
Guardian Link (3) Transmitter Kit – US approved	MMT-7810	US- Commercially available but used outside intended use
Guardian Link (3) Transmitter Charger – also included in the MMT-7810 Transmitter Kit	MMT-7715	US- Commercially available but used outside intended use
TST Tester (MMT-7736) – also included in the MMT-7810 Transmitter Kit	MMT-7736	US- Commercially available but used outside intended use
Guardian Sensor (3) Glucose Sensor	MMT-7020	US- Commercially available but used outside intended use
One-Press Serter	MMT-7512	US- Commercially available but used outside intended use
Commercially Available / Exempt Devices		
Guardian Link (3) Transmitter Charger; included in the MMT-7810 Transmitter Kit	MMT-7715	CE marked and commercially available in Israel
TST Tester –included in the MMT-7810 Transmitter Kit	MMT-7736	CE marked and commercially available in Israel
Guardian Sensor (3) Glucose Sensor	MMT-7020	Commercially available in Israel
One-Press Serter; included in the MMT-7810 Transmitter Kit	MMT-7512	CE marked and commercially available in Israel
CareLink USB	MMT-7306	US - Exempt
Paradigm Reservoir	MMT-332A	US- Cleared (K032005) CE Marked and commercially available in Israel

Medtronic MiniMed 670G Investigational System Components

Device Name	Model Number/ Part Number	Regulatory Status in US/OUS
MiniMed Silhouette Infusion Set	MMT-377, MMT-378,	US- Cleared (K002138) CE Marked and commercially available in Israel
MiniMed Sil Serter	MMT-385	US- Cleared (K002138) CE Marked and commercially available in Israel
MiniMed Quick Set Infusion Set	MMT-396, MMT-397, MMT-398, MMT-399	US- Cleared (K011071) CE Marked and commercially available in Israel
MiniMed Quick-Serter	MMT-395	US- Cleared (K011071) CE Marked and commercially available in Israel
Abbott Precision Xtra™ Meter (REF: 99837)		US- Cleared (K051213) EMEA - Not applicable
Abbott Freestyle Optium™ Blood Glucose and Ketone monitoring system		US- Not applicable CE Marked and commercially available in Israel
Medtronic CareLink Clinical Therapy Management Software	MMT-7334	US- Class 1 Exempt device in the US CE marked, but not commercially available in Israel
CONTOUR® NEXT LINK 2.4 Blood Glucose Meter by Ascensia	MMT-1352 (US) MMT-1152 (Israel)	US- Commercially available device used outside their intended use. CE marked, but not commercially available in Israel

Please note:
Study devices may be combined with other materials (e.g. accessories, user Guide) and distributed to centers in a Kit.

2.1. Hybrid Closed Loop (HCL) System

2.1.1. Medtronic MiniMed 670G Insulin Pump (MMT-1780)

The MiniMed 670G Insulin Pump is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Enlite 3 Sensor, GST3C Transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump also displays continuous glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system (e.g. MiniMed 530G System (P120010)).

The MiniMed 670G Insulin Pump also includes the Smart Guard Auto Mode algorithm and a SmartGuard Low Management feature that may be enabled by the user. The SmartGuard Low Management feature enables insulin to suspend before a sensor glucose threshold is reached. The Smart Guard Auto Mode and SmartGuard Low Management features will not be active at the same time.

When Auto Mode is enabled on the MiniMed 670G insulin pump, the sensor glucose values received from the GST3C by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five minute intervals, to achieve glycemic control.

When Auto Mode is not enabled, the user may have the SmartGuard feature enabled. Here it will suspend basal rate delivery before the sensor glucose value has reached the programmed low threshold.

2.1.2. Medtronic MiniMed 670G Insulin Pump (MMT-1780) – US approved

The MiniMed 670G Insulin Pump is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Guardian Sensor 3, Guardian Link (3) Transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump also displays continuous glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system (e.g. MiniMed 530G System (P120010) in the US, Veo System OUS, which has the threshold suspend feature).

The MiniMed 670G Insulin Pump also includes the closed loop algorithm as part of the SmartGuard® collection of features that may be enabled by the user. SmartGuard is comprised of Manual Mode Low Management, which includes the suspend on low feature (suspends insulin delivery when a pre-set low SG threshold is reached), the suspend before low feature (enables insulin to suspend 30 minutes before a pre-set low SG threshold is reached) and Auto Mode (hybrid closed loop) feature. The Auto Mode and Manual Mode -Low Management features will not be active at the same time.

The pump may also be used as a simple pump without CGM or as a sensor augmented pump without the SmartGuard features.

When Auto Mode is enabled on the MiniMed 670G insulin pump, the sensor glucose values (SGVs) received from the Guardian Link (3) Transmitter by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five minute intervals, to achieve glycemic control.

With the HCL system, subjects must still deliver bolus insulin for meals as calculated by the insulin to carbohydrate ratio. This ratio is determined by the HCP/patient. In addition, the setting for active insulin must be programmed. Basal rates are set for period of open loop therapy.

When Auto Mode is not enabled, the user may enable the Low Management feature. Here, basal rate delivery will be suspended either when the SG reached a programmed low threshold (Suspend on Low) or before the SGV has reached the programmed low threshold (Suspend before Low).

Figure 1. 670G Insulin Pump

2.1.3. Medtronic MiniMed Enlite® 3 Glucose Sensor (MMT-7020)

The Medtronic MiniMed Enlite 3 Sensor (MMT-7020), referred to as Enlite 3 Sensor in this protocol, is an investigational product that contains a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor represents the next generation in the Enlite sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle and is shorter and thinner than the previous generation of Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The electrode tubing maintains the electrode structure by providing support during and after subcutaneous insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

2.1.4. Medtronic MiniMed Guardian Sensor (3) Glucose Sensor (MMT-7020) – US approved

The Medtronic MiniMed Guardian Sensor (3) (MMT-7020_is a non-investigational product (commercially available devices used outside their approved intended use (14 years and older)) that contains a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor represents the next generation in the Medtronic sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle and is shorter and thinner than the previous generation of Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The electrode tubing maintains the electrode structure by providing support during and after subcutaneous insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

2.1.5. One-Press Serter (MMT-7512)

The One-Press Serter (MMT-7512), referred to as the Serter (Figure 2) in this protocol, is a non-investigational (commercially available devices used outside their approved intended use (14 years and older)) insertion device that is used to ensure correct placement of the Guardian Sensor (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, multi-use device. This product is not commercially available in Israel.

Figure 2. One-Press Serter

2.1.6. GST3C Transmitter (MMT-7811)

The GST3C Transmitter has the same housing and sensor interface as the MiniLink transmitter. However, the internal electronics and firmware of the GST3C Transmitter are new. Like the MiniLink transmitter, the GST3C Transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables Electrochemical Impedance Spectroscopy (EIS). The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a sensor glucose value using calibration blood glucose values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D). The new algorithm is designed to improve and optimize performance when paired with the Enlite 3 Sensor and is the same algorithm as the GST4C Transmitter. Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as “Smart Cal,” instead of strictly scheduled time-based calibration requirements.

2.1.7. Guardian Link (3) Transmitter (MMT-7811) – US approved

The Guardian Link (3) Transmitter has the same housing and sensor interface as the MiniLink transmitter. However, the internal electronics and firmware of the Guardian Link (3) Transmitter are new. Like the MiniLink transmitter, the Guardian Link (3) Transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables Electrochemical Impedance Spectroscopy (EIS). The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.
In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SGV using calibration blood glucose values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D). The new algorithm is designed to improve and optimize performance when paired with the Guardian Sensor 3 and is the same algorithm as the Guardian Link (3) Transmitter. Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as “Smart Cal,” instead of strictly scheduled time-based calibration requirements. The transmitter may be supplied as a kit that (MMT-7810) also includes a TST Tester (MMT-7736), a One-Press Serter (MMT-7512) and a Transmitter Charger (MMT-7715).

2.1.8. Charger (MMT-7715)

The Charger (MMT-7715) is used to recharge the GST3C Transmitter as needed. A fully charged battery provides up to 7 days of GST3C Transmitter use. The system includes a battery charger that will recharge the device according to the user guide. Not commercially available in Israel.

2.1.9. Charger (MMT-7715) – US approved

The Transmitter Charger (MMT-7715) is used to recharge the Guardian Link (3) Transmitter as needed. A fully charged battery provides up to 7 days of Guardian Link (3) Transmitter use. The system includes a battery charger that will recharge the device according to the user guide. Not commercially available in Israel.

2.1.10. TST Tester (MMT-7726)

The TST Tester (MMT-7726) is an investigational product and operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation.

Not commercially available in Israel.

2.1.11. TST Tester (MMT-7736) – US approved

The TST Tester (MMT-7736) operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation. It is a non-investigational product (commercially available devices used outside their approved intended use (14 years and older)). Not commercially available in Israel.

Figure 3. GST3C Transmitter and Charger

2.1.12. Bayer CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (MMT-1352 in US, MMT-1152 in Israel)

An investigational Bayer CONTOUR NEXT LINK 2.4 Blood Glucose Meter, referred to as the Study Meter throughout protocol, will be provided to study participants for use with the Medtronic MiniMed 670G Insulin Pump. The meter measures a subject's capillary blood glucose level using the Bayer CONTOUR NEXT Strips, which is then used to calibrate the pump. The Medtronic MiniMed 670G Insulin Pump uses the calibration point in the real-time algorithm which calculates the sensor glucose values (SGVs) that are displayed to the subject. The result of the finger stick (capillary SMBG) reading performed is entered into the Medtronic MiniMed 670G Insulin Pump and can be stored in its memory as a glucose point. The Medtronic MiniMed 670G Insulin Pump asks the user every time if the user wants to use the linked meter BG for calibration. If yes is selected, the glucose value will be stored in memory as a calibration point. This meter has a remote bolus feature that will not be operational with the HCL system.

2.1.13. CONTOUR® NEXT LINK 2.4 by Ascensia Blood Glucose Meter (MMT-1352 in US, MMT-1152 in Israel)

A CONTOUR Next Link 2.4 by Ascensia RF-Enabled Blood Glucose Meter, referred to as the Study Meter throughout protocol, will be provided to study participants for use with the MiniMed 670G Insulin Pump. The meter measures a subject's capillary blood glucose level using the Bayer CONTOUR NEXT Strips, which is then used to calibrate the pump. The MiniMed 670G Insulin Pump uses the calibration point in the real-time algorithm which calculates the SGVs that are displayed to the subject. The result of the finger stick (capillary SMBG) reading performed is entered into the MiniMed 670G Insulin Pump and can be stored in its memory as a glucose point. The MiniMed 670G Insulin Pump asks the user every time if the user wants to use the linked meter BG for calibration. If yes is selected, the glucose value will be stored in memory as a calibration point. This meter has a remote bolus feature that will not be operational during the closed loop system.

2.2. Non-Investigational or Exempt Devices

2.2.1. CareLink USB

The CareLink USB (MMT-7306) is an accessory to the CareLink Clinical Therapy Management Software that facilitates wireless communication between a personal computer and devices employing the Medtronic proprietary 2.4 GHz, Tel-D communication protocol. The device is only intended to transfer data, it does not have any diagnostic or therapeutic function/benefit.

2.2.2. US only: Abbott Precision Xtra™ Meter (REF: 99837)

The Abbot Precision Xtra Meter (to be used in the US), referred to as the Ketone Meter throughout the protocol, measures both blood glucose (sugar) and blood ß-Ketone. In this study, the meter will only be used to collect ß-Ketone data, which will be collected for reporting and review (see Investigator Site binder for details) and as described in the body of this study protocol. This particular meter will be used because it is the only commercially available meter which allows quantification of blood ß-Ketone levels and is the preferred patient method of testing over urine testing.

2.2.3. EMEA only: Abbott Freestyle Optium™ Blood Glucose and Ketone monitoring system

The Abbot Freestyle Optium Meter (to be used OUS), referred to as the Ketone Meter throughout the protocol, measures both blood glucose (sugar) and blood ß-Ketone. In this study, the meter will only be used to collect ß-Ketone data, which will be collected for reporting and review (see Investigator Site binder for details) and as described in the body of this study protocol. This particular meter will be used because it is the only commercially available meter which allows quantification of blood ß-Ketone levels and is the preferred patient method of testing over urine testing.

2.2.4. Medtronic CareLink® Clinical Therapy Management Software for Diabetes (MMT-7334)

Medtronic CareLink® Therapy Management Software for Diabetes is CE-marked as a Class I Exempt medical device, This Web-based system allows the device data to be viewed and easily evaluated by the physician. A personal computer (PC) links to the Medtronic CareLink® system via the Internet and allows for upload of data from Medtronic MiniMed insulin pump and third-party blood glucose meters. For the purposes of this study, uploads are performed both by the Investigational Center staff and subjects

Medtronic CareLink® Clinical Therapy Management Software for Diabetes is an Internet based software system which allows data to be viewed and easily evaluated by the subject and his/her physician. A Personal Computer (PC) is used to access the Medtronic CareLink® system via the Internet, which then allows subjects to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party blood glucose meters. The clinical support version of Medtronic CareLink used in this study was developed for use by clinical trial subjects only. For the purposes of this study, all references to CareLink Clinical in this document relate to the clinical support version of Medtronic CareLink. The data contained in CareLink is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer on an Internet enabled PC.

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

(1) The internet to the web server;

(2) Web server to the application server;

(3) Application server to the database server.

This software has been developed especially for use in clinical trials.

2.2.5. Infusion sets

- MMT-396 (43" Quick Set Infusion Set 9mm catheter)
- MMT-397 (23" Quick Set Infusion Set 9mm catheter)
- MMT-398 (43" Quick Set Infusion Set 6mm catheter)
- MMT-399 (23" Quick Set Infusion Set 6mm catheter)
- MMT-377 (Silhouette Infusion set 43")
- MMT-378 (Silhouette Infusion set 23")

Patients are instructed to change their infusion set every 3 days. This results in a total of approximately 30 infusion sets for each patient who will wear the pump for 3 months at home (average of 3 days for each infusion set)

2.2.6. Reservoirs: 1.8mL or 3ml MMT-332A

Patients are instructed to change their reservoir every 2 to 3 days. This results in a total of approximately 135 reservoirs for each patient who will wear the pump for 3 months at home (average of 2.5 days for each reservoir)

2.2.7. Infusion Set Serter Devices

Each infusion set type has a corresponding serter device.

- Quick-Serter® (MMT-395)
- Sil-Serter® (MMT-385)

The devices are medical devices Class I and CE marked by Medtronic MiniMed and are indicated for single patient multi use, i.e. a patient uses the same serter every 2 to 3 days to insert a new infusion set as described in the IFU.

2.2.8. Insulin

Patients will use their own rapid-acting analogue insulin (novolog, humalog) during this study.

2.2.9. Supplies

Study pump, study meters and sensors are supplied with additional, commercially available materials i.e., reservoirs, infusion sets, alcohol wipes, meter supplies, overtape, etc. free of charge.

3. Purpose/ Objective

The purpose of this study is to demonstrate that the closed loop system is safe.

4. Study Design

This study is a single-arm, multi-center, Home and Hotel Clinical Investigation in pediatric subjects with type 1 diabetes on insulin pump therapy.

Once 10 adult subjects in the pivotal closed loop study have completed participation (i.e. performed last study visit), the DSMB will determine whether it is safe for the pediatric subjects in this study to begin enrollment. As part of this review, the DSMB will look at data from ***all*** enrolled subjects in the adult study at this time.

Staged enrollment for 2-6 years age group:
The younger ages (2-4 years) will not be enrolled until it has been shown that all Safety criteria for the 5-6 year olds have been met as follows: Once the DMC (Data Monitoring Committee) have reviewed data for 10 subjects (5-6 years of age) during the first month of the study period and have determined that study participation is safe, subjects 2-4 years of age will be permitted to enroll.

Run-in Period
A total of up to 200 subjects (age 2-13) will be enrolled at up to 15 investigational centers (14 in the US, 1 in the Europe, Middle East and Africa (EMEA) region) in order to reach 120 subjects who will complete the HCL study. The run-in period will primarily be used to allow subjects to become familiar with the new study devices. During the run-in period, subjects will be using the Study Pump (670G) with the Sensor Augmented Pump function only activated (i.e. SmartGuard Low Management features OFF and Auto Mode OFF). At the end of the CGM run-in period at Run-in Visit 4, subjects 7-13 years of age will be asked to undergo 12 hours (maximum) of *Low Management Suspend before Low* frequent sample testing on the first day of sensor wear. Testing will begin during the day and extend for an overnight stay at the clinic. Subjects 2-6 years of age will not undergo frequent sample testing procedures at this visit. (Please see section 11.4 for further details).

Manual Mode: Run-in Pump Settings **before** frequent Sample testing, i.e.: *Low Management Suspend before Low*

- High and Low Setup limits and alert(s) will be set at investigator discretion
  - Low Setup Limit may not be set lower than 65mg/dL
  - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
- SmartGuard −Low Management must be OFF during this period
- SmartGuard − Auto Mode must be OFF during this period

Manual Mode: Run-in Settings Pump during frequent Sample testing, i.e. Low Management Suspend before Low:

- Low Setup limit for subjects 7-13 years must be set at 65 mg/dL
- Subjects 2-6 years of age will not participate in frequent sample testing, but will still complete Visit 4.Alert before low should be ON
- Resume basal alert should be ON

Prior to wearing study devices, all subjects and their parent(s)/guardian(s)/companion(s) will be trained on the devices as well as diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training regarding the need to have access to oral glucose in case of hypoglycemia and glucagon. Subjects and their parent(s)/guardian(s)/companion(s) will be instructed to

monitor blood glucose using self-monitoring of blood glucose (SMBG) 4-6 times a day. As a precaution, subjects and their parent(s)/guardian(s)/companion(s) will be told that they should keep their own insulin pump supplies in a safe place in case they should be asked during the study to revert back to their own pump. Subjects and their parent(s)/guardian(s) will also be instructed that they should always have back up to their study pump on hand such as insulin and syringe in case of study pump issues (i.e. infusion set occlusion with high glucose).

Study Period – At Home

Following the two week run-in period using the Study Pump (670G), all subjects will participate in a 3-month study period. Prior to entry into Auto Mode, subjects will use the pump in Manual Mode during the first 6 days of the study period in order to collect data on insulin utilization and sensor glucose levels which will be used by the closed loop algorithm. After this 6 day period, the subjects will be allowed to enter Auto Mode. When subjects are in Manual Mode, the SmartGuard Low Management feature is recommended (optional) to be set to Suspend Before Low with a limit setting of 70 mg/dL.

Subjects will be required to have a companion 18 years or older with them during the night for the duration of the study period. The companion will need to be under the same roof, but not necessarily in the same bedroom. During the Hotel stay where subjects are monitored closely, the presence of a companion is not necessary.

Subjects less than 11 years of age should call a parent if they are transitioned out of Auto Mode. For subjects 11-13 years of age it is at the investigator's or parents' discretion to determine if a parent should be called in the event of an exit from Auto Mode.

A lockable pouch for the pump may be distributed to subjects at the investigator's discretion. Since the pump version used in this study does not include Block Mode, the purpose of the pouch is to prevent subjects from changing pump settings.

Settings:

- Manual Mode:
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
    - Low Setup limit recommended to be set at 70 mg/dL
    - Low Setup Limit may not be set lower than 65mg/dL
    - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
  - It is recommend (optional) to have the SmartGuard Low Management turned ON
  - Alarms that are fixed in Manual Mode:
    - When Sensor glucose at or below 50 mg/dL

- Auto Mode:
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
  - Low Setup limit recommended to be set at 70 mg/dL
    - Low Setup Limit may not be set lower than 65mg/dL
    - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
  - The Temp Target is recommended to be used when subject exercises
  - Alarms that are fixed in Auto Mode:
    - When Sensor glucose at or below 50 mg/dL
    - When sensor glucose at or above 300 mg/dL for one hour
    - When sensor glucose at or above 250 mg/dL for 3 hours

Study Period - Hotel Study

Subjects 7-13 years of age will participate in a Hotel study (6 days, 5 nights), with the remainder of the study period to be spent at home. The Hotel study may be conducted at either a clinic (GCRC is acceptable), a Hotel or a House as long as staffing, meal and activity requirements are met. Subjects may leave to go to school but must return after school or school activities have finished for the day.

During the hotel stay, subjects will also participate in a daily exercise/activity regimen for a minimum of 4 hours spread throughout the day; exercise/activity may also take place in the evening. See a sample list of activities in Section 11.5.5. With respect to meals, subjects will be allowed to eat as they normally do.

Subjects 2-6 years of age are not required to participate in a hotel study. Instead, they will participate in an out-of-home study for 5 consecutive days, 4-6 hours per day. During that 5 day period, subjects should engage in significant activity/exercise. Such activities could include utilizing gym play areas appropriate for toddlers and young children, swimming, and playground games. Evidence of geographic location and exercise/activity will be documented by daily photograph. In addition, investigational center staff will be present daily for the 4-6 hours of exercise during the 5 day period.

Auto Mode Frequent Sample testing
While in Auto Mode, subjects 7-13 years of age will undergo daytime and/or nighttime Frequent Sample Testing (FST) during the Hotel study with i-STAT® used as a reference value.

Subjects 7-13 years:
Overnight frequent sample testing (10PM to 7AM) in Auto Mode will be every 30 minutes; daytime frequent sample testing (7AM to 10PM) in Auto Mode will be every 60 minutes. The exact times of FST may differ, but the interval for testing should remain as described.

Subjects 2-6 years:
During one of the days of the out-of-home study subjects should undergo frequent sample testing for 4-6 hours using SMBG as a reference method. The frequent sample testing period will be supervised by investigational center staff. Frequency of testing is every 30 minutes. .

Note 1: The Auto Mode Frequent Sample Testing may be performed at any time during the hotel study (7-13 years) or the out-of-home study (2-6 years).

Note 2: It is important that calculation of total blood draw be maintained throughout the study so that the total amount of blood volume does not exceed the maximum each subject is allowed. If the maximum is reached, FST will be stopped.

All participating investigational centers will target 3-6 subjects (7-13 years) to undergo a hotel study on Day 7 to Day 14 in Month 1 of the study period. On Days 1-6 of the Study period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON. Entry into Auto Mode will occur on day 7 whether at home or in hotel. A minimum of 4 subjects are recommended to participate in each of the hotel studies. However, the sponsor has discretion to allow more or less subjects to attend a hotel stay should the site request this.

The remaining subjects at each site will be assigned to participate in hotel studies during the last 2 months of the study period:

- Month 2 (Day 36-Day 66): 1-2 Hotel Studies N = minimum 20 subjects from all participating research centers will participate in hotel study during month 2. On Days 1-6 of the Study period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON.
- Month 3 (Day 67-Day 96): 1-2 Hotel Studies N = minimum 20 subjects from all participating research centers will participate in hotel study during month 2. On Days 1-6 of the Study period, during which data necessary for Auto Mode initiation is collected, subjects will not be permitted to turn Auto Mode ON.

Since all subjects 7-13 years of age are expected to participate in a Hotel Study, each site may conduct 3 - 4 Hotel Studies to ensure that all subjects have the opportunity to take part. After the initial hotel study, sites may schedule additional hotel studies per sponsor discretion.

Continued Access Program: Devices and Supplies:

Subjects will be given the opportunity to extend the use of their study devices for a period of up to 3 years after the end of the study period or until product is available commercially. If subjects choose to participate in this optional continued access program, they will retain the study devices at the end of study. During the continued access period, subjects will come in for office visits every 3 months. At each of the quarterly visits, subjects will be asked about the occurrence of adverse events and device complaints. They will also be tested for A1C at each of those visits.

Continued Access Program - Participation in ancillary studies not outlined in this protocol:

Subjects will be permitted to participate in other studies during the continued access period of the study with Sponsor permission, provided that the studies do not include the use of drugs or devices, i.e. devices not used in this study.

5. Sample Size and Investigational Sites

A total of up to 200 subjects (age 2-13) will be enrolled at up to 15 investigational centers (14 in the US, 1 EMEA) in order to reach 120 subjects who will complete the HCL study. A minimum of 20 subjects 2-6 years of age will be enrolled (N=10 5-6 years of age, N=10 2-4 years of age). There will be 4-20 subjects per site.

6. Study Duration

The study is anticipated to last no longer than 12 months from investigational center initiation to completion of all data entry and monitoring procedures with an optional 2 -3 year period for continued access to study devices and supplies after the end of the study period. It is estimated that all subjects will be enrolled into the study within approximately 6 months of study start. Subjects can expect to participate for approximately 5 months through the study period and an optional 2-3 year program for continued access to study devices and supplies.

7. Inclusion / Exclusion Criteria

7.1. Inclusion Criteria

Subjects will be considered for enrollment in the study if they meet all of the following criteria:

7.1.1. General Inclusion Criteria

1. Subject is age 2-13 years at time of screening
2. Subject age 7-13 has a clinical diagnosis of type 1 diabetes for 1 year or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
3. Subject age 2-6 years has a clinical diagnosis of type 1 diabetes for 3 months or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis

7.1.2. Study-specific inclusion criteria

4. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units
5. Subjects 7-13: Subjects and their parent(s)/guardian(s) are willing to participate in an overnight visit at the end of the run-in period.
6. Subject 7-13 years of age and their parent(s)/guardian(s) are willing to participate in a hotel study for the specified duration of hotel stay.
7. Subject 2-6 years of age and their parent(s)/guardian(s) are willing to participate in an extended visit during the study period to perform Frequent Sample Testing.
8. Subject must have companion 18 years or older who will sleep in the same dwelling place every night during the study period. This requirement may be verified by subject report at screening visit.
9. Subject is willing to perform ≥ 4 finger stick blood glucose measurements daily
10. Subject is willing to perform required sensor calibrations
11. Subject is willing to wear the system continuously throughout the study
12. Subject has a Glycosylated hemoglobin (A1C) value less than 10.0% (as processed by Central Lab) at time of screening visit
    Note: All HbA1C blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.
13. Subject has TSH in the normal range **OR** if the TSH is out of normal reference range the Free T3 is below or within the lab's reference range and Free T4 is within the normal reference range.
14. Subject 7-13 years of age has had pump therapy for greater than 6 months prior to screening (with or without CGM experience)
15. Subject 2-6 years of age has had pump therapy for greater than 90 days prior to screening (with or without CGM experience)
16. Subjects and their parent(s)/guardian(s) are willing to upload data from the study pump; must have Internet access and a computer system that meets the requirements for uploading the study pump
17. If subject has celiac disease, it has been adequately treated as determined by the investigator
18. Subjects and their parent(s)/guardian(s) are willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount)
    - Humalog® (insulin lispro injection)
    - NovoLog® (insulin aspart)
19. Subjects and their parent(s)/guardian(s)/companions must be able to speak and be literate in English as verified by the investigator

7.2. Exclusion Criteria

1. Subject has a history of 2 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening:
    - Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization)
    - Coma
    - Seizures
2. Subject is unable to tolerate tape adhesive in the area of sensor placement
3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)
4. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator.
5. Subject has a cardiovascular condition which the investigator determines should exclude the subject, i.e. ventricular rhythm disturbance, hypertrophic cardiomyopathy
6. Subject is being treated for hyperthyroidism at time of screening
7. Subject has diagnosis of adrenal insufficiency
8. Subject 7-13 years of age has had DKA in the 6 months prior to screening visit.

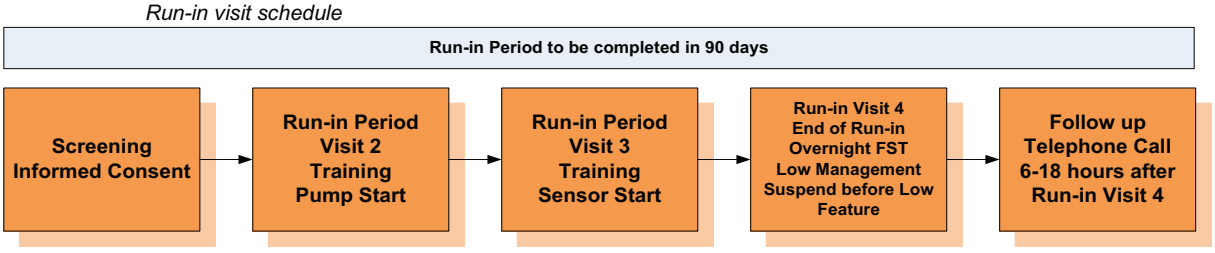
9. Subject 2-6 years of age has had DKA in the 3 months prior to screening visit
10. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study
11. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks
12. Subject 7-13 years of age has been hospitalized or has visited the ER in the 6 months prior to screening resulting in a **primary diagnosis** of uncontrolled diabetes
13. Subject 2-6 years of age has been hospitalized or has visited the ER in the 3 months prior to screening resulting in a **primary diagnosis** of uncontrolled diabetes
14. Subject is currently abusing illicit drugs
15. Subject is currently abusing marijuana.
16. Subject is currently abusing prescription drugs
17. Subject is currently abusing alcohol
18. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of screening
19. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator
20. Subject has elective surgery planned that requires general anesthesia during the course of the study
21. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
23. Subject diagnosed with current eating disorder such as anorexia or bulimia
24. Subject has been diagnosed with chronic kidney disease that results in chronic anemia
25. Subject has a hematocrit that is below the normal reference range of lab used.
26. Subject is on dialysis
27. Subject has serum creatinine of >2 mg/dL.

8. Study Timeline

8.1. Run-in Period Visits: To be completed in 90 days

- Screen **Visit 1** (Office): Consent and Screening
- Run-in **Visit 2** (Office): Study and device training; Pump Start
- Run-in **Visit 3** (Office): Start of CGM Run-in; Pump Follow-Up; Start CGM with Enlite 3/Guardian Sensor (3) Sensor; (CGM run-in with two week window of wearing SAP)
  Note 1: Run-in Visit 2 and Run-in visit 3 may be combined
- Run-in **Visit 4** (Office): Low Management Suspend before Low Overnight Frequent Sample testing; End of CGM run-in
- Run-in **Visit 4B** (Telephone): Call to subjects 6-18 hours after completion of overnight visit

Run-in visit schedule



8.2. Study Period Visits: This period lasts 96 - 110 days

Overview

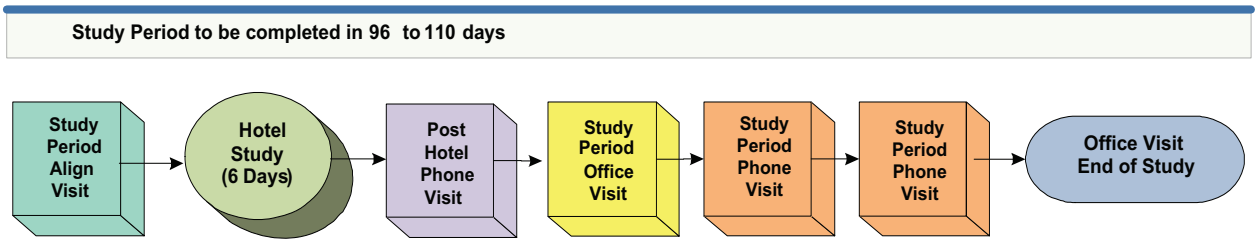
- All enrolled subjects will be asked to participate in 1 of the hotel studies
  - Subjects who cancel or are otherwise unable to participate in the hotel study may be re-scheduled for the next available hotel study
- Each site will target 6 subjects who must come in for the Hotel Study on Day 1 - Day 6 in Month 1 of the study period
  - If site has less than 4 subjects for a Hotel study the sponsor will determine whether or not the Hotel Study should proceed.
- Remaining subjects will be assigned to participate in the hotel study(ies) during Month 2 (Day 36-Day 66) or Month 3 (Day 67- Day 96)
- Telephone Visit windows are counted from the start of the study period (Day 1)
- Sponsor may guide the speed of enrollment during the study

Visit Schedule:

Hotel Visit Month 1 Cohort Schedule

- Office Visit Day 1 - Study Period Alignment Visit
- Hotel Study (Day 7- Day 14)
  - Subjects 2-6 years may do FST during this period of time
- Phone Visit (Day 30 – Day 37)
- Office Visit (Day 44 – Day 51)
- Phone Visit (Day 60 – Day 67)
- Phone Visit (Day 74 – Day 81)
- **End of Study** Period (Office Visit): Day 96 - Day 110

Sample visit schedule for subjects completing the Hotel visit in Month 1:

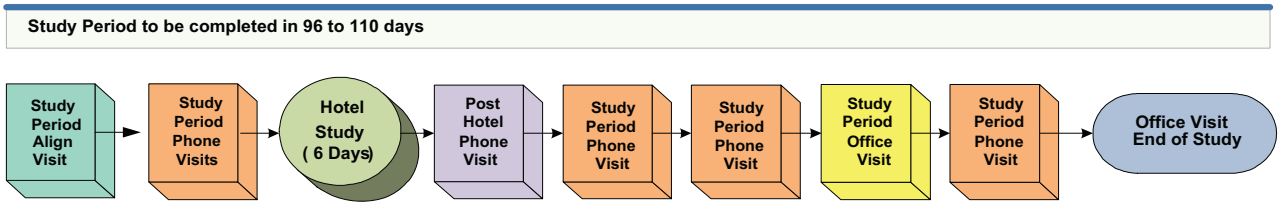


Hotel Visit Month 2 Cohort Schedule

- Office Visit Day 1 - Study Period Alignment Visit
- Telephone Visit (option of office visit) Day 7
- Telephone Visit (option of office visit) Day 8
- Telephone Visit (option of office visit) Day 9
- Telephone Visit (option of office visit) Day 10
- Telephone Visit (option of office visit) Day 11

- Telephone Visit (option of office visit) Day 12
- Telephone Visit (option of office visit) Day 13
- Hotel Study (Day 36 – Day 66)
  - Subjects 2-6 years may do FST during this period of time
- Post Hotel Phone Visit:
  - This Phone visit is to occur within 5 days from the last day of the Hotel study.
- Phone Visit (Day 36 – Day 43)
  - Phone visit not required if any of these days overlap period of hotel stay
- Phone Visit (Day 50 – Day 57)
  - Phone visit not required if any of these days overlap period of hotel stay
- Office Visit (Day 66 – Day 73)
- Phone Visit (Day 80 – Day 87)
- **End of Study Period** (Office Visit): Day 96 – Day 110

Sample visit schedule for subjects completing the Hotel visit in Month 2:

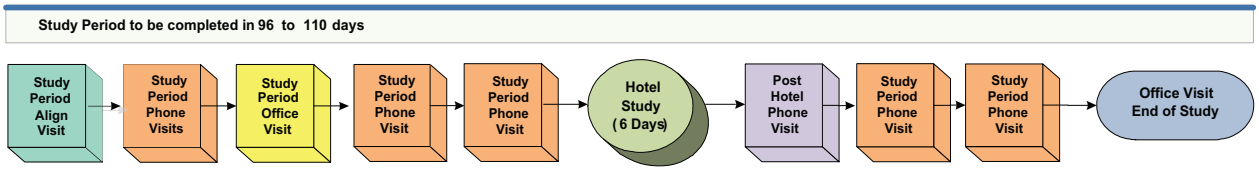


Hotel Visit Month 3 Cohort Schedule

- Office Visit 1 - Study Period Alignment Visit
- Telephone Visit (option of office visit) Day 7
- Telephone Visit (option of office visit) Day 8
- Telephone Visit (option of office visit) Day 9
- Telephone Visit (option of office visit) Day 10
- Telephone Visit (option of office visit) Day 11
- Telephone Visit (option of office visit) Day 12
- Telephone Visit (option of office visit) Day 13
- Office Visit (Day 14 – Day 21)
- Phone Visit (Day 30 – Day 37)
- Phone Visit (Day 44 – Day 51)
- Hotel Study (Day 67 – Day 96)
  - Subjects 2-6 years may do FST during this period of time
- Post Hotel Phone Visit:
  - This Phone visit is to occur within 5 days from the last day of the Hotel study.
  - If the Phone visit after Hotel study occurs within the window period of an interim Phone visit, the corresponding interim Phone visit is not required.
  - If the End of Study visit occurs within 2 days after the Hotel study, the Phone visit after Hotel study is not required. For example: The Hotel study ends on Day 90. The End of Study visit occurs on Day 91.
- Phone Visit (Day 66 – Day 73)
  - Phone visit not required if any of these days overlap period of hotel stay
- Phone Visit (Day 80 – Day 87)
  - Phone visit not required if any of these days overlap period of hotel stay

- **End of Study Period** (Office): Day 96 – Day 110

Sample visit schedule for subjects completing the Hotel visit in Month 3:



Continued Access Program: Devices and Supplies

Visit Schedule
Subjects will come in for quarterly office visits for a period of approximately 3 years.

Office Visit Day 180 Continued Access (Day 150-210)
Office Visit Day 270 Continued Access (Day 240-300)
Office Visit Day 360 Continued Access (Day 330-390)
Office Visit Day 450 Continued Access (Day 420-480)
Office Visit Day 540 Continued Access (Day 510-570)
Office Visit Day 630 Continued Access (Day 600-660)
Office Visit Day 720 Continued Access (Day 690-750)
Office Visit Day 810 Continued Access Period (Day 780-840)
Office Visit Day 900 Continued Access (Day 870-930)
Office Visit Day 990 Continued Access (Day 960-1020)
Office Visit Day 1080 Continued Access (Day 1050-1110)

9. Subject Number Assignment

In the Oracle Clinical Remote Data Capture (OC-RDC) database, the investigational centers will be identified numerically, i.e. from 001 to 010 (depending on center number). At the Screening visit, investigational center staff will assign each subject a sequential ID number that corresponds to a pre-defined casebook in the OC-RDC database.

Each case book will contain all relevant Case Report Forms for each subject. Each subject will be assigned a unique 9-digit identifier that will be structured such that the first 3 digits correspond to the study number (XXX), the next 3 digits correspond to the investigational center number, and the final 3 digits correspond to the subject number. An example of a typical subject's unique identifier is shown in the following example: The numerical sequence XXX001001 translates into: Study number (XXX), investigational center number (001), Subject number (001).

All study documents, electronic Case Report Forms (eCRFs) and correspondence will use this identifier sequence in lieu of a subject's name or initials.

10. Informed Consent

Informed Consent/Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50 (US only) or ISO14155:2011 (EMEA only). The Investigator or designee must obtain written informed consent/assent before any clinical study related activity takes place. Prior to entry into the study, the California Experimental Subject's Bill of Rights (if applicable), the IRB/EC and Medtronic-approved Informed Consent Form (ICF)/Assent form, and the Health Insurance Portability and Accountability Act

(HIPAA) Authorization Form (US only) will be given to each subject and legally authorized representative (if applicable) . The Investigator or designee will fully inform the subject to subjects and parent(s)/guardian(s) of all aspects of the clinical study that are relevant to the subject's or parents'/guardians' decision to participate in the clinical study (e.g. purpose and duration of the study, requirements of the subject during the study, potential risks and possible benefits associated with participation in this study.

Subjects will be considered enrolled in the study upon signing the Informed Consent/Assent form(s)

All items addressed in the Informed Consent/Assent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subjects and parent(s)/guardian(s).

The subject and parent(s)/guardian(s) must have ample time and opportunity to read and understand the Informed Consent/Assent 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 subject and parent(s)/guardian(s).

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

When the subject and parent(s)/guardian(s) decides to participate in the clinical study, the California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form (US only) and the Informed Consent/Assent Form must be signed and personally dated by the patient or parent(s)/guardian(s) or legally authorized representative. In the EMEA region also the investigator or authorized designee must countersign the Informed Consent/Assent Form. The consenting process must be documented in each subject's source files.
After all persons have signed and dated the Informed Consent/Assent Form, the investigator must provide the subject and parent(s)/guardian(s) with a copy.

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 and parent(s)/guardian(s) in a timely manner.

Medtronic will revise the written Informed Consent/Assent 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 IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects and parent(s)/guardian(s), and the informed consent process as described above needs to be repeated.

If the ICF is amended during the course of the study, the IRB/EC will determine:

- Whether or not active subjects and parent(s)/guardian(s) should be re-consented at their next visit and
- Whether or not subjects who have completed the study at the time of the amendment should repeat the informed consent process.

Subjects and parent(s)/guardian(s) will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), agencies such as the FDA/local regulatory authority in EMEA and/or the IRB/EC may have access to clinic records that reveal their identity.

The investigational center must report the following violations to their IRB/EC:

- Failure to obtain informed consent from subject and parent(s)/guardian(s).
- Failure to obtain informed consent prior to performing one or more study procedures.
- Failure to maintain ICFs on file for all subjects who have provided informed consent.
- Use of an ICF that has not received approval from the IRB/EC.

- Use of an incorrect version of the ICF.

11. Study Visits – Enrollment and Run-In Period

11.1. Run-in Period Synopsis

Run-In Period Synopsis (Visit 1-4)

The primary purpose of the run-in period is to allow study subjects to become familiar with the study devices and to assure they meet criteria for study participation. Subjects will also be asked to undergo overnight frequent sample testing to evaluate the *Low Management Suspend before Low* feature of the study pump at Run-in Visit 4. There is a window of 90 days from the end of Visit 1 to Visit 4 during which time subjects should complete run-in. If the run- in period is repeated an additional 30 days will be added to the run-in period window. If a repeat of the *Low Management Suspend before Low* testing is necessary, Sponsor discretion will be used to determine timing of the repeat.

Success criteria for run-in:

- Subject must have 3 or greater than 3 SMBG per day
- Subject must show sensor compliance (i.e. 2,880 glucose sensor data points equivalent to 10 days of sensor wear)
- Subject does **not** turn on the SmartGuard Low Management features before the *Low Management Suspend before Low* Frequent Sample Testing at Run-in visit 4
- Subject does **not** turn on the Auto Mode feature

The run-in period should be repeated if the subject does not meet all run-in success criteria as listed above or if the Investigator believes the subject needs to gain greater familiarity with study devices.

Subject should be withdrawn if they turn on the Auto Mode feature during this period.

- **Devices Worn:**
  - Subjects are trained on all study devices prior to receiving them
  - Subjects 2-13 years of age: Sensor is inserted by subject or with assistance from parent(s)/guardian(s)/companion(s) into either the abdomen or buttocks and connected to GST3C Transmitter

- **Calibration Requirements with Study Meter:**
  - Approximately 30 minutes to 2 hours after the Sensor is initialized, the Study Pump will alert the user to enter meter BGs to perform initial calibration
  - After the first calibration, the user must calibrate the Sensor within 6 hours of the first calibration
  - The user must calibrate when prompted by the study pump via the Smart Cal feature
  - The user must calibrate every 12 hours after last calibration

- Recommend 3-4 calibrations per day
- Other recommendations:
  - Always have clean dry fingers when you check your blood glucose
  - Only use your fingertips to obtain blood samples for calibration

- **Run-in Settings <u>before</u> frequent Sample testing, i.e. *Low Management Suspend before Low*:**
  - High and Low Setup limits and alert(s) will be set at investigator discretion
    - Low Setup Limit may not be set lower than 65mg/dL
  - SmartGuard −Low Management must be OFF during this period
  - SmartGuard − Auto Mode must be OFF during this period

- **Run-in Settings <u>during</u> frequent Sample testing, i.e. *Low Management Suspend before Low*:**
  - Subjects 7-13 years: Low Setup limit must be set at 65 mg/dL
  - Subjects 2-6 years of age will not participate in frequent sample testing, but will still complete Visit 4.
  - Alert before low should be ON
  - Resume basal alert should be ON

- **Monitoring Method:**
- Study meter
- YSI during frequent sample testing of *Low Management Suspend before Low* feature

11.2. Study Period Synopsis

Window of 96-110 days from end of Run-in Visit 4 to End of Study for each subject.

Overview:

The 3 month study period is to determine safety of the use of the Hybrid Closed Loop algorithm with the study devices. Subjects will have study devices for 3 approximately months which includes a hotel study either in month 1 (at the beginning of the study) or months 2 or 3. The Hotel study portion is to assess the hybrid closed loop system against a reference value during the day and night, and with daily exercise/activity and unrestricted eating. Safety measure will

include daily pump uploads for first 14 days during Auto Mode, as well as parent(s)/guardian(s)/companion(s) and DSMB oversight.

Study Period Device Procedures

- **Devices Worn:**
  - Study Pump
  - Subjects 2-13 years of age: Sensor is inserted by subject or with assistance from their parent(s)/guardian(s)/companion(s) into either the abdomen or buttocks and connected to GST3C Transmitter
- **Calibration Requirements with Study Meter:**
  - Approximately 30 minutes to 2 hours after the Sensor is initialized, the Study Pump will alert the user to enter meter BGs to perform initial calibration.
  - After the first calibration, the user must calibrate the Sensor within 6 hours of the first calibration.
  - The user must calibrate when prompted by the study pump via the Smart Cal feature
  - The user must calibrate every 12 hours after last calibration.
  - Recommend 3-4 calibrations per day
  - Other recommendations:
    - Always have clean dry fingers when you check your blood glucose
    - Only use your fingertips to obtain blood samples for calibration
- **Auto Mode Settings:**
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
  - Low Setup limit recommended to be set at 70 mg/dL
    - Low Setup Limit may not be set lower than 65mg/dL
    - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
  - The target for the closed loop algorithm is set at 120 mg/dL.
  - A temporary target may be used when subject exercises.
  - Alarms that are fixed into system:
    - Sensor glucose at or below 50 mg/dL
    - When sensor glucose at or above 300 mg/dL for one hour
    - When sensor glucose at or above 250 mg/dL for 3 hours
- **Manual Mode Settings:**

- High Set up Limit recommend to be set at 300 mg/dL
  - Alert Setting Options may be set per investigator discretion
- Low Set up Limit recommend to be set at 70 mg/dL
  - Low Setup Limit may not be set lower than 65mg/dL
  - For subjects 2-6 years of age, Low Setup Limit should be set at 80mg/dL and no lower than 70mg/dL
- Predictive alerts and rate of change alerts are optional
- It is recommend (optional) to have the SmartGuard Low Management turned ON with suspend before low activated and a low limit set at 70 mg/dL
- Please note that the basal insulin rate setting in Manual mode may need to be adjusted due to changes in insulin sensitivity when using Auto Mode. For example, the average hourly basal rate setting may be calculated by multiplying 35%-40% or less (i.e., ages 2-12 years old may require less basal insulin) by the Total day dose and dividing by 24 = XX Units/hour

- **Monitoring Method:**
  - Hotel Study: i-STAT

11.3. Visit Schedule tables

Study Activities (Site Staff Activities)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 4B Follow-up Call	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic/ Out-of-Home Study	End of Study Period Visit	Continuation Period Visits
Informed Consent/Assent Process	X										
Screening Labs[1]	X										
Subject Eligibility Assessment	X										
Obtain demographic and baseline characteristics including [2] ○ Age ○ Gender ○ Race (US only) ○ Ethnicity (US only) ○ Prior medical history ○ Duration of diabetes mellitus ○ Height ○ Weight ○ Percentage of time using real- time CGM based on subject report: ○ Within 1 month from time of screening visit ○ Within 2 months from time of screening visit ○ Within 3 months from time of screening visit ○ If subject is already enrolled and is past Visit 1, site may collect this information at a later visit.	X										
Collect concomitant medication data	X										
Questionnaires (DTQ Baseline)		X									
Questionnaires (DTQ End of Study Period)										X	
Questionnaires (Satisfaction – End of Study Period)										X	

Study Activities (Site Staff Activities)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 4B Follow-up Call	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic/ Out-of-Home Study	End of Study Period Visit	Continuation Period Visits
Ask subjects and parent(s)/guardian(s) about the occurrence of adverse events • Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition		X	X	X	X	X	X	X	X		X
Register subjects in CareLink Clinical [3]		X									
Upload the study pump during office visit		X	X	X		X	X	X	X	X	X
Review EZ reference guide [4]		X	X	X		X	X	X	X	X	
Perform control solution testing - Study Meter(s) [5]		X	X	X		X	X		X		
Perform control solution testing - Ketone meter [6]		X							X		
Provide subjects and parent(s)/guardian(s) with study reference materials, e.g. Pump User Guide, Getting Started Guide, EZ reference guide, etc.		X									
Provide The ADA handbook: Insulin Pumps and Continuous Glucose Monitoring: A User's Guide to Effective Diabetes Management; Copyright American Diabetes Association, Inc. (Kaufman F, 2012) [7]		X									
Disburse informational flyers to parents of pediatric subjects to be provided to school staff if questions about study devices or their function should arise		X									
Print CareLink Reports to include (at minimum) subjects' device settings at each study visit.		X	X	X		X	X		X		
Ask subjects and parent(s)/guardian(s) about device performance issues and if they called the 24 -Hour HL to report them		X	X	X		X	X	X	X	X	X
Provide subjects and parent(s)/guardian(s) with the opportunity to bring up study-related questions and concerns.		X	X	X	X	X	X	X	X	X	X
Supervise subjects as a Sensor is self- inserted or with assistance from parent(s)/guardian(s)/companion(s) into abdomen or buttocks as per labeling instructions [8]			X	X							

Study Activities (Site Staff Activities)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 4B Follow-up Call	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic/ Out-of-Home Study	End of Study Period Visit	Continuation Period Visits
Connect Sensor to Transmitter			X								
Remind subjects and their parent(s)/guardian(s)/companion(s) to bring in the Study Meter for meter operation testing (with control solution per IFU) to each office visit.		X	X	X		X	X		X		
Evaluate sensor wear compliance (End of Run-in Period)				X							
Review weekly surveillance reports		X	X	X		X	X	X	X	X	
Perform overnight Frequent Sample Testing of the *Low Management Suspend before Low* feature: Refer to Section 11.4, the Low Management FST Procedure Guidelines and the Low Management FST Discharge Guidelines for further information				X							
Discuss/Schedule dates for the Hotel component of the study; discuss Logistics and all other requirements as applicable		X		X		X	X				
Supervise (in person) exercise activities during each day of the 5-day Out-of-Home study for subjects 2-6 years of age. Follow separate instructions for exercise start/stop.									X		
Additional A1C Test						X				X	X
Enter eCRFs into the study database as appropriate	X	X	X	X		X	X	X	X		
Schedule the next visit date and time	X	X	X	X		X	X	X	X		X
Inform subjects that observation by Sponsor may occur at any time during study at an office visit or Hotel stay	X										
Measure subject weight (End of Study)										X	
Provide subjects 7 years and older the opportunity to participate in a transition program for the 670G pump and the Guardian Link Transmitter (US Only)										X	
Return subject to personal standard of Care (End of Study)										X	
Provide information about continued access to study devices for a period of up to 3 years. Participation in the program is optional										X	

[1] Screening labs include: A1C, Creatinine, TSH, Free T3, Free T4, Pregnancy test (urine/serum)

Note regarding A1C: *Specimens collected for A1C testing will be sent to and tested by a NGSP certified Central Laboratory; A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards*
Note regarding TSH Testing (local lab): Initial test is TSH; If the TSH level is out of range, Free T3 and Free T4 will be tested; Subject may be included with TSH out of range as long as: a) Free T3 is low or within the normal reference range and b) Free T4 is within the normal reference range; TSH, including Free T3 and Free T4, may be repeated once within 14 days of screening for values that are out of reference range; 7 additional days may be added to the run- in period window for subjects who repeat thyroid function tests
Note regarding Urine pregnancy testing: Collect Urine pregnancy test for female subjects of child bearing potential

[2] Body Mass Index (BMI) will be calculated automatically in the study database, based on height and weight measurements entered.

[3] CareLink Registration:

- Subjects' study information will be entered and subjects will select a password.
- Subject information will be documented on the investigational center's Subject Contact Log (see Investigator/Site binder for details).
- Subjects will use their ID/Password throughout the study;
- Investigational centers will use individual ID/Passwords to access subjects' CareLink account for study purposes

[4] EZ Reference guide Details

- Phone number(s) of study staff and the after–hours telephone number(s) for the study doctor(s) who are assigned to respond to calls from subjects who have questions or experience problems.
- Reporting device issues to 24 Helpline
- Completing electronic diary for use-related issues not requiring 24 Helpline Assistance
- Subjects and parent(s)/guardian(s) will be requested to call study staff if they have glucose levels above 300 mg/dL with elevated ketone levels accompanied by nausea, vomiting, or inability to drink fluid.
- Ketone testing requirements

[5] **Study Meter:** If the Study Meter reading falls outside the stated control solution (control solution for Study Meter is investigational must only be used with the Bayer meter) range, then testing with new test strip(s) will be repeated until the reading falls within the appropriate control solution range (see Study Meter user guide materials). If a Study Meter's reading remains outside the control solution range after 3 attempts, a new Study Meter will be provided.

[6] **Ketone Meter:** If the Ketone Meter reading falls outside the stated control solution (control solution for Ketone Meter is specific to device) range, then testing with new test strip(s) will be repeated until the reading falls within the appropriate control solution range (see Ketone Meter user guide materials). If a Ketone Meter's reading remains outside the control solution range after 3 attempts, a new Ketone Meter will be provided.

[7] One handbook will be provided per subject and parent(s)/guardian(s)/companion(s); the handbook will be reviewed for the following:

- Train subjects and their parent(s)/guardian(s)/companion(s) on the devices as well as diabetes management principles such as the treatment of hyperglycemia or hypoglycemia and having access to oral glucose in case of hypoglycemia.

- Instruct subjects and their parent(s)/guardian(s)/companion(s) to change infusion sets when infusion set catheter occlusion is suspected. Insulin via syringe may need to be given, especially if ketones are present.
- Review general pump management with parent(s)/guardian(s)/companion(s). It is understood that in order to be eligible for the study, patients must be pump users. This part of training will be a refresher.

[8] Sensor Details:

- The sensor must be calibrated to ensure correct operation.
- The Investigator may allow a subject to leave the center prior to sensor initialization.
- If subjects encounter any calibration problems with the sensor, the sensor may be replaced to ensure correct operation.
- Subjects, with the assistance of parents/guardians, should replace the sensor after 7 days of use (upon receiving a "Sensor expired" alert) or as events dictate throughout the course of the study.

Study Activities (Training and Instruction)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Train subjects and their parent(s)/guardian(s)/companion(s) on the use of the 670G study pump		X								
Instruct/Remind subjects to replace the pump battery 3 times per week		X	X		X	X	X	X	X	X
Instruct/Remind subjects to wait at least 10 minutes to insert the new battery after removing the used battery. This should occur at least once per month.		X	X		X	X	X	X	X	X
Train subjects, their parent(s)/guardian(s)/companion(s) on the use of the Study Meter, according to the Study Meter's user guide		X								
Instruct subjects, their parent(s)/ guardian(s)/ companion(s)on the use of the bolus calculator (for meal and/or correction doses)		X								
Train subjects and their parent(s)/guardian(s) on how to upload the pump [1]		X								
Train subjects and their parent(s)/guardian(s) on the use of CareLink		X								
Train subjects, their parent(s)/guardian(s)/companion(s) on the use of the ketone meter, according to the ketone meter's user guide		X								
Train subjects on the EZ Reference Guide		X								

Study Activities (Training and Instruction)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Instruct subjects and parent(s)/guardian(s) that they must have a parent(s)/guardian(s)/companion(s) for the duration of the study period (starting at Visit 4 - End of Run In) [2]		X								
Instruct subjects and their parent(s)/guardian(s) to enter blood Ketone Meter values, if collected, into CareLink weekly (every 7 days) – see EZ Reference Guide		X								
Instruct subjects and their parent(s)/guardian(s) about ketone-related reporting requirements and actions to be taken in response to symptoms, (see EZ reference guide)		X	X	X	X	X	X	X		
Train subjects and their parent(s)/guardian(s)/companion(s) on CGM, the proper use of the Sensor and the Study Pump. The investigator or qualified research staff will provide recommendations whether or not the sensor glucose low and high alerts should be turned on or off and, if turned on, at which threshold they should be set.			X							
Instruct subjects on sensor calibration requirements [3]			X							
Train subjects on Run-in Period requirements [4]			X							
Instruct subjects and their parent(s)/guardian(s)/companion(s) that sensors must be worn continuously throughout the study and that successful sensor wear with pump CGM will be a condition for continued study participation			X	X	X	X	X	X		
Instruct subjects and their parent(s)/guardian(s)/companion(s) to check blood glucose at least 4-6 times per day for diabetes self-management (SMBG), using the supplied Study Meter according to the user guide. Subject compliance with SMBG will be encouraged and will be used at the end of the run-in period to determine whether or not subjects are suitable to move into the study period		X	X	X	X	X	X	X		
Train subjects and their parent(s)/guardian(s)/companion(s) on the Auto Mode feature of the study pump					X					
Train subjects and their parent(s)/guardian(s)/companion(s) on specific considerations regarding Auto Mode [5]					X					

Study Activities (Training and Instruction)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Instruct subjects and their parent(s)/guardian(s)/companion(s) that they should **not** assume that Auto Mode is able to prevent all hypoglycemia or all hyperglycemia including diabetic ketoacidosis					X					
Instruct/Remind subjects that the use of Acetaminophen is not allowed during the study • If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels. • Subjects will be instructed to exit AutoMode					X	X	X	X	X	X
Instruct subjects and their parent(s)/guardian(s) that the investigational center staff will receive surveillance reports from the Sponsor which identify non-compliant subjects who may be using the Auto Mode function. If this occurs, the subject should be withdrawn (See Withdrawal Procedures, Section 18)			X		X					
Out-of-Home study (subjects 2-6 years of age): Instruct parent/guardian to take appropriate measures regarding high and low blood sugars during the Out-of-Home study. Provide appropriate training materials.					X					
Out-of-Home study (subjects 2-6 years of age): Discuss with subjects and parent(s)/guardian(s) the plan for the Out-of-Home study, e.g. staff will be performing SMBG testing and will need to coordinate with the family.					X					
Hotel/House/Clinic Study (7-13 years): Discuss with subjects and parent(s)/guardian(s) the plan for the hotel stay, e.g. ground rules, availability of staff, Logistics, etc.					X					
Hotel/House/Clinic Study: Instruct subjects and parent(s)/guardian(s) about the requirements for overnight FST testing with i-STAT® as reference, e.g. frequency, duration, etc.					X			X		
Hotel/House/Clinic Study (7-13 years): Communicate that Parent(s) or Guardian(s) should be present during hotel study. Immediate family members may attend hotel stay.					X			X		

Study Activities (Training and Instruction)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Instruct subjects and parent(s)/guardian(s) that they should call the investigational center as soon as possible with any changes to their health status (adverse events) - see EZ reference guide		X	X	X	X	X	X	X	X	X
Instruct subjects and parent(s)/guardian(s) that they should keep their own insulin pump supplies in a safe place in case they should be asked during the study to revert back to their own pump		X								
Instruct subjects and parent(s)/guardian(s) that they should always have back up to their study pump on hand such as insulin and syringe in case of study pump issue (e.g. infusion set occlusion with high glucose)		X								
Instruct subjects and parents to report to the investigator any time the device could not be worn due to a device performance issue		X	X	X	X	X	X	X	X	X
Instruct subjects and their parent(s)/guardian(s) that they will be required to source their own insulin. As indicated in inclusion criterion # 13 all subjects must agree to provide and use one of the following rapid acting u100 insulin brands: • Humalog® (insulin lispro injection) • NovoLog® (insulin aspart)		X								
Instruct subjects and their parent(s)/guardian(s) to contact the Medtronic 24-Hour HelpLine (HL) in the event they experience problems with their study devices. The 24-Hour HL will be able to assist with troubleshooting and answer questions (Call number provided on EZ reference guide)		X	X	X	X	X	X	X	X	X
Instruct subjects and their parent(s)/guardian(s) to contact the investigational center (Call number provided on EZ reference guide) for therapy related questions including changes in pump settings		X	X	X	X	X	X	X	X	X
Instruct subjects and their parent(s)/guardian(s) to complete the electronic diary for any for use-related issues not requiring 24 Helpline Assistance (web access provided on EZ reference guide)		X	X	X	X	X	X	X	X	X
Instruct subjects and their parent(s)/guardian(s) to always base their diabetes therapy decisions on a confirmatory finger stick (per user guide). In this study, finger stick measurements will be used exclusively; no alternate site testing will be allowed		X								

Study Activities (Training and Instruction)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Instruct subject's parent(s)/guardian(s)/companion(s) on administration of glucagon and when to give it to subject		X								
Train subjects and their parent(s)/guardian(s)/companion(s) to try to give meal bolus of insulin 10-15 minutes prior to meal for entire study as much as possible		X								
Remind subjects and their parent(s)/guardian(s)/companion(s) to verify appropriate meter operation for both the Study Meter and the Ketone Meter during home use. The respective user guides should be consulted to determine frequency of testing		X	X	X	X	X	X	X		

[1] Pump and Study Meter Uploading requirements:

- Uploads must occur weekly for the entire run-in period
- Upload must occur weekly throughout the study period except for a daily uploading requirement during the first 14 days after subjects enter Auto Mode (Hotel/House/Clinic or at home)

[2] The parent(s)/guardian(s)/companion(s) must be available at night while at home; Parent(s)/guardian(s)/companion(s) must be trained on study requirements at Visit 2; Parent(s)/guardian(s)/companion(s) must be available for the duration of the study period; Parent(s)/guardian(s)/companion(s) are not required to be present during the hotel study.

[3] Calibration requirements (with Study Meter):

- Approximately 30 minutes to 2 hours after the Sensor is initialized, the Study Pump will alert the user to enter meter BGs to perform initial calibration
- After the first calibration, the user must calibrate the Sensor within 6 hours of the first calibration
- The user must calibrate when prompted by the study pump via the Smart Cal feature
- The user must calibrate every 12 hours after last calibration
- Recommend 3-4 calibrations per day
- Other recommendations:
  - Always have clean dry fingers when checking blood glucose
  - Only use your fingertips to obtain blood samples for calibration

[4] Run-in Period requirements

- Subject must do 3 or more SMBG per day
- Subject must show sensor compliance (i.e. 2,880 glucose sensor data points equivalent to 10 days of sensor wear – see Visit 3 for details)
- Subject must not turn on any of the SmartGuard Low Management features

The run-in period should be repeated if the subject does not meet all run-in success criteria as listed above or if the Investigator believes the subject needs to gain greater familiarity with study devices
Subjects will be withdrawn if they turn on the Auto Mode feature during the Run-in period

[5] It is recommended that Auto Mode should be switched OFF in the study pump or that subjects switch to manual injections if:

- Hospital admission for any reason
- Glucose is persistently elevated (i.e. above 300 mg/dL)
- Illness that prevents ability fluid ingestion due to nausea and vomiting
- Subject experiences an occlusion alarm where glucose becomes elevated and the subject is not able to address the occlusion by changing the infusion set.
- Subject experiences an episode of severe hypoglycemia
- Subject experiences an episode of DKA

Note: When Auto Mode is switched OFF, it is recommended (optional) that SmartGuard Low Management is turned ON

Study Activities (Device Disbursement / Collection)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Disburse the Study Pump [1]		X			X					
Disburse lockable pouch for the pump as needed, per investigator discretion		X								
Disburse GST3C transmitter [1]			X							
Disburse additional Sensors for home use. All sensors must be accounted for and all unused sensors returned to the study center		X	X	X	X	X		X	X	X
Disburse the Study Meters (each subject to receive 2 BG meters) [1]		X			X					
Disburse the Ketone Meter for Ketone testing [1]		X			X					
Provide sufficient stock of supplies (e.g., infusion sets, reservoirs, glucose meter test strips, control solution, ketone test strips for blood ketone testing, batteries, tape, etc.) to subjects		X	X	X	X	X		X	X	X
Provide subjects and parent(s)/guardian(s) with Glucogel® (or equivalent product) and a glucagon emergency kit; • Instruct subjects and parent(s)/guardian(s)/companion(s)s to keep these supplies available at all times.		X						X		

Study Activities (Device Disbursement / Collection)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone/Office Visits	Study Period Hotel/House or Clinic	End of Study Period Visit	Continuation Period Visits
Remind subjects and parent(s)/guardian(s) to check on the adequacy of their supplies			X	X	X	X	X	X	X	X
Disburse Study Meter strips, Ketone Meter strips, control solution and other supplies as needed		X	X	X	X	X		X	X	X
Allow subjects 7 years and older to retain used 670G pump and Guardian Link Transmitter if subject chooses to participate in an optional transition program. (US Only)									X	
Collect devices (i.e. study pump, transmitter, study meter, unused sensors, serter, tester)				X					X	X

[1] Same devices that were disbursed at Visit 2 and were collected at Visit 4 are returned to same subjects at Visit 5

Study Activities (Sponsor)	Screening Visit 1	Visit 2	Visit 3 (Start Run-in)	Visit 4 (End Run-in)	Visit 5 (Start Study Period)	Study Period Interim Office Visit	Study Period Phone Visits	Study Period Hotel/House or Clinic	End of Study Period Visit
Surveillance – Run-in Period [1]			X	X					
Surveillance – Study Period [2]					X	X	X	X	X
Surveillance – Blood Ketone Testing CRF			X	X	X	X	X	X	X

[1]The Sponsor will provide Surveillance reports data via Oracle Clinical eCRF uploads (starting at Office Visit 3) based on weekly pump uploads in CareLink to assist subjects and investigators. The purpose of the weekly surveillance report is to identify subjects who are not compliant with study procedures and who potentially need to be withdrawn for safety reasons (see Withdrawal Procedures). The reports are provided weekly and contain information about:

- Sensor wear based on sensor tracings (available after Office Visit 3)
- Sensor re-start occurrences
- Use of SmartGuard Low Management function (not allowed during Run-In period)
- Use of SmartGuard Auto Mode function (not allowed during Run-In period)
- Study Meter Uploads

[2] Based on pump uploads to CareLink Clinical, the Sponsor will provide Surveillance report data via Oracle Clinical eCRF s during the study period to assist subjects and investigators. Reports will be based on weekly pump data uploads except when subjects first enter Auto Mode (i.e. subjects upload pump data daily for the first 14 days). The purpose of the surveillance report is to identify subjects who are not compliant with study procedures and who potentially need to be withdrawn for safety reasons (see Withdrawal Procedures). The reports are provided weekly (approximately) and contain information about:

- Sensor wear based on sensor tracings
- Sensor re-start occurrences

- SmartGuard Auto Mode use
- Smart Guard Low Management use
- Temp Target use
- Study Meter Uploads

11.4. In-Clinic Procedures at Run-in Period Visit 4 – *Low Management Suspend before Low* Frequent Sample Testing (YSI Reference Method)

11.4.1. *Low management Suspend before Low* Testing: Guidelines for Investigational Center Staff before start of In-Clinic procedures

Investigational center staff will:

- Set up the YSI instrument according to the directions provided in separate YSI Guidelines document
- Synchronize time on Study Pump, Study Meter, study laptop and YSI instrument(s), using the investigational center's designated study clock
- Confirm individual subjects' pump settings

11.4.2. *Low management Suspend before Low* Testing: Guidelines for Investigational Center Staff during In-Clinic procedures

Investigational center staff will:

- Follow In-Clinic Procedure Guidelines (by age group) and Discharge Criteria
- Assess subjects for the occurrence of adverse events during in-clinic procedures, document on the appropriate source (see Safety Section) and record on the appropriate eCRF
- Consult the Medtronic 24-Hour HL for any device problem that occurs during the in-clinic visit
- If a subject develops ketones, he/she should be managed according to the study's ketone protocol

11.4.3. *Low management Suspend before Low* Testing: Guidelines for Investigational Center Staff after completion of In-Clinic procedures

Investigational center staff will:

- Encourage subjects to ingest unlimited sugar-free, caffeine-free fluids to maintain hydration in order to avoid ketosis
- Upload Study Pump to CareLink
- Upload YSI data to sponsor's secure site at the end of the visit
- Schedule a follow-up phone call to take place within 6-18 hours from discharge to address any questions or concerns subjects may have
- Enter eCRFs into the study database as appropriate

11.4.4. Follow-up Telephone Call

Investigational center staff will contact subjects within 6-18 hours following the overnight in-clinic procedures to check on subjects' well being

Investigational center staff will:

- Ask subjects how they have been doing
- Assess whether or not any adverse events have occurred
- Record adverse events on the appropriate eCRF in the event subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition
- Provide subjects with the opportunity to bring up study-related questions and concerns
- Enter eCRFs into the study database as appropriate

11.4.5. Repeat Rules for *Low management Suspend before Low* In-Clinic Procedures

Subjects may repeat in-clinic procedures once on a different day; however, the total amount of blood drawn must not exceed 2 mL/kg of body weight during any 24 hour period and 4 ml/kg over a 1 month period for the entire study. Criteria to allow the repeat of an in-clinic visit are as follows:

- Subject arrives for in-clinic visit with blood ketone concentration greater than 1.5 mmol/L
- Concurrent failure of both the primary and back-up YSI instruments during frequent sample testing
- Investigational center staff enters the incorrect Low Limit setting
- If a sensor fails prior to the start of YSI or before 8hours of YSI, the in-clinic procedures will be re-scheduled
- When *Low management Suspend before Low* is turned ON and triggers prior to exercise, the in-clinic procedures will be re-scheduled
- An insulin pump infusion set catheter occlusion is suspected (i.e. occlusion alarm)
- Subjects 7-13 years: Less than 8 hours of YSI data collected and subject never reached 65 mg/dL or less (2 contiguous YSI samples)
- Less than 4 hours of observation from the time that *Low management Suspend before Low* activates

11.4.6. Subject Stopping Rules for *Low management Suspend before Low* In-Clinic Procedures

- Prior to starting in-clinic testing, ketone level is greater than 1.5 mmol/L.
- Subjects 7-13 years: Twelve hours have passed since the start of exercise without *Low management Suspend before Low* activation.
- If *Low management Suspend before Low* is activated, observation with YSI frequent sample testing will include the Suspend period (30 minutes minimum to 2 hours maximum) and insulin resumption period (approximately 4 hours from time insulin resumes). This may include insulin re-suspension during this period. Maximum observation with YSI frequent sample testing should be performed no longer than 12 hours for subjects 7-13 years of age. If *Low management Suspend before Low* does not trigger then observation with YSI frequent sample testing will be performed for no longer than 12 hours (Subjects 7-13 years)..
- Sensor fails prior to the start of YSI or before 8 hours of YSI (Subjects 7-13 years).
- An insulin pump infusion set catheter occlusion is suspected (i.e., occlusion alarm).
- YSI glucose is greater than 500 mg/dL regardless of ketone levels.
- Ketones are greater than or equal to 3 mmol/L, regardless of blood glucose.
- Suspected DKA
- Severe hypoglycemia
- Persistent elevation of ketone greater than or equal to 1.5 mmol/L after hydration

11.4.7. Success Criteria

Study success criteria for *Low management Suspend before Low* safety is achieved by meeting the following criteria:

- No UADE
- No device related SAEs
- No DKA

11.5. Study Period Visit Details

11.5.1. Office Visit 5 – Study Period Alignment Visit

The purpose of this office visit is to provide subjects and their parent(s)/guardian(s)/companion(s) with study devices and training. Subjects will wear the device in Manual Mode for 6 days prior to entering into Auto Mode at the hotel or at home. **The use of the Auto Mode feature during the first 6 days of the study period will not be permitted.**

11.5.2. **Daily Surveillance** for First 14 days During Auto Mode:

Review Pump uploads daily for first 14 days once **subject has entered Auto Mode (CL)** Therefore, it is important to note the protocol timelines in order to understand when the subject will enter CL.

- Questions to ask when reviewing the report may include:
  - Is the subject's glucose control worse from baseline
  - Is the subject experiencing too much hypoglycemia – for example hypoglycemia at night
  - Is the subject checking glucose

Note: Subjects are required to perform the daily pump uploads during Hotel portions of this study as well

11.5.3. For subjects who are participating in Month 1 Hotel studies:

- Instruct subjects and their parent(s)/guardian(s)/companion(s) that they may not turn ON the Auto Mode function on the study pump prior to Day 7.

11.5.4. For subjects who are participating in Month 2 or Month 3 Hotel studies:

- Instruct subjects and their parent(s)/guardian(s)/companion(s) that they may not turn ON the Auto Mode function on the study pump prior to Day 7.

11.5.5. Hotel Study (All subjects who are participating in a Hotel/Clinic study)

Overview

- **Cohorts**
  - Hotel Study Month 1 (Day 7 – Day 14)
  - Hotel Study Month 2 (Day 36 – Day 66)

- Hotel Study Month 3 (Day 67 – Day 96)

- **Duration:** 6 days
- **Location: Hotel, House or clinic**
- **Goal: Activities in the mornings and afternoons**
- **Safety: All study Safety Criteria apply to hotel study equally.**
- **Activity Plan (Exercise and other activities):**
  - Subjects will not be forced or coerced to complete activities if they do not feel they are capable to complete them. Activity intensity may be adjusted so that subjects are able complete the activity.
  - Site research staff will record subject activities, including the types of activity and the time they are performed.
  - Information on subject activity will be collected in eCRF.
  - There will be numerous activity periods throughout each day for a minimum of approximately 4 hour minimum - 6 hours maximum in total per day. It is understood that exercise/activity on the days subjects are doing FST may be limited. For example, subject would not be able to go swimming with IV in their arm. Activity choices may include the following but not limited to:
    - Walking including walking up and down stair case or hiking
    - Shopping
    - Swimming – such as water aerobics, playing in water, water volleyball, marco polo
    - Aerobics
    - Dancing – such as slow dance
    - Any sport activity which involves ongoing physical movement (i.e., tennis, golf, basketball, tee ball or volleyball)
    - Yoga/stretching
    - Biking

  Note: Subjects should perform BG check prior to any aerobic exercise and only start to exercise if BG is >120mg/dL.

- **Auto Mode Frequent Sample Testing (i-Stat® reference for subjects 7-13 years of age)**
  - Placement of IV may be performed.
  - Subjects 7-13 years: During one day and one night of the hotel or clinic stay (any day or night may be selected) each subject will undergo FST in Auto Mode.
    - Night time Auto Mode FST will be between 10PM and 7AM (start no earlier than 8PM)
    - Day time Auto Mode FST will be between 7AM and 10PM (start no earlier than 5AM)
  - Subjects 2-6 years: Frequent sample testing in Auto Mode will be required for approximately 4-6 hours during one day of the Out-of Home study, using SMBG as a reference method. The frequent sample testing period will be supervised by investigational center staff. Testing frequency will be every 30 minutes. The exact times of FST may vary, but the interval for testing should be followed as described.
  - Maximum blood draw for all subjects is 2 ml/kg for any 24 hour period and 4 ml/kg over a 1 month period.
  - Subjects 7-13 years: Overnight frequent sample testing in Auto Mode will be required for approximately 24 hours. Nighttime frequent sample testing (10PM to 7AM) in Auto Mode will be every 30 minutes; daytime frequent sample testing (7AM to 10PM) in Auto Mode will

be every 60 minutes. The exact times of FST may differ, but the interval for testing should remain as described The exact times may be changed, but overnight FST should start no earlier than 8PM and daytime FST should start no earlier than 5AM. Approximately 24 hours of Auto Mode FST (15 daytime hours and 9 nighttime hours) should be performed.

- **Meals:**
  - No specific food intake restrictions for scheduled meals or snacks
  - Subjects may eat breakfast, lunch and dinner on their own

- **Subject Sleep Attire**
  Subjects will wear pajamas or clothes which cover torso and undergarments.

- **Research staff monitoring:**
  - **During night** – subjects have fingerstick glucose checks starting at 12AM and again at 3AM
    - At each required time, fingerstick checks for all subjects may take 1-1.5 hours to be completed
    - 1 Medical staff who is able to test SMBG, accompanied by 1 research coordinator
    - Privacy/safety protocols (i.e., knock on door first, identify)

  - **During FST**
    - Every 30- 60 minutes
    - i-STAT® as reference method
    - Additional monitoring by SMBG made be performed based on i-STAT® glucose and management decisions will be made by SMBG in order to reflect actual use

- **Minimum Staffing**
  - MD should be on call as per routine study procedures and attend hotel/house visit for approximately 8 hours throughout the hotel/house stay.
  - One registered nurse, Nurse Practitioner or Physician Assistant for every 2 subjects, on site who is able to test SMBG. This medical professional should have experience in the treatment of hypoglycemia, including severe hypoglycemia with glucagon, hyperglycemia, including severe hyperglycemia and management of ketones and sick day rules.
  - One additional staff member for every 2 subjects to assist with frequent sample testing.
  - Subjects 2-6 years of age: One staff member will supervise subjects during each day of the Out-of-Home study (approximately 4-6 hours). The staff member should be a health care professional able to treat low or high glucose level such as an RN.

11.5.6. End of Study Period Visit

Subjects will be provided with an option for continued access to study devices for a period of up to 3 years. During that time, quarterly visits will be conducted.

12. Medical Oversight

In order to conduct the study, staffing with the appropriate training is required

12.1. Medical staff

A physician who has managed patients on both CGM and insulin pump will be included in the study as the principal investigator.

12.2. Qualification

The investigator (or designee) will need to have one of the following qualifications; Endocrinology fellowship, management in patients with diabetes in a clinical practice or experience running prior studies

performing YSI/i-STAT with rescue for low or high glucose. The provider must be qualified to treat diabetic emergencies.

12.3. Experience

Investigator (or designee) must also have at least one year experience in managing patients with insulin carbohydrate ratios and insulin sensitivity ratios in his/her practice

13. Safety Monitoring/Risk Analysis

13.1. Glucose Monitoring risk:

Subjects and their parent(s)/guardian(s)/companion(s) will be instructed to use clean fingers when performing finger stick glucose testing. Subjects and their parent(s)/guardian(s)/companion(s) will be instructed to test blood glucose 4-6 times a day. Subjects and their parent(s)/guardian(s)/companion(s) will have training on diabetes self-management principles. Subjects will have parent(s)/guardian(s)/companion(s) with them at night for the duration of the study

13.2. Hypoglycemic/Hyperglycemic Risk:

Intervention and treatment for hypoglycemia and hyperglycemia is addressed in Section 20.4.

Hypoglycemic/Hyperglycemic Risk specific to *Low Management Suspend before Low* in clinic procedures: To decrease the risk of severe hypoglycemia and hyperglycemia, the following schedule for monitoring blood glucose concentrations during the in-clinic session will be adhered to . Study Meter will be used as a back-up method in the event there is a problem that renders YSI unavailable.

Blood Glucose (mg/dL)	Frequency of BG Measurement
Less than 70 mg/dL	Every 5 minutes
70 – 80 mg/dL	Every 15 minutes
Greater than 80 mg/dL	Every 30 minutes

13.3. Calibration of CGM risk:

When an erroneous glucose value is used to calibrate a CGM, the bias is carried through until the next opportunity to re-calibrate the CGM. This can result in an incorrect bias. In order to mitigate this risk, every new sensor will have an initial calibration.

13.4. Reuse risk:

All study devices (including the Serter) will be single patient use.

13.5. Sterilization risk:

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- Glucose sensors

13.6. Misuse risk:

Comprehensive Training will take place for clinical staff regarding the operation of the 670G system, all of its functional components and all other study devices to be used during the study at the investigational center initiation visit.

13.7. Risk of blood sample collection, contamination from sampling techniques:

Detailed mitigations to blood sampling risk are provided in Section 20.

13.8. A1C risk:

A central laboratory will be used for A1C testing.

14. Glucose and Glycemia Measurements

During the course of the study, the subjects' blood glucose, sensor glucose (SG) levels, A1C, blood ketone, will be assessed using the following methods in this section.

14.1. Daily Blood Glucose

Values will be assessed during the study by all subjects using the Study Meter. Control solution testing will be performed on the Study Meter assigned to each subject before being dispensed (V2), all office visits and at the beginning of the hotel stay. The results of the control solution test will be documented in the subject's source documents. The control solution test will be done following the manufacturer's IFU during Home use. Subjects and their parent(s)/guardian(s)/companion(s) will be trained on the use of the Study Meter per the manufacturer's instructions for use.

14.2. Hotel Frequent Sample Testing Blood Glucose Values

During the FST at hotel, the blood plasma glucose will be determined using the i-STAT®.

14.3. Blood Ketone Values

Blood ketones will be determined by all subjects using the Ketone Meter during home use and the hotel stay. A Control Solution test will be performed at the time the Ketone Meter is assigned to each subject before being dispensed (V2) and at the beginning of the hotel stay. The results of the control solution test will be documented in the subject's source documents. The control solution test will be done following the manufacturer's IFU during Home use. Study staff will be trained on the use of the Ketone Meter per the manufacturer's IFU. All ketone measurements will be recorded on the appropriate eCRF.

14.4. Sensor Glucose Values

Assessed using the following methods:
Sensor Glucose (SG) data collected by subject's Study Pump and calibrated by subject's Study Meter

14.5. A1C

Collected at baseline and will be used as demographic information and at end of study.

15. Device Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational device used in a research trial. It is expected that all investigational devices or commercially available devices used outside their approved intended use will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions and that they will be used only by (on) subjects who have consented to participatein the study.

Any investigational device or commercially available devices used outside their approved intended use being used in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, IRB/EC) have been received. This includes keeping records of:

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

US: Investigational devices or commercially available devices used outside their approved intended use will be labeled “Investigational Device” in accordance with 21 CFR Part 812. 140.
EMEA: In accordance with the MDD directive, the investigational devices for EMEA will be labeled “Exclusively for Clinical Investigations”

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

Table 1. Device Accountability Requirements

Device	Center Receipt (packing slip)	Disbursement to Site (eCRF)	Center Return to Sponsor (eCRF)
670G Insulin Pump (MMT-1780)	Yes	Yes	Yes
670G Insulin Pump (MMT-1780) – US approved	Yes	Yes	**USA** Yes** • If unused • If used and subject does not participate in an optional transition program **No**** • If used and subject chooses to participate in an optional transition program
			EMEA **Yes** Used or unused

Device	Center Receipt (packing slip)	Disbursement to Site (eCRF)	Center Return to Sponsor (eCRF)
Bayer CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (MMT-1352 in US, MMT-1152 in Israel)	Yes	Yes	Yes
CONTOUR® NEXT LINK 2.4 by Ascensia Blood Glucose Meter (MMT-1352)– US approved	Yes	Yes	Yes (only if unused)
Enlite 3 Glucose Sensor (MMT-7020)	Yes	Yes	Yes (only if unused)
Guardian Sensor (3) Glucose Sensor (MMT-7020) – US approved	Yes	Yes	Yes (only if unused)
One-Press Serter (MMT-7512)	Yes	Yes	Yes
One-Press Serter (MMT-7512)* – Israel approved	No	No	No
One-Press Serter (MMT07512)* – US approved	No	No	No
GST3C Transmitter (MMT-7811)	Yes	Yes	Yes
Guardian Link (3)Transmitter (MMT-7811) – US approved	Yes	Yes	**USA** Yes** • If unused • If used and subject does not participate in an optional transition program **No **** • If used and subject chooses to participate in an optional transition program **EMEA** **Yes** Used or unused
TST Tester (MMT-7726)	Yes	Yes	Yes
TST Tester (MMT-7736)* – Israel approved	No	No	No
TST Tester (MMT-7736)* – US approved	No	No	No
Charger (MMT-7715)	Yes	Yes	Yes
Charger (MMT-7715)* – Israel approved	No	No	No
Charger (MMT-7715)* - US approved	No	No	No

Device	Center Receipt (packing slip)	Disbursement to Site (eCRF)	Center Return to Sponsor (eCRF)
Ketone Meter	Yes	Yes (EMEA only)	Yes (if unused – EMEA only)
CareLink USB	Yes	Yes	Yes

* Unit could be supplied as part of a Transmitter Kit
** The Sponsor will provide study subjects with an opportunity to participate in a transition program for the 670G pump and the Guardian Link Transmitter. The 670G transition program applies only to the FDA approved age group, 7years and older, in US.

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

15.1. Receipt and Inventory of Investigational Devices or Commercially available devices used outside their approved intended use by Investigational Center

15.1.1. Upon receipt of the study devices, investigational center staff take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:

- Ship To
- Reference Number
- Device Type
- Quantity
- Quantity per package
- Lot number
- Serial number

15.1.2. Ensure that devices and supplies received have not reached their expiration date

15.1.3. Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder

15.1.4. Notify the study Monitor of any discrepancies

15.1.5. Enter the study device information on the appropriate eCRF in the study database.

15.2. Storage of Study Devices at Investigational Center

Study devices are to be stored in a secure environment with access limited to authorized research personnel. Study devices are to be stored in the proper environmental conditions, as identified in the user guide/labeling.

15.3. Disbursement of Study Devices

Each time a study device is disbursed to a Subject by the Investigator or authorized member of the research team, all required eCRF and source documentation will be completed. Documentation may include:

- Date of disbursement

- Subject ID
- Lot number(s)
- Serial Number
- Reference Number
- Amount dispensed

15.4. Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in Table 1; and store them in a secure environment. If containers/units/devices are missing, document the reasons in the eCRF. If discrepancies between amounts used by subjects and amounts expected to be returned exist, document the reasons in the eCRF.

The study devices required to be accounted, as described in Table 1, will be returned by subjects to the investigational center and then to the Sponsor. Serialized devices provided to the investigational center may be returned as subjects complete the study, at the end of study or upon sponsor request. The quantity received by the investigational center and the quantity returned to sponsor should be equal. The investigational center will provide details of the disposition of all unreturned serialized devices (excluding the Study Meter and Ketone Meter) in the eCRF.

Used glucose sensors are not expected to be returned by subjects to the investigational center and therefore are not expected to be returned to the sponsor. Other unused consumable devices (i.e., infusion sets, alcohol wipes, Study Meter supplies, overtape, etc.), supplies or materials may be returned to the sponsor or retained by investigational center for educational purposes only, or may be disposed of properly by the investigational center staff.

Disposable devices and supplies that have been ***used*** by a subject will be disposed of properly by the subject or the investigational center staff during the conduct of the study. This would include glucose sensors, meter testing strips and supplies, infusion sets and adhesive overtape.

All study devices that were required to be entered into the study database are required to be accounted for as described herein prior to return to sponsor or at the end of the study.

The Sponsor will provide study subjects with an opportunity to participate in a transition program for the 670G pump and the Guardian Link Transmitter. The 670G transition program applies only to the FDA approved age group, 7years and older, in US.

16. Safety

16.1. Adverse Event

The Medtronic Clinical Research Department, in conjunction with the Regulatory Affairs Department, in Northridge, California will monitor and manage adverse event reporting for the study and determine whether the event requires reporting to regulatory agencies. The sponsor will ensure timely Adverse Event reporting to meet regulatory requirements.

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events or untoward findings. The study personnel will elicit reports of adverse events from the subject at each visit (including phone calls) documenting the medical diagnosis, date of event start and end, severity, causality (relationship to device or procedure), treatment, resolution and description that includes the details of the event.

16.2. Reporting of Adverse Events

The Investigator or designee will record ALL adverse events while the Subject is enrolled in the clinical study. This includes AE that are device or study procedure related as well as those events with no relationship to the study. Examples include:

- Device related (ADE): insertion site infection
- Serious adverse device effect: cellulitis at device insertion site requiring hospitalization
- Procedure related AE: bruising at IV insertion site
- Not related to study: cold, flu, appendicitis

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

Narratives gathered from completed questionnaires will not provide the basis of an adverse event report however could lead to discussions that result in the identification of a reportable AE.

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

16.3. Notification of Adverse Events

Within 24 hours of investigator or study coordinator awareness, the investigational center staff must report all Severe Hypoglycemia; DKA; Serious Adverse Events; Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects and any Unanticipated Adverse Device Effect to Medtronic. Regulatory authorities should be notified per local requirements. The AE eCRF will be completed with all known details within 24 hours of investigational center awareness – this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the Sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected the event should be entered onto an AE eCRF. All other reportable adverse events should be entered on the eCRF within 14 days of subject report to the investigational center.

16.4. Expedited Safety Reporting Requirements

For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB/EC as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).

The Sponsor will notify the investigator and IRB/EC of any event that results in a safety report to the FDA/local regulatory authority within EMEA. Documentation of IRB/EC notification of any safety event must be kept at the investigational center and a copy sent to the Sponsor.

It is the responsibility of the investigator to follow their IRB/EC and regulatory authority reporting requirements.

16.5. Reporting of Glycemic Events

1. **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)**

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

   Hyperglycemic events will be recorded as an adverse event if the event involved DKA with 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

3. **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.

16.6. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in ISO 14155:2011 and 21 CFR 812 for adverse event definitions. Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

The term “investigational device” is part of ISO14155 definitions. The term “investigational device” refers to any device used in the study including market released devices.

Adverse Event (AE) (ISO14155-2011)

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) (ISO 14155-2011)

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

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

Note 2: This includes any event that is a result of a use error or intentional misuse of the investigational device.

Serious Adverse Event (SAE) (ISO 14155-2011)

An adverse event that

- Led to a death
- Led to a serious deterioration in the health of the subject, that either resulted in
  - life threatening illness or injury,
  - a permanent impairment of a body structure or a body function
  - in-patient* or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

**Inpatient Hospitalization is defined as: 24 hour acute admission to the hospital based on urgent medical need rather than elective admission.*

Note 1: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.

Note 2: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (ICH Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. EMEA 2006)

Serious Adverse Device Effect (SADE) (ISO 14155-2011)

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

Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3(s)) equivalent to USADE (ISO14155-2011 3.42)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

16.7. Causality Assessment

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

Causality assessment is the determination of the relationship between an adverse event and the device being studied. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the device or a study procedure. It is expected

that the investigational center will review all elements surrounding the adverse event to properly assess the causality of the event to the study device or to a study procedure.

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

The following definitions should be considered when determining the relationship of the event to the device or study procedure:
Causal Relationship – clearly related to the device or procedure

Probable – likely related to the device or procedure
Possible – may be related to the device or procedure

Unlikely – doubtful that event is related to the device or procedure
Not Related – clearly not related to the device or procedure

16.8. Anticipated or Unanticipated

If the adverse event is determined to be related to the study device or study procedure the Investigator must then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; report of priors or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; report of priors, Investigator brochure, or user guide.

16.9. Severity of Event (Intensity)

A clinical determination of the intensity of the event will be made. The following guidelines should be used:

- **Mild:** transient, needing no special treatment, and/or does not interfere with the subject's daily activity.
- **Moderate:** low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually improved by simple therapeutic remedy.
- **Severe*:** interrupts a subject's daily activity and typically requires intervening treatment.

*Please Note: In the classification of adverse events, the term "**severe**" is not the same as "**serious**." The term "**severe**" relates to an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

17. Data Safety Monitoring Board

A DSMB consisting of external physicians with an expertise in Endocrinology and the management of insulin requiring diabetes including CGM, along with an external statistician will be convened to review study progress, endpoints and safety.

The DSMB will perform a number of functions:

1. Adjudication of the following events:

    - Serious Adverse Event
    - Serious Adverse Device Effect
    - Unanticipated Adverse Device Effect
    - Severe Hypoglycemia

- Diabetic Ketoacidosis

The DSMB will assess these events to determine agreement or disagreement with the Investigator classification of the event. The Sponsor will notify the Investigator of any disagreement in assessment of an event by the DSMB. The DSMB will meet a minimum of every 6 weeks to adjudicate these events unless there are no events to adjudicate.

2. DSMB will track and trend the overall Safety of the study.

Incidence for the following will be reviewed by the DSMB:

- Incidence of all SAEs.
- Incidence of severe hypoglycemia
- Incidence of DKA
- Incidence of device related adverse events.

Applicable information for device related adverse events may include:

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

3. The DSMB will meet sooner if there is a DKA event, a UADE or a severe hypoglycemia event as outlined in the stopping rules for the entire study:

    - DSMB is to review the event within 48 hours from the time that the sponsor is notified. If possible, the investigator should be available to answer questions by DSMB.
    - DSMB will recommend a decision to the sponsor on the following:
        - Whether or not enrollment will continue to be on hold
        - Whether or not the entire study will need to be stopped including for those subjects who have received study devices already.

4. The DSMB will provide a recommendation to the sponsor on whether or not pediatric subjects 2-4 years of age will be permitted to enroll into the study. The recommendation is based on a review of data from 10 subjects 5-6 years of age after they have completed the first month of the study period.

General guidance for DSMB's recommendations to sponsor should be based on the following:

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

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

The following factors should be carefully considered in the DSMB's recommendation to sponsor:

1. Was the severe hypoglycemia or DKA related to the HCL algorithm, SmartGuard with predictive threshold suspend or was it related to a known insulin pump risk? For example, a question that may

be considered in DKA would be whether the event was related to an infusion set issue or caused by the HCL algorithm.

2. Another important consideration would be if the severe hypoglycemia or DKA event was related to a device malfunction versus patient non-compliance. For example, if a software anomaly leading to an under-delivery of insulin is discovered versus the subject repeatedly ignoring alarms prompting the subject to take action.

3. Severe hypoglycemia or DKA caused directly by an infusion set issue when the study pump is functioning as intended would likely result in acceptance to proceed with the study versus severe hypoglycemia or DKA that are directly caused by the HCL algorithm or a device malfunction might stop study enrollment or entire study altogether.

4. It should be noted that the final determination of causality related to the HCL System or SmartGuard with predictive threshold suspend that is made by the DSMB may include additional factors which the members consider to be clinically relevant and important.

5. The DSMB may take into account the thresholds listed below for the number of subjects experiencing hypoglycemia requiring assistance from another person, hypoglycemia resulting in seizure or loss of consciousness or DKA to identify when the number of subjects experiencing these events exceeds the number that would be anticipated for the study population over the duration of this study. These thresholds should be interpreted with caution due to potential differences in study populations and study design.

Adverse Event	Reference Rate (<26 years old)	Reference Rate (≥26 years old)
Hypoglycemia requiring assistance from another person to administer oral carbohydrates, glucagon or other resuscitative actions	≤4 subjects experiencing one or more events during study[1]	≤7 subjects experiencing one or more events during study[1]
Low blood glucose resulting in seizure or loss of consciousness	≤2 subjects experiencing one or more events during study[2]	≤3 subjects experiencing one or more events during study[3]
DKA	≤ 3 subjects experiencing one or more events during study[2]	≤ 2 subjects experiencing one or more events during study[3]

The event thresholds for hypoglycemia requiring assistance from another person is derived from the JDRF study of continuous glucose monitoring and intensive treatment of type 1 diabetes. The event thresholds for low blood glucose resulting in seizure or loss of consciousness is derived from the rate reported in T1D Exchange Clinic Registry. The rates reported in these previous studies are adjusted for the 3 month study period with 130 expected subjects to determine the maximum number of subjects expect to experience one or more of these events during the study.

1. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76

2. Cengiz E, Xing D, Wong JC, Wolfsdorf JI, Haymond MW, Rewers A, Shanmugham S, Tamborlane WV, Willi SM, Seiple DL, Miller KM, DuBose SN, Beck RW; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54

3. Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL, Bergenstal RM, Harris B, Dubose SN, Miller KM, Beck RW; T1D Exchange Clinic Network Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013 Aug;98(8):3411-9

18. Withdrawal Procedures

Subjects may choose to withdraw from the study at any time by notifying investigational center staff of their intent.

Individual subjects will not be replaced

If a subject chooses to end his or her study participation or if a subject is removed from the study at the Investigator's discretion, the reason for termination must be documented both in source documents and on the appropriate eCRF. All study devices and supplies must be returned and the return documented both in source documents and on the appropriate eCRF.

Subjects may also be withdrawn from the study at the discretion of the Investigator. A subject will be withdrawn from the study if:

- In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the Investigator, it is in the subject's best interest to discontinue participation in the study
- During the course of the study, subject begins participation in another investigational study (drug or device).
    - Please note should the subject elect to remain in the continued access program: Subjects will be permitted to participate in other studies during the continued access period of the study with Sponsor permission, provided that the studies do not include the use of drugs or devices, i.e. devices not used in this study.
- During the course of the study, subject begins abusing illicit drugs or marijuana.
- During the course of the study subject begins abusing prescription drugs.
- During the course of the study subject begins abusing alcohol.
- During the course of the study subject begins using pramlintide (Symlin) DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors).
- During the course of the study, subject receives red blood cell transfusion or erythropoietin.
- During the course of the study, subject persistently wears sensor for longer than the labeled 6 days.
- During the course of the study, the subject demonstrates that he/she is not able to comprehend instructions for study procedures, as evaluated by the appropriate research staff.
- During the course of the study, subject takes any oral, injectable, or IV glucocorticoids.
- During the study, (female) subject becomes pregnant.
- During the study, the subject experiences a severe hypoglycemic episode
- During the study, the subject experiences DKA
- During the study subject has a cardiovascular event or any vascular event such as stroke
- Subject proceeds into Auto Mode during the **run-in period**.

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

For EMEA only: If patient withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

19. Stopping Rules

If it is decided to prematurely terminate the patients participation in the study or prematurely terminate the entire study the subjects will be followed-up in accordance with standard practice.

19.1. Subject Stopping Rules

1. Any event of DKA will result in withdrawal of subject from study.

2. Severe hypoglycemia secondary to subject non-compliance or other individual safety concerns:
   - Subject is not using the bolus wizard
   - Subject is not checking blood glucose using finger sticks
   - Subject is non-compliant with sensor wear
   - Subject is not following protocol procedures
   - Subject experiences a study pump malfunction

19.2. Stopping Rules for Entire Study

During the study period, the following steps will be taken for:

1. UADE
2. DKA
3. Severe hypoglycemia events that result in subject requiring paramedic assistance, an ER visit or subjects who experience seizure, coma or death:
   - Site will notify the sponsor on the same day after receiving knowledge of the event. If the event becomes known to the site after hours, then it should be reported to the sponsor the next day.
   - Sponsor will notify FDA and the country-specific regulatory agency in the EMEA region within 24 hours of knowledge of event and provide updates to those agencies as information becomes available.
   - Enrollment will be stopped after the above events have been reported
   - DSMB is to review the event within 48 hours from the time that sponsor is notified. If possible, the investigator should be available to answer questions by DSMB.
   - DSMB will provide recommendation to sponsor on the following:
     - If enrollment may resume
     - If the entire study has to be stopped, including subjects who have already received study devices.

20. Ethical and Regulatory Considerations

20.1. Risk Determination

In the opinion of the sponsor, this study is considered to be a significant risk (SR) study. Results of an evaluation of the requirements per 21 CFR Part 812.3, led to the SR determination as follows:

- The devices could present a potential for serious risk to subject health, safety or welfare.

- The devices are for a use of substantial importance in treating disease, and presents potential for serious risk to subject health, safety or welfare.

Therefore, submission of an Investigational Device Exemption (IDE) application to the United States Food and Drug Administration is required

20.2. Institutional Review Board (IRB) / Ethics Committee (EC)

This protocol, any subsequent amendments to this protocol, the Informed Consent form, subject material and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible EC/IRB in accordance with 21 CFR Part 56 in the US and local regulatory requirements as applicable. The study will not start until IRB/EC approval has been granted, the Sponsor has cleared the investigational center to begin the study, and the investigational clinical staff has been appropriately trained to conduct the study. Copies of all relevant correspondence between the investigational center and the IRB/EC will be retained at investigational center with copies forwarded to the Sponsor for their files.

20.3. This section applies only to EMEA: Ethical and Regulatory Considerations

20.3.1. Regulatory Submission

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.

20.3.2. Regulatory Compliance

This clinical study will be conducted in compliance with the Declaration of Helsinki 2013, the international standard ISO 14155:2011 ('Clinical Investigation of medical devices for human subjects'), laws and regulations of the country/ies in which the clinical study is conducted (including data protection laws), the Clinical Investigation Agreement, the Clinical Investigation Plan and FDA regulations CFR, Title 21, Part 54 (Financial Disclosure by Clinical Investigators) and CFR, Title 21, Part 11 (Electronic Records; Electronic Signatures).

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

20.3.3. Ethical Considerations

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 IRB/EC, and if applicable regulatory authority, approval.

20.4. Potential Risks and Benefits

20.4.1. Potential Risks and Mitigations

Table 2. Potential Risks and Benefits; Potential Risks and Mitigations

Potential Risk with Infusion Sets	Mitigation
Potential side effects related to infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or site failure • Hyperglycemia secondary to site falling off	Prevention and mitigation risks of infusion sets include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insertions and care of infusion sets. If an infusion site becomes irritated or inflamed, the infusion set should be removed and another placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion subjects and their parent(s)/guardian(s)/companion(s) will be instructed to remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study on device use and diabetes management principles and told to call with problems.
Potential Risk with Insulin Administration and Pump Use	**Mitigation**
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	Prevention and mitigation risks of infusion sets include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study on device use and diabetes management principles and told to call with problems. • Subjects and their parent(s)/guardian(s)/companion(s) will be instructed that they are required to check SMBG 4-6 times a day. • Subjects and their parent(s)/guardian(s)/companion(s) will be told to have glucose on hand for hypoglycemia • Subject and their parent(s)/guardian(s)/companion(s) will be told they may need to change their infusion set if they suspect catheter occlusion or administer insulin with syringe with persistent hyperglycemia especially if ketones develop.

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 priming 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 /MiniLink 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	Prevention and mitigation risks of infusion sets include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles and told to call with problems. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study on device use and diabetes management principles.

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 of infusion sets include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles and told to call with problems. • Subjects and their parent(s)/guardian(s)/companion(s)will be trained prior to study on device use device and diabetes management principles.
Potential Risk with Sensor	**Mitigation**
Potential risks with Sensor include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted • Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive and or tapes • Scarring • Incorrect sensor glucose reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia	Prevention and mitigation risks of Sensor include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insertions and care of sensors. If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location. • Subjects and their parent(s)/guardian(s)/companion(s) are instructed to use fingerstick glucose reading for diabetes management and diabetes management decisions and told to call with problems.
Potential Risk with Serter	**Mitigation**
Potential risks with Serter use include:	Prevention and mitigation risks of Serter include:

• Skin infection around the area where the Serter is used.	• Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insertions and care of Serters. The investigational centers and subjects and their parent(s)/guardian(s)/companion(s) will receive training on proper use of the Serter and skin preparation prior to insertion.
Potential Risk with Finger Stick	**Mitigation**
Potential risks with frequent finger stick testing include: • Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers • Potential risks associated with drawing blood include discomfort and bruising • Syncopal episode can occur secondary to needle insertion	Prevention and mitigation risks of finger stick testing include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for use of meter with fingerstick testing. The investigational centers and subjects and their parent(s)/guardian(s)/companion(s) will receive training on proper use of the meter and fingerstick testing.
Potential Risk with IV Catheter Insertion	**Mitigation**
Risks of IV catheter insertion include: • Pain • Bruising • Infection • Irritation • Syncopal episode secondary to catheter insertion • Swelling.	Prevention and mitigation risks of IV catheter insertion include: • Qualified individual to perform insertion of IV catheter • The subject is under constant observation and monitoring at all times during the challenges • Sterile technique will be used to insert the IV • Management of IV will be as per protocol of investigational center • Use of universal precautions to avoid infection • Observation for redness at IV insertion site by qualified staff Treatment of these risks include: • Removal of IV catheter if the subject experiences significant discomfort and bruising • Removal of IV catheter if infection develops • Antibiotics should be given
Potential Risk with Drawing Blood	**Mitigation**
Potential risks with drawing blood include:	Prevention and mitigation of drawing blood risks include: • Qualified staff to perform blood draw investigator presence during experiment • Use of universal precautions to avoid infection • Patients who are below reference range for Hct will not be included in study Treatment of these risks include:

• Discomfort and bruising • Insertion of an IV catheter and drawing blood may also result in faintness, inflammation of the blood vessel, pain and bruising at the needle site • There is also a slight possibility of infection During this study, there will be a maximum blood draw of 2 ml/kg during any 24 hour period and 4 ml/kg for a 1 month period for all subjects	• If infection develops antibiotics should be given
Potential Risk with Saline Infusion	**Mitigation**
Risks for saline infusion can include: • Edema • CHF • Third spacing	Prevention and mitigation of these risks include: • Qualified investigator presence during experiment • The subject is under constant observation and monitoring at all times during the challenges Treatment of these risks include: • Reduction of IV fluid if subject shows signs of CHF, lower extremity edema, crackles on lung auscultation or S3 heart sound Subjects who still exhibit signs of fluid overload at time of discharge will be transported to the ER or follow guidelines of the local institution for the disposition of subject
Potential Risk with HCL	**Mitigation**
Risks for HCL include:	**Mitigations specific to the HCL System:** • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study on device use and diabetes management principles and told to call with problems. • Subjects and their parent(s)/guardian(s)/companion(s) will be instructed that they are required to check SMBG 4-6 times a day. • Subjects and their parent(s)/guardian(s)/companion(s) will be told to have glucose on hand for hypoglycemia • It will be required that subjects avoid the use of products containing Acetaminophen • If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels. • Subjects will be instructed to exit AutoMode

• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• DKA
• User Entry Error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypo and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypo or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypo or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyper or hypoglycemia
• Voluntary insulin delivery (with the pump or even worse – with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Patient takes insulin via injection while in Auto Mode
• Hypoglycemia or hyperglycemia related to entering or exciting Auto Mode
• Insulin over-delivery due to Acetaminophen	

Risks associated with hyperglycemia include • DKA • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation hyperglycemic risks include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study device use and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be instructed that they are required to check SMBG 4-6 times a day. • Subjects and their parent(s)/guardian(s)/companion(s) will be told to have glucose on hand for hypoglycemia
Risks associated with Hypoglycemia include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Rebound hyperglycemia with ketosis	Prevention and mitigation of hypoglycemia risks include: • Investigational center staff and subjects and their parent(s)/guardian(s)/companion(s) will be instructed to follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s)s will be present at night with subjects and will be trained on study device and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be trained prior to study device use and diabetes management principles. • Subjects and their parent(s)/guardian(s)/companion(s) will be instructed to check SMBG 4-6 times a day.. • Subjects and their parent(s)/guardian(s)/companion(s) will be told to have glucose on hand for hypoglycemia

20.4.2. Benefits

Subjects are not expected to benefit from participation in this study; however, they may gain increased awareness of emerging technologies for diabetes management as a result of their participation.

20.5. Payments for Participants

Subjects will be compensated financially for their participation.

20.6. Subject Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject identification code in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only.

20.7. Investigator's Responsibilities

This study will be conducted at up to 15 investigational centers where all study-related activities will take place; at each center, the study will be led by a principal investigator. Per 21 CFR 812.3(i), *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

It is expected that the investigator(s) are familiar with the regulations governing the conduct of clinical research on human subjects. Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects provides clarification for investigators and sponsors
FDA's expectations concerning the investigator's responsibility

(1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and
(2) to protect the rights, safety, and welfare of study subjects

The investigator's responsibilities include:

- Ensuring that a clinical investigation is conducted according to the signed investigator agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations set forth in 21 CFR Part 812 and all other applicable FDA/EMEA regulations, and any conditions of approval imposed by an IRB/EC or FDA/EMEA regulatory requirements.
- Protecting the rights, safety, and welfare of subjects under the investigator's care
    - Providing reasonable medical care for study subjects for medical problems that arise during participation in the trial that are, or could be, related to the study intervention
    - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
    - Adhering to the protocol so that study subjects are not exposed to unreasonable risks
- Controlling devices under investigation (21 CFR 812.100 for US / ISO14155:2011 6.9 for EMEA)
- Investigator is responsible for providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- Ensuring that informed consent is obtained from each subject in accordance with 21CFR Part 50 for the US and ISO14155:2011 for EMEA and that the study is not commenced until FDA/local regulatory authority and IRB/EC approvals have been obtained.
- Supervising the use of investigational device. In US, an investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. In US, an investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it. In EMEA, the investigational devices shall only be used in the clinical investigation and according to the protocol (ISO14155:2011 6.9).
- Disposing of device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- Continuously monitoring, assessing and documenting risks
- An investigator shall maintain at a minimum the following accurate, complete and current records relating to the investigator's participation in an investigation (21 CFR 812.140 140 for US, ISO14155:2011 7.4 for EMEA):
    - Correspondence with another investigator, an IRB/EC, the sponsor, a monitor or FDA/ local regulatory authority in EMEA
    - Records of receipt, use or disposition of study devices
    - Records of each subject's case history and exposure to the study devices
- Documents showing the dates of and reasons for each deviation from the protocol
- Any other records the FDA/ local regulatory authority in EMEA requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation

- Investigators are required to permit FDA/ local regulatory authority to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.(21 CFR 812.145 in US / ISO14155:2011 6.7)
- An investigator shall prepare and submit the following complete, accurate, and timely reports as defined in Table 3 and Table 4:

Table 3. Investigator records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. *(21 CFR 812.150(a)(2)).*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3))*.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(21 CFR 812.150(a)(4))*
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 4. Investigator Reports Applicable to EMEA

Report	Submit To	Description/Constraints
Withdrawal of MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing MEC of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or EC. (ISO 14155:2011)
Study Deviations	Sponsor and Ethics Committee and Regulatory Authority	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ECs, regulatory authorities or the appropriate regulatory bodies should be informed. (ISO 14155:2011) Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (*Medtronic Requirement)*
Final investigator report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(Medtronic Requirement)*

    - To the sponsor and IRB/EC (per their requirements):
        - Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect)
- It is prohibited to promote and commercialize a device that has not been first cleared or approved for marketing by the FDA (per IDE regulations) or local regulatory authority in EMEA.
- The principal investigator(s) are required to assess whether or not to continue the clinical study at the respective investigation site.

- The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic personnel. 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

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

20.8. Quality Audits

Medtronic reserves the right to conduct quality audits at the investigational centers in order to verify adherence to external regulations as well as internal policies and procedures, to assess adequacy and effectiveness of clinical policies and procedures, to assure compliance with critical study document requirements, to confirm integrity and accuracy of clinical study data and to protect the safety, rights and welfare of study subjects.

These audits are done in addition to the regular monitoring visits.

Regulatory bodies may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the sponsor contact person.

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.

20.9. Investigational Center Disqualification

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

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

A written statement fully documenting the reasons for such a termination will be provided to Medtronic, the Institutional Review Board (IRB) or Ethics Committee (EC) and other regulatory authorities, as required.

20.10. Protocol Deviations

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

- Observation in the monitoring report
- Deviation to document the event
- Corrective action plan
- Investigational center disqualification
- Notification to the regulatory authorities / IRB/EC depending on the severity of the deviation and reporting requirements

The investigator is responsible for protecting the safety and welfare of the clinical research subjects.

20.11. Compliance with Protocol

The investigator or person designated by the investigator will document and explain any deviation from the approved protocol that occurs during the course of the clinical trial. The date and reason for each deviation will be documented. (21 CFR 812.140 Records for US/ ISO14155:2011 9.6g for EMEA)

The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- To the IRB/EC for review and approval/favorable opinion
- To the sponsor for agreement and, if required
- To the regulatory authority or authorities

Except in an emergency, prior approval by the sponsor, FDA/local regulatory authority in EMEA and IRB/EC is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects. (21 CFR 812.35(a)) for US / ISO14155:2011 4.5.4 b)) .

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. The investigator shall report a deviation as soon as possible to Medtronic and the reviewing IRB/EC, according to IRB/EC reporting guidelines, as applicable. Medtronic will inform the regulatory authorities, if required.

Emergency deviations must be reported to the sponsor and IRB/EC within 5 days.
The following examples are deviations that could impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study. These deviations are significant and require immediate sponsor notification upon investigator awareness:

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB/EC
- Failure to report serious adverse event to the IRB/EC and sponsor
- Investigational study device dispensed without obtaining informed consent

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 (see section 20.10).

The investigator will 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 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 IRB/EC. The investigator will only implement the amendment after approval of the IRB/EC, regulatory authority and sponsor. Administrative amendments to the Clinical Investigation Plan will be submitted to the IRB/EC for notification. Furthermore investigators shall sign any approved amendment for agreement.

21. Device Deficiencies and Troubleshooting

The Medtronic 24-Hour HL will be consulted for device troubleshooting (e.g. assistance is needed by subject to operate their device(s)). When subjects call the Helpline (HL), they are instructed to notify the HL operator that they are currently participating in a clinical study. All device deficiencies that are reported to the HL will be documented by the HL staff. Medtronic will review all device deficiencies and determine whether the deficiency requires reporting to regulatory agencies. The sponsor will ensure timely Device Deficiency reporting to meet regulatory requirements.

Note: For commercially available devices, device deficiency reporting will be documented per study and relevant regulatory requirements
The investigational center will be provided with a copy of all HL calls for their subjects. The HL calls should be reviewed for investigational center staff awareness and for the possibility of an AE. If an AE is detected the investigational center staff will also complete an AE eCRF.

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the HL by the subject or investigational center staff. Any device deficiency the investigational center may have should be reported to the HL. A device deficiency is any communication that alleges 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 labeling. (**Adapted from ISO14155:2011**)

All device returns will follow the 24-Hour HL procedures. To return a study device as part of a device deficiency, the investigational center and or subject are to call the 24-Hour HL.

It is the responsibility of the Investigator to follow the center's IRB/EC and local regulatory authority reporting requirements.

For EMEA region only:

Device deficiencies that did not lead to an Adverse Event but could have led to an SADE
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate, require immediate reporting to the sponsor and to IRB/EC and regulatory authority per local reporting requirements ISO14155:2011 (section 6.4.2).

22. Study Endpoints

22.1. Descriptive Endpoints

22.1.1. During the Home Period

- The mean change in A1C will be presented from baseline to end of study
- Change of Total Daily Dose (TDD) of insulin from baseline to end of study
- Change of weight from baseline to end of study
- Time spent in Auto Mode versus time spent in Manual Mode

- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤SG ≤ 180 mg/dL, SG>180, 250 mg/dL, 350 mg/dL
- Number of Events, AUC and Time in the hyperglycemic range: sensor glucose (SG) > 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL

22.1.2. During the Run-In Period

***Low Management Suspend before Low* Evaluation:**

- Success rate of prevention of hypoglycemia (i.e. 1 - percent of *Low Management Suspend before Low* experiments that have 2 or more consecutive reference glucose values of <= 65 mg/dL)
- *Low Management Suspend before Low* Performance
- Sensor performance

22.1.3. During the Hotel Period in the Study Period

Auto Mode Evaluation:

- Time in different range (% of i-STAT): BG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤ BG ≤ 180 mg/dL, BG > 180, 250 mg/dL
- Number of Events, AUC and Time in the hyperglycemic range: i-STAT® glucose > 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: i-STAT® glucose < 50, 54, 60, and 70 mg/dL

22.2. Exploratory Analysis

22.2.1. Analysis of Primary Endpoint

The primary effectiveness endpoint is change in A1C from baseline to end of 3-month treatment period, defined as A1C measured at the 3-month treatment visit minus A1C measured at the randomization visit. The goal is to show simple superiority in reducing A1C from baseline to end of 3-month study period.

22.2.2. Analysis of Secondary Endpoint

The secondary endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study phase.

- **Secondary Endpoint: % of Time in Euglycemia (70 – 180 mg/dL)**

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- **Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)**

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- **Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)**

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

22.3. Safety Data Summarized

- Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

23. Administrative Considerations

23.1. Study Closure Procedures

Upon completion of the study, when all subjects have completed their visit schedules, all eCRFs have been entered and all related queries have been resolved. The study devices, unused study materials and equipment will be collected and returned to Medtronic and/or its designees (see table 1). Medtronic and/or its designees will notify the investigational center of its intention to close out the study and a close-out visit will be conducted. The Monitor will ensure that the Investigator's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include discussing retention of study files, possibility of investigational center audits, and notifying the IRB/EC of study closure.

23.2. Document Storage and Retention

The Sponsor and Investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 2 years (or longer/shorter if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The Investigator should not dispose of these records without the approval of the Sponsor**.** The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

23.3. Data Handling

All data required for analysis will be captured on eCRFs using OC-RDC module. Original eCRFs will not be as source data and supporting documentation will be required. However, in cases where center-administered, web-based subject questionnaires are considered source data, said source data is electronic and associated systems must comply with CRF 21 Part 11 requirements. Electronic device data will be collected from the 670G Pump System using Medtronic CareLink Clinical. The system uses Secure Sockets Layers (SSL) technology, which encrypts all data it stores (21 CFR Part 11 compliant). Certain data points stored in the uploaded information may also be captured on the appropriate eCRF.

The Investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Information on case report forms must conform to the information in the source documents. Medtronic will provide detailed

instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the RDC system; otherwise, irresolvable data-related issues will be routed to the Sponsor for review and final disposition. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. If a person is only authorized to complete CRFs or to make changes to an already signed CRF, the investigator shall re-sign this CRF. System backups for data stored in the OC-RDC system will be consistent with Medtronic standard procedures.

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

23.4. Data Preparation

Prior to data extraction, all collected data will undergo a final verification by Data Management. Documentation of this verification will be maintained in the sponsor study files. Upon the completion of the verification, data will be extracted and transferred to the appropriate personnel for analysis.

23.5. Training of Clinical Staff

Training of the investigational center staff on the conduct of the study and system being studied will be initiated before the protocol is implemented. All participating physicians and coordinators will be familiarized with the system. Specific investigational center staff will be trained on each of the system's components. Training will contain both lecture and hands-on experience.

23.6. Study Binders

Investigator Binders will be provided by the Sponsor to be maintained by the designated investigational center staff. Each binder will have tabs to facilitate filing of study documents. Examples include:

- Medtronic Contact Information
- CV's & Medical Licenses
- Agreement(s)
- Delegation of Authority Log
- Training Records
- Subject Screening/Enrollment Logs
- Randomization Documentation (if applicable)
- Laboratory Documentation
- Case Report Forms (CRFs) & Instructions
- Sponsor/Monitor Visit Log
- Investigator Brochure
- Protocol and Amendments
- Device Instructions for Use (IFU)
- IRB/EC Documentation & Approvals
- IRB/EC Approved Consent Documents
- IRB/EC approved Investigator's Brochure/ Report of Priors
- Regulatory Authority approval or notification
- Financial Disclosures
- Insurance certificates (EMEA only)
- Reports
- Essential Correspondence
- Product Accountability
- Regulations and Guidance Documents
- Site Study Materials

- Subject Study Materials
- Note to File
- Miscellaneous
- Relevant communication

There will be an individual file for each subject which will include, but will not be limited to:

- Source Documents
- Signed and dated Informed Consents
- Adverse Event Notifications, if any
- Questionnaires
- Study Logs, if any

For EMEA only: The investigator will clearly mark the clinical records to indicate that the subject is enrolled in this clinical study.

For EMEA only: 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.

23.7. Monitoring Plan

Monitoring will be conducted to ensure the protection and safety of human subjects, the quality and integrity of the clinical data, and compliance with the protocol. The Monitoring Plan will give details on how and when data review will be conducted by clinical monitors. It will be updated and revised as needed due to changes in documents or processes.

Employees of the Sponsor, or its designees, who have received appropriate training, will serve as the Study Monitor(s). Monitoring visits will be conducted based on Medtronic's Standard Operating Procedures and the needs of the study. Quality documents will be followed for the conduct of all activities related to monitoring for this study.

Site Qualification and Initiation Visits will be completed prior to enrollment of the first subject. On Site study monitoring activities will include an inspection of completed study documents, source document verification and reporting, verification of database accuracy and completeness. All subjects enrolled in the trial will be monitored and the eCRF data verified against the subjects' source documents. Following each monitoring visit, a report will be prepared and submitted to the Sponsor. From initiation of study to close out visit, the Study Monitor(s) will assume primary responsibility for communications between the Study Investigators and the Sponsor.

The Principal Investigator is responsible for ensuring that investigational center staff is appropriately trained to manage the protocol. Initial and ongoing investigational center training will be provided during the Site Initiation Visit, subsequent monitoring visits, and regular investigational center contact. All investigational center staff must complete and sign the Study Training Record(s) and maintain the record(s) in the investigational center regulatory binder. Prior to enrollment of the first subject, Investigators and study coordinators who will be participating in enrollment, eCRF completion, device insertion/application, device training, and consenting subjects must complete the Sponsor-required training. Investigators and staff who are actively engaged in the study after the start of subject enrollment must complete all required training before their involvement starts.

All monitoring visits and visits from the Sponsor to the investigational center will be recorded using the Monitoring Visit Log. The log will be kept in the investigational center regulatory binder and the original will be collected and submitted to the sponsor.

23.8. Publication Policy

The contents of this protocol, the manuals pertaining to this study and the results of the investigation are confidential and may not be published or disclosed without the written consent of Medtronic Diabetes. The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The results of the clinical study will be submitted for publication.

24. Statistical Methods and Data Analysis

DURING HOME PERIOD:

24.1. Descriptive Endpoints

- The mean change in A1C will be presented from baseline to end of study
- Change of Total Daily Dose (TDD) of insulin from baseline to end of study
- Change of weight from baseline to end of study
- Time spent in Auto Mode versus time spent in Manual Mode
- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤ SG ≤ 180 mg/dL, SG > 180, 250 mg/dL, 350 mg/dL
- Number of Events, AUC and Time in the hyperglycemic range: sensor glucose (SG) > 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL

24.2. Safety Data Summarized

- Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

DURING HOTEL STUDY

During the Run-In Period

Low Management Suspend before Low Evaluation:

- Success rate of prevention of hypoglycemia (i.e. 1 - percent of *Low Management Suspend before Low* experiments that have 2 or more consecutive reference glucose values of <= 65 mg/dL)
- *Low Management Suspend before Low* Performance
- Sensor performance

During the Hotel Period in the Study Period

Auto Mode Evaluation:

- Time in different range (% of i-STAT): BG < 50, 54, 60, 70 mg/dL, 70 mg/dL ≤ BG ≤ 180 mg/dL, BG > 180, 250 mg/dL
- Number of Events, AUC and Time in the hyperglycemic range: i-STAT® glucose > 180, 250, 350 mg/dL

- Number of Events, AUC and Time in the hypoglycemic range: i-STAT® glucose < 50, 54, 60, and 70 mg/dL

24.3. Exploratory Analysis

24.3.1. Analysis of Primary Endpoint

The primary effectiveness endpoint is change in A1C from baseline to end of 3-month treatment period, defined as A1C measured at the 3-month treatment visit minus A1C measured at the randomization visit. The goal is to show simple superiority in reducing A1C from baseline to end of 3-month study period.

24.3.2. Analysis of Secondary Endpoint

The secondary endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study phase.

- **Secondary Endpoint: % of Time in Euglycemia (70 – 180 mg/dL)**

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- **Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)**

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- **Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)**

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

24.3.3. Sample Size Justification

24.3.3.1. Sample Size for Primary Endpoint

The overall mean change in A1C from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$
Ha: $\mu < 0\%$

Where μ is the mean of % of change in A1C (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in A1C is less than 0%.

Assuming the mean of change in A1C from baseline to the 3-month follow-up visit is zero, the standard deviation of change in A1C is 1.1%, SAS power and sample size calculator shows that a total of 80 subjects(7-13 years old) will provide 90% power to detect the difference of 0.4% and with one-sided type I error of 0.025.

A minimum of 95 subjects will be enrolled to account for subject attrition

24.3.3.2. Sample Size for Secondary Endpoint: % of Time in Euglycemia (70 – 180 mg/dL)

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

Ho: $\mu \leq 0\%$
Ha: $\mu > 0\%$

Where μ is the mean of change in % of time in euglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% lower confidence limit of the mean change in % of time in euglycemia is greater than 0%.

Assuming the mean of change in time in euglycemia (%) from baseline to the 3-month follow-up visit is zero, the standard deviation of change in percentage time in euglycemia is 11.0%, SAS power and sample size calculator shows that a total of 80 subjects (7-13 years old) will provide 90% power to detect the difference of 4.0% and with one-sided type I error of 0.025.

A minimum of 95 subjects will be enrolled to account for subject attrition

24.3.3.3. Sample Size for Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$
Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hyperglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hyperglycemia is less than 0%.

Assuming the mean of change in time in hyperglycemia (%) from baseline to the 3-month follow-up visit is zero, the standard deviation of change in percentage time in hyperglycemia is 11.0%, SAS power and sample size

calculator shows that a total of 80 subjects (7-13 years old) will provide 90% power to detect the difference of 4% and with one-sided type I error of 0.025.

A minimum of 95 subjects will be enrolled to account for subject attrition

24.3.3.4. Sample Size for Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$
Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hypoglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hypoglycemia is less than 0%.

Assuming the mean of change in time in hypoglycemia from baseline to the 3-month follow-up visit is zero, the standard deviation of change in percentage time in hypoglycemia is 4.0%, SAS power and sample size calculator shows that a total of 80 subjects (7-13 years old) will provide 90% power to detect the difference of 1.5% and with one-sided type I error of 0.025.

A minimum of 95 subjects will be enrolled to account for subject attrition

24.4. Coding of Adverse Events

Adverse events will be coded based on the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

24.5. Subject Feedback

Descriptive summary will be used to characterize data from questionnaires that are given to subjects to record feedback,

24.6. Interim Analysis

After 1200 patient days an interim report will be generated.

24.7. Final Reports

24.7.1. Study Phase Final Report for Subjects 7-13 Years Old

A study phase final report will be generated once the 7-13 year old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 7-13 years old subjects will be summarized and presented in the final report.

24.7.2. Study Phase Final Report for Subjects 2-13 Years Old

An addendum study phase final report will be generated once the 2-6 year old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 2-13 years old subjects will be summarized and presented in the final report.

24.7.3. Continued Access Phase Final Report for Subjects 2-13 Years Old

An addendum continuation phase final report will be generated once the 2-13 year old cohort have completed the continuation phase visits. Safety data will be summarized and presented in the final report

25. Human Factors

25.1. Electronic Diary

Use-related problems related to Auto Mode can only be experienced by subjects after run in period.

During the run-in period, starting at Visit 2, when subjects receive device training, they will be instructed to call the Medtronic 24-Hour HL to report technical problems (referenced in study protocol and EZ reference guide). In addition, all subjects and their parent(s)/guardian(s) will be asked to complete an electronic diary that captures use-related difficulty (see definition below) with the 670G insulin pump, e.g. issues that were resolved without help from the Medtronic 24-Hour HL, but nevertheless presented subjects with a challenge in terms of general understanding of the device.

Subjects and their parent(s)/guardian(s) will be instructed to complete an electronic diary entry as soon as possible after the time the difficulty occurred. The electronic diary online address will be provided to subjects. As part of the EZ reference guide given to all subject (see Investigator Site binder for details regarding subject training materials), the following brief explanation of use-related difficulty will be provided

Use-related difficulty is any scenario or situation in which you had trouble completing a task and you believe the device was the source of the issue. For instance:

- The pump did not perform as expected or as you were trained
- The task took more steps than you thought necessary
- You were frustrated with the pump when you performed the task
- The screens and/or controls on the pump were confusing

The following questions will appear on the electronic diary page:

1. Did the use-related difficulty involve the Medtronic study device (Y/N)?

2. Please describe the use-related difficulty you experienced (open-ended)?

3. What were you attempting to do when you experienced the difficulty (open-ended)?

4. What did you expect to happen and what actually did happen (open-ended)?

5. If the device did not seem to operate as you expected, were you using it in an unusual condition (e.g. extreme heat, cold, humidity)? (Y/N)
    a. If the answer to question 5 is “Yes”: Please describe what actually you were doing at the time (open-ended)

6. Did you receive an alarm (Y/N)?

a. If yes, please describe the alarm.

7. Did you have to refer to the user guide or training material (Y/N)?
   a. If yes, please describe the alarm.

8. Did you encounter any unexpected or unanticipated situations when the pump did not perform as expected (Y/N)?
   a. If the answer to question 8 is "yes": Please describe the situation and what you expected to happen (open-ended)

9. Was the difficulty overly burdensome (Y/N)?

The Human Factors Engineer (HFE) assigned to the study will retrieve the survey forms and review the answers provided to the above set of questions. The HFE will work with the Clinical Study team to make sure that none of the forms contain information about potential safety issues that would require intervention by any of the investigators. All use-related data from the diaries and from Help Line reports will be used to inform the system design, the user guide and/or relevant training materials.

25.2. Questionnaires

As subjects start using the Study Pump during the study phase, there will be additional focus on the Auto Mode feature that is being tested. To aid in this effort from a Human Factors perspective, subjects and their parent(s)/guardian(s) will be asked at the end of study participation to answer a set of questions that capture possible use-related issues specifically related to the Auto Mode feature. The questionnaire is available online. Subjects instructed to relate their experiences during the time the system was used in Auto Mode. The form will contain the following questions:

1. Did you have any difficulties using the pump while the pump was in Auto Mode? (Y/N)
   a. If the answer is "Yes": What were the difficulties and how did you resolve them? (open-ended)

2. Did you encounter any situations using the pump in which you did not know what action to take? (Y/N)
   a. If the answer is "Yes": What were the situations and how did you resolve them? (open ended)

3. Did you encounter any situations when you were unsure whether the pump was in Auto Mode or not? (Y/N)
   a. If the answer is "Yes": What were the situations and how did you resolve them? (open ended)

4. Did you receive any alarms for which you did not have enough information to understand what needed to be done? (Y/N)
   a. If the answer is "Yes": What were the alarms and what information was missing? (open-ended)

Medtronic 24-Hour HL staff will be given instructions by the Human Factors Engineer (HFE) on how to collect the above data, and what details to look for when recording use-related difficulties. In addition, the Medtronic HFE will review all call log reports provided by the 24-Hour HL, which may also contain information about use-related problems experienced by study subjects using the Auto Mode feature.

All use-related data from diaries and help line reports will be included in both the final usability validation report and the clinical report.

During regular meetings with the clinical study team, the HF team will discuss the information that has been obtained and raise issues that may require intervention with Investigational Centers or particular subjects (identified only by subject number), such as safety-related concerns. The clinical study team will bring any such issues to the attention of the appropriate Investigational Center staff. The responses of all subjects will be analyzed to examine whether or not known risks were adequately mitigated and if the risk of unacceptable use-related errors exists. This information may also be used to inform the final system

design, use guide, and/or training material prior to final validation.

Human Factors will also produce a separate report will be produced with analysis of the survey results in relation to known risks, in accordance with internal procedures. This report will communicate the survey analysis to the system design team.

26. Sponsor Contact Information

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List of investigation sites and investigators will be kept separate from the CIP and provided to the investigators. The sponsor will maintain an updated list.

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