Reduction of Nocturnal Hypoglycemia and Hyperglycemia in the Home Using Predictive Algorithms, Pump Suspension, and Insulin Dosing in Children and Young Adolescents (PHM3)

Version 6.0

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VERSION HISTORY

The following table outlines changes for the PHM3 protocol:

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Nelly Njeru John Lum	Roy W. Beck	2/22/2016	First version of Document
2.0	Nelly Njeru	John Lum	3/15/2016	Change in CGM sensor Removal of Canadian site listing
3.0	Nelly Njeru	John Lum	3/22/2016	Clarification on Tanner Staging Assessment – subjects younger than 9 yo are not required to complete this examination; changes to subject-specific stopping criteria
4.0	Nelly Njeru	John Lum	3/25/2016	Change in hypoglycemia alarm threshold during Algorithm Assessment Phase and external reviews, clarifications of guardian language
5.0	Nelly Njeru	John Lum	5/11/2016	Corrections to sections 4.6.1 (Hyperglycemia) and 1.4 (Synopsis of protocol) regarding maximum cumulative pump suspension time, and to Figure 2 regarding purpose of CGM run-in Change in the definition for a reportable Adverse Event (Section 4.1.1)
6.0	Nelly Njeru	John Lum	10/21/2016	Correction to listing of Enlite CGM sensor part number from MMT-7014 to MMT-7008A Optional remote monitoring for additional safety

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CHAPTER 1: INTRODUCTION

1.1 Study Rationale

Most episodes of severe hypoglycemia occur during the night, specifically during sleep (1; 2). Even with the advent of real-time continuous glucose monitoring (CGM), patients do not awaken to over 70% of nocturnal alarms (3). As detailed in Appendix Section 1.2, preliminary CRC-based and in-home studies have been conducted which demonstrated that reducing nocturnal hypoglycemia by using a CGM device with hypoglycemic prediction algorithms to interrupt an insulin pump's basal insulin delivery is both safe and effective. However, this benefit has been accompanied by modest increases in mean overnight sensor glucose and morning fasting blood glucose.

The goal of this study is to assess the safety and feasibility of use of a modified algorithm that will dose insulin to minimize projected hyperglycemia overnight in addition to suspending the pump if hypoglycemia is projected overnight in the home environment in children and young adolescents. A study of the same modified algorithm in adults and older adolescents is nearing completion. The hypothesis is that the use of CGM when coupled with predictive algorithms and an insulin infusion system can safely reduce overnight and morning hyperglycemia exposure while also continuing to protect against nocturnal hypoglycemia.

The study will collect data that could be used for a planning a pivotal study, but the study data are not intended to be used to support a Premarket Approval (PMA) application.

1.2 Hypoglycemia and Hyperglycemia Minimization Strategy

Hypoglycemia minimization will be achieved in the proposed study with the same Kalman filter-based predictive low-glucose suspend algorithm component used in the prior safety and efficacy studies described in Appendix sections 1.2.7 through 1.2.10. Additional implementation details are provided in section 3.9.3.

Hyperglycemia minimization will be achieved with a separate Kalman filter-based algorithm component triggered by elevated predicted glucose levels. Small correction boluses of insulin will be delivered when the system predicts that hyperglycemia above a pre-set threshold will occur, with insulin-on-board constraints and cumulative delivery limits to minimize the likelihood of excessive insulin delivery. This algorithm component has been evaluated with older adolescents and adults in the two prior studies described in sections 1.2.10 and 1.2.11. Additional implementation details are provided in section 3.9.4.

1.3 Closed-loop Control System

The CGM-pump subsystem used in this study will be the Paradigm Veo Insulin Pump Model MMT-754, labelled for investigational use in the United States, and the Enlite CGM sensor (MMT-7008A), both developed by Medtronic MiniMed. The sensor is inserted subcutaneously and connected to the MiniLink REAL-Time transmitter (MMT-7703XNA) that will transmit data every 5 minutes to the study laptop via the ComLink device (MMT-7304NA). The laptop includes the algorithm described in section 1.2 that will issue commands to the Paradigm Veo Insulin Pump

Model MMT-754 via the ComLink device (Figure 1).

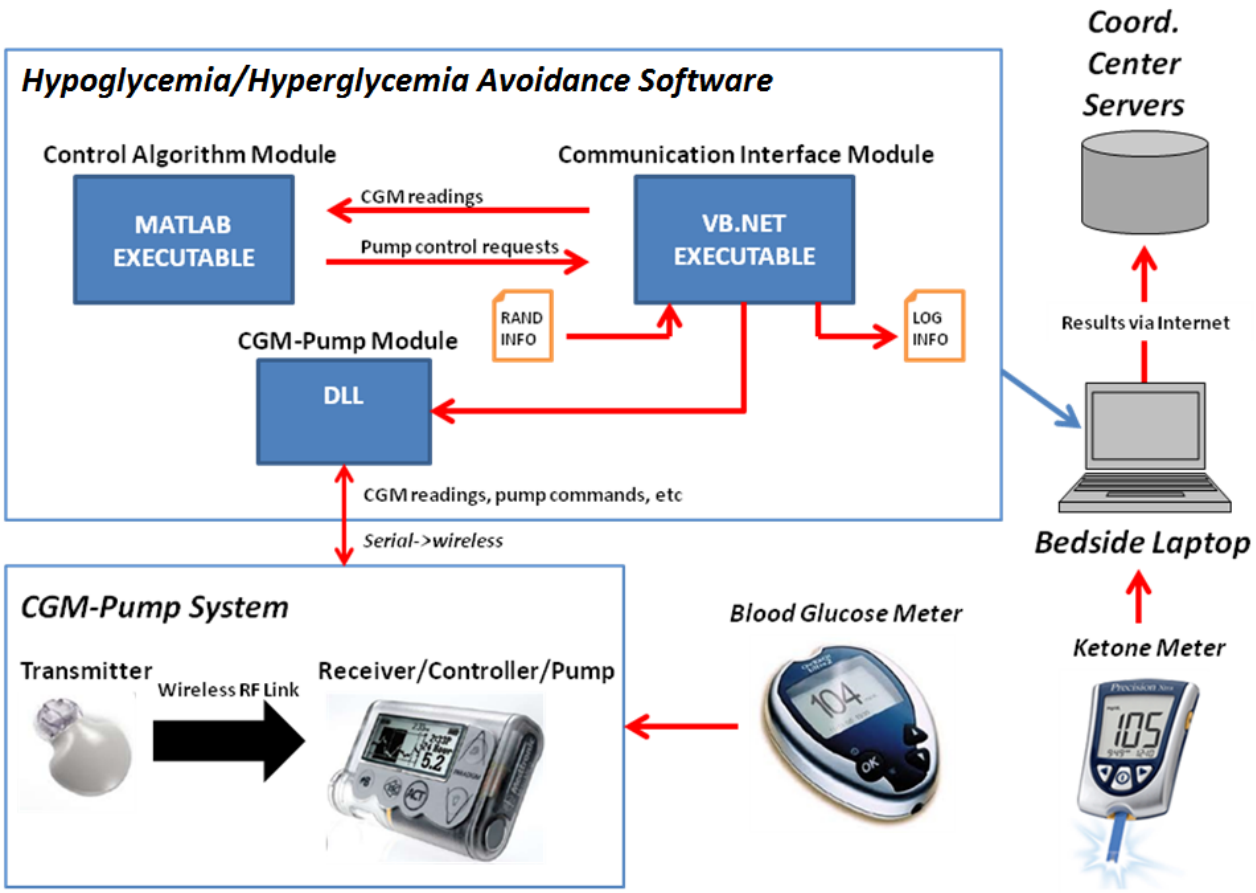


Figure 1: Closed-loop control system, with Medtronic CGM-pump subsystem and closed-loop control software for suspension of insulin delivery when hypoglycemia is predicted and dosing of insulin when hyperglycemia is predicted

1.4 Synopsis of Study Protocol

Objective: to gain experience in children and younger adolescents with in-home use of an algorithm that will dose insulin to minimize projected hyperglycemia overnight in addition to suspending the pump if hypoglycemia is projected overnight and to obtain feasibility, safety, and initial efficacy data

Study Design: randomized controlled trial, with randomization on a night level within subject

Patient Population: Youth 6.0 - <15 years old with type 1 diabetes treated with daily insulin therapy for at least one year and an insulin infusion pump for at least 6 months who have HbA1c < 10.0% *(see section 2.2 for listing of inclusion and exclusion criteria).*

Sample Size: 30 subjects

Study Duration and Visit Schedule: duration approximately 3 months, with preliminary run-in activities followed by up to 90 days spent in clinical trial phase of study; clinic visits at enrollment, following CGM and system assessment run-in phases, at start of clinical trial phase, at 21-day point of clinical trial phase, and after 42 nights of successful system use

Major Efficacy Outcomes:

- **Primary:** time in range (70-180 mg/dl, 3.9-10.0 mmol/L) overnight.

- **Secondary**: time spent in hypoglycemia (<70 mg/dl, 3.9 mmol/L) and time spent in hyperglycemia (>180 mg/dl, 10.0 mmol/L) overnight.

Major Safety Outcomes: CGM measures of hypo- and hyperglycemia, including morning blood glucose and mean overnight sensor glucose; adverse events including severe hypoglycemia and diabetic ketoacidosis

Summary of Protocol

Subjects who are eligible for the clinical trial initially will use a Veo insulin pump and Enlite CGM sensor at home for a minimum of 6 days/week over a 2-week period to verify that the subject is able to use the CGM and insert sensors (Section 3.3).

The first 10 subjects enrolled will be 11 to <15 years of age and will participate in an Algorithm Assessment Phase of approximately 10 nights of system use each with PLGS and Hyper Minimization active. Results of the approximate 100 nights will be reviewed with the study DSMB to assess safety and determine whether any adjustments to the algorithm parameters are needed. If adjustments are needed, the Algorithm Assessment Phase will be repeated with the same age restriction, using the same 10 subjects if possible. If no adjustments are needed and the DSMB judges it safe to continue the study, enrollment will continue across the full 6 to <15 age range.

Subjects who enroll in the study after the completion of the Algorithm Assessment Phase will use the closed-loop system at home for 5 nights of system use each with PLGS and Hyper Minimization active to demonstrate their ability to use the system and submit study data to the Coordinating Center.

Subjects who successfully demonstrate their ability to use the system at home as described above will be eligible for the randomized trial phase. This phase consists of use of the full system in the home for approximately 42 nights:

- Each night the blood glucose level will be checked with the BG meter and used to perform a calibration of the CGM. This calibration must occur no more than 90 minutes prior to activation of the system. NOTE: Subjects will be instructed to calibrate the CGM per manufacturer guidelines.
- Then the system will be activated, linking the CGM and insulin pump to the computer at the bedside.
- A randomization schedule on the laptop will be used to determine whether the system will run in PLGS+Hyper Minimization mode or PLGS-only.
    - Subjects will be blinded as to whether the system is running in PLGS+Hyper Minimization mode or PLGS-only.
    - There will not be an alarm if the pump shuts off or if automated insulin dosing occurs. The CGM alarm will be set to 60 mg/dL (3.3 mmol/L). When a CGM alarm occurs, the subject will be asked to measure the blood glucose with a BG meter, if he/she is aware of the alarm.
    - The time period for outcome assessment each night will be from the time the system is activated until it is turned off in the morning.
- Pump Suspension:
    - Maximum shutoff of 180 minutes during a given session as long as no automated insulin dosing occurs after reaching 180 minutes
    - Maximum shutoff of 300 minutes during a given session if automated insulin dosing occurs after reaching the 180 minutes

- Small correction boluses of insulin will be delivered when the system predicts that hyperglycemia above a pre-set threshold will occur, with insulin-on-board constraints and cumulative delivery limits to minimize the likelihood of excessive insulin delivery.
- Subjects will be asked to check blood glucose with the study BG meter each morning prior to breakfast and enter the results using the controller software interface. The subject will be instructed to contact the study physician if the morning blood glucose value is <60 mg/dl (3.3 mmol/L) or >300 mg/dl (16.7 mmol/L). Monitoring processes detailed in section 3.10 will ensure that the subject can be contacted if these values are not reported as required or are out of range.
- Subjects will be asked to record all overnight carbohydrate intake using the controller software interface.
- Subjects will be asked to perform periodic CGM data uploads using the controller software interface as detailed in section 3.10. Monitoring processes detailed in section 3.10 will ensure that the subject can be contacted if these uploads do not occur as required, or if review of an upload reveals any extreme, prolonged episodes of hypoglycemia or hyperglycemia, or elevated morning blood glucose values.

Once approximately 200 nights of randomized clinical trial phase data are available, the study DSMB will perform another data review to determine whether it is safe to continue the study. Subjects already using the study system at home will continue to use it during the DSMB review process, but no additional subjects will begin home use of the system until the DSMB review is complete.

Upon completion of the study, subjects as well as study clinicians will be asked to complete a human factors usability questionnaire regarding use of the study system.

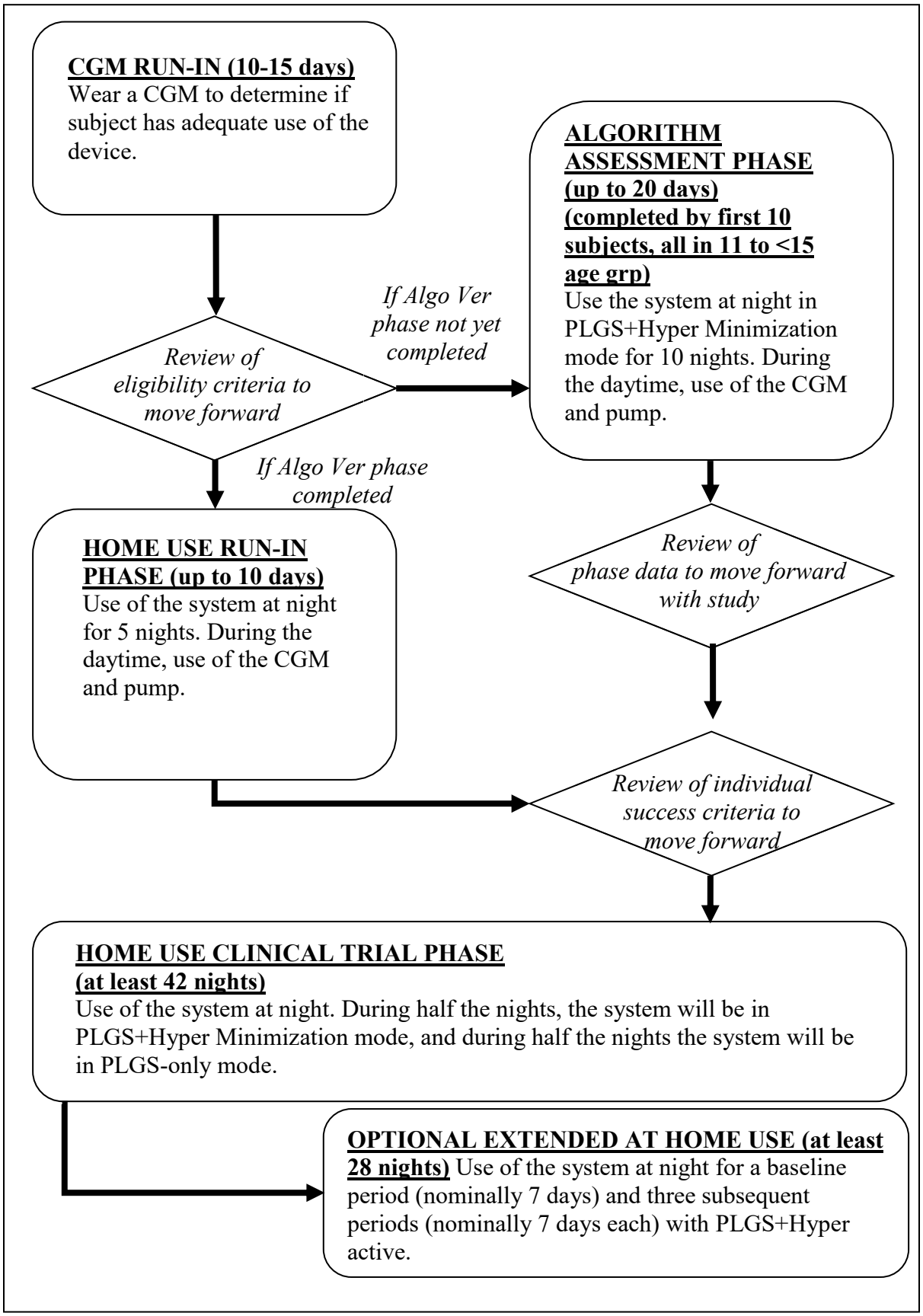
There will be a follow-up (optional) extension phase for subjects who exhibit safe and competent use of the system at home. They may be given the option to continue home use of the system for up to 56 days to assess whether data-driven, subject-level customization of algorithm parameters improves glycemic outcomes compared with generic algorithm parameters that are identical for each subject.

1.4.1 Schedule of Study Visits/Phone Contacts

There will be one follow-up visit after 21 days (window -2 to +7 days) in the clinical trial and a second follow-up visit after completion of the 42 nights of successful use of the closed loop system (window 0 to +12 days). A night of successful system use is defined as collecting a minimum of four hours of data. Subjects who participate in an Algorithm Assessment phase will have one or more additional follow-up visits depending on how many algorithm adjustments are made.

Phone contacts will be made with the subject once a week during each calendar week.

293 **Figure 2: Flowchart Depiction of Study Components**
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1.5 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

The protocol is considered a significant risk device study, due to the fact that the closed loop system is experimental. Therefore, an IDE from the FDA is required to conduct the study.

CHAPTER 2: SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Enrollment will proceed with the goal of 30 total subjects 6.0 to <15.0 years old completing the protocol. A maximum of 90 may be enrolled in the study in order to achieve the goal of protocol completion by 30 subjects. Subjects may be replaced if the protocol is not completed. There is no restriction on the number of subjects to be enrolled by a site.

Subjects will include both males and females and an enrollment goal will be to achieve an approximately equal sex distribution.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

To be eligible for the study, a subject must meet the following criteria:

1) Clinical diagnosis of type 1 diabetes and using daily insulin therapy for at least one year and an insulin infusion pump for at least 6 months
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not required.
2) Age 6.0 to <15.0 years
3) HbA1c < 10.0%
   - Measured with DCA2000 or equivalent device for assessing eligibility
   - HbA1c measurements performed as part of usual clinical care within 2 weeks prior to obtaining informed consent for participation in the trial may be used.
4) Uninterrupted internet access while study system is being used overnight and for upload of study data in the morning
5) Living with a family member/legal guardian committed to participating in all study activities, and being present and available to provide assistance when the system is being used at night
6) An understanding of and willingness to follow the protocol and sign the informed consent

2.2.2 Exclusion

The presence of any of the following is an exclusion for the study:

1) Diabetic ketoacidosis in the past 6 months
2) Hypoglycemic seizure or loss of consciousness in the past 6 months
3) History of seizure disorder (except for hypoglycemic seizure)
4) History of any heart disease including coronary artery disease, heart failure, or arrhythmias
5) Cystic fibrosis
6) Current use of oral/inhaled glucocorticoids, beta-blockers or other medications, which in the judgment of the investigator would be a contraindication to participation in the study.
7) History of ongoing renal disease (other than microalbuminuria). Creatinine level must have been obtained within the last year if subject has diabetes of >10 years duration. If creatinine is > 1.5 mg/dL (132 μmol/L), the subject is excluded.
8) Medical or psychiatric condition that in the judgment of the investigator might interfere with the completion of the protocol such as:
   - Inpatient psychiatric treatment in the past 6 months
   - Uncontrolled adrenal disorder
   - Abuse of alcohol
9) Pregnancy
   Negative urine pregnancy test required for females who have experienced menarche as well as agreement from subject and parent/legal guardian to use a form of contraception to prevent

pregnancy while participant is in the study. Subjects who become pregnant will be discontinued from the study.

10) Liver disease as defined by an ALT greater than 3 times the upper limit of normal

2.3 Patient Enrollment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history and performance of a physical examination by a study investigator. Clinical sites may keep a record of the reason why screened subjects are not enrolled.

2.3.1 Historical Information and Physical Exam

A history will be elicited from the subject and extracted from available medical records with regard to the subject's diabetes history, current diabetes management, other past and current medical problems, past and current medications, and drug allergies. A standard physical exam (including vital signs and height and weight measurements) will be performed for all subjects. An assessment of Tanner Staging for subjects who are post-pubertal will also be completed. Both examinations will be completed by the study investigator or his or her designee (an endocrinologist, endocrine fellow, endocrine nurse practitioner or a physician assistant).

2.3.2 Informed Consent

For eligible subjects, the study will be discussed with the subject and parent/legal guardian. (referred to subsequently as 'parent'). The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Subjects of appropriate age will either be given the Child Assent Form to read or it will be read to the child. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent form will be provided to the subject and his/her parent and another copy will be added to the subject's clinic chart.

Written informed consent must be obtained from the parent prior to performing any study specific procedures that are not part of the subject's routine care.

2.3.3 Authorization Procedures

As part of the informed consent process, each subject and parent will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject and parent, questions will be answered about the details regarding authorization.

2.3.4 Special Consent Issues

The study population for this study includes individuals 6 to <15 years old. The consent form and study procedures will be discussed with each such subject at a level in which he/she can understand. The study staff will ask questions of each subject to assess the autonomy and understanding of the study. Each subject will be asked to sign an assent form. Additionally, the parent of each subject will be asked to sign the consent form. They will be given the opportunity to ask questions throughout the study on all study related procedures.

CHAPTER 3: STUDY PROTOCOL

3.1 Initial Visit

During the initial visit, informed consent will be obtained and eligibility will be assessed. The following procedures will be performed:

- Signed and dated informed consent by the subject and parent
- HbA1c assessment via fingerstick and DCA2000 or equivalent NGSP-certified point-of-care method (measurement within 2 weeks prior to enrollment acceptable)
- Collection of medical history information including
    - Demographics (date of birth, gender, race and ethnicity), diabetes history, medical history, concomitant medications, physical examination including weight, height, and vital signs (oral temperature and orthostatic measurement of blood pressure and pulse)
- Urine pregnancy test for all women who have experienced menarche
- Blood draw for:
    - Creatinine level if subject has had diabetes of >10 years duration (value within 12 months from enrollment acceptable).
    - Liver function tests in subjects taking medications known to affect liver function or diseases known to affect liver function (values within 3 months prior to enrollment acceptable).
- Physical Exam
- Tanner Staging assessment

3.2 CGM Run-in

During the CGM Run-in Initiation visit, each subject not already using a Medtronic CGM identical to the type used in the study, will be provided with a CGM and sensors. While in the office, a CGM sensor will be placed. The subject will be instructed on use of the CGM and will be provided with a manual describing its calibration and use. The subject will be asked to attempt 24/7 use of the CGM. Instructions will be given with regard to how the CGM glucose data should be used for diabetes management. This will be done as per our standard teaching developed in the JDRF randomized clinical trial.

The subject also will be provided with a blood glucose (BG) meter and test strips to be used during the study in addition to a blood ketone meter and test strips. The blood glucose meter will be used to calibrate the CGM as well as to check the glucose level before real-time management decisions are made based on the CGM. The ketone meter will be used to check ketone levels as a safety measure. Prior to the subject leaving the clinic to begin each home-use study phase and during each clinic visit, quality control testing using the standard solution(s) provided by the manufacturer and specific to the study home glucose meter and ketone meter will be performed. The quality control testing will be performed with at least two different concentrations of control solution if available and a tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.

The subject will be instructed to perform fingerstick tests before going to bed, each morning upon waking, anytime insulin is administered, and to confirm sensor readings that are in a hypo- ($\leq$70 mg/dl) or hyperglycemic (>250 mg/dl) range.

Successful use is defined as use of the CGM for at least 6 days per week over a period of 2 consecutive weeks (two sensors), including insertion of the second sensor at home (the first sensor will be inserted in the clinic). If there was an overriding reason to explain why the subject was unable to use CGM for 6 days per week (e.g., problem with the device or illness) and the investigator believes that the subject will use a sensor daily, the subject can wear the CGM for an additional week during the run-in.

Subjects and their families may optionally use the FDA-approved MiniMed Connect system to allow remote monitoring of the study CGM and other data during the study.

3.3 Clinic Visit to Review CGM Use and Data

After completing 14-21 days of use, the subject will have a clinic visit. The site will download the CGM to evaluate whether it was used each day for 6 days minimum per week for 2-weeks' time. If the CGM is used successfully during the 14-21 days of CGM use, the subject will be eligible to continue in the study and will be instructed to avoid use of any personal CGM device during subsequent study periods when the closed-loop system is being used. Otherwise, the subject will not continue in the study.

Subjects already using a Medtronic CGM identical to the type used in the study will skip the CGM Run-in phase; however, these subjects will have to have demonstrated adequate use of their personal CGM sensor for a minimum of 6 days/week over a 2-week period in the most recent nights of use (must be within the past 42 days) prior to moving to the next phase.

3.4 Algorithm Assessment Phase

The first 10 eligible subjects age 11 to <15 who successfully complete CGM Run-In will participate in an Algorithm Assessment phase. This phase is intended to assess the safety and effectiveness of the algorithm in a small number of subjects for a limited amount of time at home to determine if adjustments need to be made to the adjustable algorithm parameters prior to proceeding with the randomized portion of the study. This phase will be completed independently as described above in section 1.4. Subjects will be given up to 20 days to collect 10 nights of data during which the system will run with its PLGS+Hyper Minimization algorithm active on every night of use. The approximately 100 total nights of data will be reviewed to determine if changes need to be made to the algorithm parameters. If changes are made, the 10 nights will be repeated with the same 10 subjects if possible (or as needed with eligible replacement subjects who first complete the CGM Run-In), and the results will again be evaluated to determine if the algorithm is sufficiently safe and effective. Subjects participating in the Algorithm Assessment Phase do not need to complete the Home Use Run-in Phase.

Once the Algorithm Assessment Phase has been completed with a positive DSMB review, enrollment will continue with subjects across the full 6 to <15 age range.

3.5 Home Use Run-in Phase Using Closed Loop System

Eligible subjects who did not participate in the Algorithm Assessment Phase will participate in a Home Use Run-In Phase. The objective of this phase is for the subject to use the closed-loop control system in PLGS+Hyper Minimization mode at home for 5 nights to verify that the subject can start and stop the system appropriately and transmit system data to the Coordinating Center. The subject will be given up to 10 days to successfully complete this phase, during which the system will run with its PLGS+Hyper Minimization algorithm active on every night of use. Instructions will be given to the subject on the use of the CGM-pump system and linking to a

bedside computer at bedtime. The protocol will follow that of the intervention nights in the randomized trial described in section 3.7.

To proceed to the randomized trial, the subject must successfully use the system for five nights and transmit the data to the Coordinating Center each morning. Subjects will be asked to perform daily CGM data uploads using the controller software interface as detailed in section 3.10. Monitoring processes detailed in section 3.10 will ensure that the subject can be contacted if these uploads do not occur as required, or if review of an upload reveals any extreme, prolonged episodes of hypoglycemia or hyperglycemia, or elevated morning blood glucose.

3.6 Clinical Trial Baseline Visit

After completing the in-home system use in either the Algorithm Assessment phase or the Home Use Run-In phase, subjects will return for the baseline clinical trial visit.

Subjects who successfully completed their preliminary in-home system use period will be eligible to enter the randomized trial. For these subjects, the study protocol again will be explained to the subject to assure that they are committed to participate in the study. If the subject is uncertain about participation, it is prudent to not continue the subject in the study.

HbA1c will be measured with the DCA2000 or equivalent device.

3.7 Overview of Randomized Trial

Each subject will use the closed-loop control system in the home for approximately 21 nights with the PLGS+Hyper Minimization algorithm active and 21 nights in which only the PLGS algorithm active. A night only will be counted towards the 21 night goal if there are at least 4 hours of sensor glucose data. All nights with any sensor data will be included in the safety analysis, while only nights with at least 4 hours of sensor glucose data will be included in the efficacy analysis. Thus, most subjects will take longer than 42 days to complete the trial. The maximum number of days to complete the study will be 90 days.

Subjects will be limited to insulins approved for pump use, i.e. Novolog, Humalog or Apidra. While using the closed-loop system, the subject will be instructed to avoid deviating from his/her regular daily routine in regards to diet and exercise and to maintain his or her usual sleep schedule during the course of the study. The subject will specifically be asked to avoid consuming more than 3 alcoholic drinks in any one day. The subject will be instructed to contact the study investigator prior to making any pump setting or management changes during the study.

Subjects will be encouraged to use the closed-loop control system on consecutive nights as much as possible. However, they will be instructed not to use it during periods of significant illness and extreme stress, if subject's blood glucose is not between 90 mg/dL (5.0 mmol/L) and 270 mg/dL (15.0 mmol/L), or during periods of use of medications such as epinephrine for the emergency treatment of a severe allergic reactions or asthma attack. In addition, it is recognized that there may be a hiatus during periods of travel.

System operation and data upload details are given in section 3.10 below.

Subjects who complete fewer than 10 algorithm-active and 10 algorithm-inactive nights may be replaced to achieve the protocol completion goal, within the enrollment limit described in section 0. However, data from these subjects will be included in the analysis.

3.8 Optional – Extended Night Closed-Loop Home Use

Subjects who exhibit safe and competent use of the system at home may be given the option to continue home use of the system for up to 56 days to assess whether data-driven, subject-level customization of algorithm parameters improves glycemic outcomes compared with generic algorithm parameters that are identical for each subject. Criteria for participation include:

- Did not experience severe hypoglycemia or hyperglycemia as defined in section 4.1.1
- Did not develop >1.0 mmol/L ketones on 3 or more nights due to prolonged pump shut off
- Study staff were able to contact the subject or the care partner without difficulty and in a timely manner overnight
- The subject used the system appropriately including the following:
  - Responded to system alarms and treated hypo- and hyperglycemia appropriately
  - Avoided study system use during periods of illness or travel away from home
- Subject did not become pregnant. If female and sexually active, subject agrees to continue to use a birth control method to prevent pregnancy while a participant in the study and understands that the use of a "highly effective" birth control method is the best way to avoid accidental pregnancy

Each subject will continue to use the study system at home with the PLGS+Hyper Minimization algorithm active each night the system is used. Subjects will be given up to 14 days to complete a baseline period of 7 nights of system use with at least 4 hours of CGM data with system parameters unchanged from the prior randomized phase. Data from the baseline period will be assessed using an automated procedure to determine whether any adjustable algorithm parameters should be modified to improve glycemic outcomes for the subject. Any recommended modifications will be subject to clinician review. The subject will then complete three additional use periods (each with at least 7 nights of system use in a 14-day window as above), with an opportunity for further algorithm parameter adjustment after periods 1 and 2.

Monitoring processes detailed in section 3.10 will remain in place. Phone or email contact will be made with the subject weekly (on a calendar week basis) by the study staff to respond to any questions the subject has and to remind the subject of their need to upload data to the Coordinating Center. Prior to each use period, the subject will be provided with a modified system configuration file for use in the upcoming period if any algorithm parameters were changed.

Continued participation will be dependent on the subject continuing to fulfill the criteria above. Subjects will be asked to follow the same usage constraints described in section 3.7 above.

After completion extended use of the system at home, subjects will return to the clinic for a final visit. An HbA1c sample will be collected.

3.9 System Operation Details

3.9.1 Activation and Calibration of the Closed-loop Control System

The subject will activate the closed-loop control system at bedtime. The system will ask the subject to perform a blood glucose fingerstick check with the study BG meter to calibrate the system if it has been more than 90 minutes since the last calibration. The subject will be instructed to calibrate the system with a glucose value that is stable at a time when the subject's blood glucose is not

rapidly fluctuating (no rate of change arrow). If calibration is not possible due to fluctuation in the subject's glucose level, the subject will be instructed to not use the system for that evening.

The system will also ask the subject to enter a blood glucose fingerstick value obtained in the past 15 minutes. The subject's blood glucose must be between 90 mg/dL (5.0 mmol/L) and 270 mg/dL (15.0 mmol/L) for the system to activate. During system activation, the subject will also be asked to enter whether or not a bedtime snack was eaten and whether he/she exercised that day.

During the randomized study phase, an encrypted randomization list will reside on the bedside computer. Each night when the system is activated, a program will run to select the randomization assignment for that night and the appropriate functionality of the algorithm will either be in PLGS+Hyper Minimization or PLGS-only. Subjects will be unaware of the assignment for that night.

3.9.2 CGM Hypo- and Hyperglycemia Threshold Alarm Settings

During the Algorithm Assessment phase, the CGM hypoglycemia threshold alarm will be set to 70 mg/dL (3.9 mmol/L). Following completion of the Algorithm Assessment phase and a safety data review as described in section 4.5, the CGM hypoglycemia threshold alarm will be set to 60 mg/dL (3.3 mmol/L) for the remainder of the study. The subject will be asked to measure the blood glucose with the study BG meter if aware of an alarm. There will not be an alarm at the time the pump infusion shuts off, and trend alarms will not be used. This is to allow the system to function without subjecting the subject to multiple overnight alarms.

The CGM hyperglycemia threshold alarm will be set to 300 mg/dL (16.7 mmol/L). The subject will be asked to measure the blood glucose with the study BG meter if aware of an alarm. There will not be an alarm if insulin is given by the automated controller, and trend alarms will not be used. As above, this is to allow the system to function without subjecting the subject to multiple overnight alarms

3.9.3 Pump Shut Off for Predicted Hypoglycemia

Automated pump shut off, when it occurs, will be for a maximum of 120 minutes for an individual suspension event and will not exceed a cumulative maximum of 3 hours for a single night.

If during a shutoff event the individual event maximum or cumulative maximum time is reached, or the CGM glucose has met controller defined rebound criteria, then the pump basal insulin infusion will be automatically restarted at the usual basal rate for the current time of day. If the pump has been suspended for more than 120 minutes in a 150 minute time window, the algorithm will automatically restart the pump at its usual basal infusion rate. Multiple instances of pump suspension can occur if there are recurrent predictions of hypoglycemia during the night.

3.9.4 Insulin Dosing for Predicted Hyperglycemia

Hyperglycemia minimization is achieved with a Kalman filter-based algorithm component triggered by elevated predicted glucose levels. Specifically, we subtract a hyperglycemia threshold from the predicted glucose level and ensure that the insulin on board is sufficient to bring the glucose levels down to the threshold. The insulin on board calculations reflect any recent boluses in addition to any basal insulin "removed" via recent pump suspensions. If we determine that a correction bolus is needed, we deliver only a fraction of the calculated insulin bolus in any single closed-loop control cycle. The algorithm then reassesses the need for additional insulin during subsequent control cycles, spreading the insulin dosing out over 30 to 60 minutes to allow corrections for any new sensor measurements obtained over that time period. By comparison to Kovatchev et al.'s sCTR

algorithm we choose to give the extra insulin slowly over time rather than as a single bolus (4). For additional safety, the algorithm includes rules to limit maximum insulin delivery over a several-hour time period as well as cumulatively for the entire night.

To prevent patient confusion we implement the extra insulin as boluses rather than changes to the basal profile. This means that the native insulin on board calculations of the insulin pump's bolus wizard will reflect any automated boluses and help prevent insulin "stacking" if any manual insulin boluses are given to correct hyperglycemia in the middle of the night.

3.10 Safety Measures

3.10.1 System Design Safety Features

The system will not activate in the evening unless the subject has a blood glucose between 90 mg/dL (5.0 mmol/L) and 270 mg/dL (15.0 mmol/L). Following activation, the subject may deactivate the closed-loop control system at any time by clicking a large "Stop" button in the main user interface. Normal basal insulin delivery will be restored immediately if the pump is in a suspended mode when the system is deactivated, and automated insulin dosing will cease. Subjects can give manual boluses to correct for hyperglycemia and the system will continue to function; however, if they want to make temporary changes to their basal rate, they will need to turn the system off.

Risk of excessive insulin dosing in response to persistently elevated sensor glucose values is mitigated by several design factors. First, only a small fraction (approximately 10%) of a calculated correction bolus may be delivered in a single five-minute control interval. As a result, corrections are gradual and the system reacts conservatively to any transient high excursions of the CGM signal. Second, there is an insulin-on-board-based dosing constraint that prevents excessive dosing (over and above a multiple of open-loop basal delivery) in any given ~4-hour period. Third, there is a cumulative dosing constraint that prevents excessive dosing (over and above a multiple of open-loop basal delivery) in any single overnight session.

Because pump suspension is achieved by requesting a temporary basal setting of 0 U/hr for up to 30 minutes, the maximum possible duration of pump suspension following any sudden, unexpected termination of the system (e.g. complete loss of power) will be 30 minutes. If the software terminates itself in response to an unexpected error, it will first attempt to cancel any active automated pump suspension before exiting.

An automated remote monitoring system may be active to ensure that clinical staff are immediately notified: if the subject's CGM sensor glucose goes below a predefined hypoglycemic level or above a predefined hyperglycemic level for a predefined period of time; if the system delivers an automatic bolus larger than a predefined maximum amount; or if the system has communication problems for a predetermined period of time. Regardless whether automated notifications are active, clinicians will have access to a Web-based interface for on-demand remote assessment of sensor glucose and insulin dosing history.

Subjects and their families may optionally use the FDA-approved MiniMed Connect system to allow remote monitoring of the study CGM and other data during the study.

3.10.2 Data Collection and Daily Monitoring

Subjects will be asked to check the blood glucose level each morning prior to breakfast and enter the result using the controller software interface. The subject will be instructed to contact the study physician if the blood glucose is elevated (BG ≥300 mg/dL (16.7 mmol/L)) or low (BG <60 mg/dL (3.3 mmol/L). Instructions for ketone treatment are provided in the study procedures manual.

Subjects will also be asked to record all overnight carbohydrate intake using the controller software interface.

Session datafiles for each night automatically record the CGM data and insulin delivery data logged by the system overnight and the blood glucose and carbohydrate data entered by the subject in the morning. These datafiles will be uploaded to the study Coordinating Center via a simple button click by the subject in the study software interface.

During home use, the subject will be required to upload the previous night's session data to the Coordinating Center by noon Pacific Time each day. The subject will not be able to reactivate the system for a subsequent night until these data have been transmitted. An automated e-mail will notify clinical staff if a subject's morning blood glucose reading is out of the expected ranges defined above, if the CGM data reflect extreme, prolonged episodes of hypoglycemia (sensor glucose readings <50 mg/dL (2.8 mmol/L) for more than 30 minutes overnight) or hyperglycemia (sensor glucose readings >300 mg/dL (16.7 mmol/L) for more than 30 minutes overnight), or if no data upload has been received by noon.

Phone or email contact will be made with the subject weekly (on a calendar week basis) by the study staff to respond to any questions the subject has and to remind the subject of their need to upload data to the Coordinating Center.

3.10.3 Use of CGM

Subjects will be given advice as indicated for use of CGM as they would be given as part of standard care.

The importance of entering calibration values when the blood glucose level is fairly stable as well as calibrating the CGM per manufacturer recommendations will be stressed.

3.11 Schedule of Study Visits/Phone Contacts

Each subject will have a follow-up visit after 21 days (window 19 to 28 days) and then after completion of 42 successful nights or 90 total days (window 0 to 12 days after this point is reached) of use of the closed-loop control system. Additional visits will occur as indicated.

The following procedures will be performed at the 21-day follow-up and final study visit:

- Eliciting interval medical history including adverse effects, new medical problems, and changes in medications.
- Downloading of CGM, BG meter, ketone meter and pump
- Skin assessment
- HbA1c determination using the DCA2000 or equivalent device

3.12 Diabetes Management During the Study

Treatment adjustments are permitted during the course of the study for diabetes management purposes. If a subject is seeing a physician unfamiliar with the study who could potentially advise the subject on treatment adjustments, a study physician will contact that individual to discuss the study prior to any use of the study device by the subject.

CHAPTER 4: ADVERSE EVENT REPORTING AND SAFETY MONITORING

4.1 Adverse Event Reporting and Monitoring

4.1.1 Definition

A reportable adverse event for this protocol includes any untoward medical occurrence that meets criteria for a serious adverse event or any unanticipated medical occurrence in a study subject that is study- or device-related, including hypoglycemia as defined below and hyperglycemia/diabetic ketoacidosis (DKA) as defined below. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Hypoglycemic events are recorded as Adverse Events only if the event required assistance of another person due to altered consciousness and required another person 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 herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, 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.

Hyperglycemic events are only recorded as Adverse Events if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or in the absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis.

Hyperglycemic events are classified as DKA if the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

4.1.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the participant, and appropriate medical intervention will be made.

The investigator will elicit reports of adverse events from the participant at each visit and phone call and complete all adverse event forms online. Each adverse event form is reviewed by the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event

is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

Adverse events will be coded using the MedDRA dictionary. Definitions of relationship and intensity are listed on the website data entry form.

4.2 Reporting Serious or Unexpected Device-related Adverse Events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect
- Could have resulted in death or significant disability if treatment had not been given

An *Unanticipated Adverse Device Event* is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the Coordinating Center immediately via completion of the online serious adverse event form.

The Coordinating Center will notify all participating investigators of any adverse device event that is both serious and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event. Such events will be reported to the FDA according to regulatory requirements.

Each principal investigator is responsible for informing his/her IRB of serious study related adverse events and abiding by any other reporting requirements specific to their IRB.

4.3 Device Malfunctions and Other Issues

All study device related malfunctions or device issues not previously identified in nature, severity, or degree of incidence will be reported to the Coordinating Center via completion of the device issues form regardless of whether the malfunction or issue was related to an adverse event. The effect on study treatment/device as well as likelihood that the device issue could have led to an adverse event will be recorded.

Device issues will be reported to the FDA and/or the study Data and Safety Monitoring Board (DSMB) according to regulatory requirements and any additional requirements in the study-specific risk-based monitoring (RBM) plan.

4.4 Medical Monitor

The trial's medical monitor will review all reported adverse events and determine if any require expedited reporting. The medical monitor is:

Roy W. Beck, M.D., Ph.D.
Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Phone: (813) 975-8690
Fax: 888-795-2859
Email: rbeck@jaeb.org

4.5 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled adverse event data at periodic intervals. The DSMB will perform interim safety reviews during the course of the study at the following times, with details in standalone DSMB procedural documentation:

- Review of approximately 100 nights of system data collected during the Algorithm Assessment Phase in the first 10 subjects 11 to <15 years of age before proceeding with further system use and additional subject enrollment
- Review of first approximately 200 randomized nights of data from the randomized clinical trial phase, during which subjects already using the system at home will continue its use, but all other subjects will delay initiation of home system use until after the DSMB review

Data from each of these safety reviews will be submitted in parallel to FDA. Details regarding the safety review procedures are located in separate documentation.

4.6 Potential Risks and Side Effects

The primary objective of the initial study is the reduction of hypoglycemia, with a secondary outcome of reduction of hyperglycemia. Loss of confidentiality is a potential risk, and is protected by the safeguards discussed above. Hypoglycemia, hyperglycemia and ketone formation are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. When wearing sensors and insulin infusion sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site. There is always a risk for a small piece of a sensor remaining under the skin or a sensor or infusion set breaking off under the skin.

4.6.1 Hyperglycemia

Hyperglycemia and ketonemia could occur with prolonged pump suspension. Although the system will restart insulin delivery after a maximum of 120 minutes of pump suspension, it is possible for a subject to have multiple episodes overnight. Basal insulin may initially be suspended for up to 180 minutes total, and then if further automated dosing occurs, up to 120 additional minutes for a maximum cumulative total of 300 minutes. This could result in hyperglycemia or even ketonemia. A sensor which was functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery. This has not been a problem in prior inpatient and in-home studies of the system, where there has been no significant clinical ketonemia following undesirable pump suspensions (5). Subjects will be asked to check blood ketones with the study ketone meter if the subject has a fingerstick BG result ≥300 mg/dL (16.7 mmol/L) for over one hour

or ≥400 mg/dL (22.2 mmol/L) at any point. Individuals with type 1 diabetes are trained to handle hyperglycemia and ketone formation and have the knowledge and equipment to detect both. They are trained in insulin administration by syringe when ketones occur. Phone support will be available 24/7 if problems develop.

4.6.2 Hypoglycemia

Hypoglycemia could occur if the system delivers an inappropriate amount of insulin given the subject's underlying glycemic state. This could occur if, for example, a sensor is functioning poorly and significantly over-reading glucose values. Over-delivery may be minimized if the sensor's trend data remains accurate despite inaccurate level values, or by the safety constraints described in section 3.10. However, there is a risk of having a low blood sugar (hypoglycemia) that may exceed the risk present as part of normal daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at with normal daily living, there is the possibility of fainting or seizures (convulsions) and that for a few days you may not be as aware of symptoms of low blood sugar. Even if severe low blood sugar does occur, it almost always goes away quickly with treatment to raise the blood sugar.

4.6.3 Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the CSII. If these reactions occur, different adhesives or "under taping" (such as with IV 3000, Tegaderm, etc.) will be tried and sites will be rotated frequently.

Whenever the skin is broken there is the possibility of an infection. The CGM and pump infusion sites are inserted under the skin. It is possible that any part of what is inserted under the skin may cause an infection. These occur very infrequently, but if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM, pump, and the home glucose meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers having such detailed information about their daily diabetes habits.

4.6.4 Study Stopping Criteria

4.6.4.1 Criteria for Individual Subjects

Rules for stopping the study for an individual subject are as follows:
System or controller malfunction that imposes on the safety of the subject; such a malfunction will also result in suspension of the study for all subjects, as described below

1. Severe hypoglycemia or hyperglycemia as defined in section 4.1.1
2. Frequent occurrence of nights with CGM sensor glucose values <60 mg/dL continuously for ≥1 hour:
    a. 2 or more nights out of the first 7 intervention nights of the randomized phase
    b. 3 or more nights out of the first 14 intervention nights of the randomized phase
    c. 4 total intervention nights at any point during randomized phase
    d. 2 or more nights during the extension phase, if subject is participating
3. Developing >1.0 mmol/L ketones on 3 or more nights due to prolonged pump shut off
4. The subject or parent requests the study be stopped

5. Subject pregnancy

4.6.4.2 Criteria for Suspending/Stopping Overall Study

Stopping the Study At Any Time

More than two instances of severe hypoglycemia or hyperglycemia as defined in section 4.1.1 will result in stopping additional enrollment of subjects and suspension of the study for enrolled subjects until reviewed by the DSMB. The study may resume if the DSMB determines that it is safe to continue.

In case of a system malfunction imposing on the safety of a subject, the overall study will be suspended for all subjects while the problem is diagnosed and the DSMB reviews the event. The study may resume with DSMB approval if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

Stopping the Study for System Performance Reasons Unrelated to Subject Safety

If the system is unable to deliver at least 75% of the correction bolus insulin recommended by the control algorithm during the pooled nights comprising one of the DSMB review periods described in section 4.5, the overall study will be suspended for all subjects while the problem is diagnosed. The study may resume with DSMB approval if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

4.6.5 Risk Assessment

Based on the fact that (1) adults and adolescents with diabetes experience mild hyperglycemia and hypoglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic temporary suspension of insulin delivery overnight that may cause an increase in overnight or morning blood glucose, and periodic insulin dosing that may increase the likelihood of hypoglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the overall duration of pump suspension to no more than three hours in a single night and implement a conservative insulin dosing strategy with constraints to prevent excessive dosing, and (4) rapid reversal of hyperglycemia and hypoglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes as described in section 5.1.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Benefits

The purpose of this research is to reduce hypoglycemia and hopefully, severe hypoglycemic reactions while also reducing hyperglycemia exposure. Hypoglycemia is the number one fear of families with a member having type 1 diabetes and often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about hypoglycemia and how to prevent hypoglycemia while also controlling hyperglycemia. As brain damage and death can both be side effects of hypoglycemia, this is obviously an important area of research. This research will also provide an important foundation for development of a fully closed loop system.

5.2 Subject Compensation

Subjects will be compensated $50 for each outpatient visit and $5 for each night of successful use of the closed-loop control system up to a maximum of 42 nights.

5.3 Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. Withdrawal of a subject will be considered for the reasons listed in section 4.6.4 as well as the following reasons: 1) Any failure to achieve or maintain adequate communication between the study laptop and the pump and sensor for more than 2 hours during 50% of the nights; 2) failure to initialize the system on at least 50% of nights. For subjects who withdraw, their data will be used up until the time of withdrawal.

5.4 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the Coordinating Center, the Jaeb Center for Health Research in Tampa, FL. Information also may be provided to laboratories involved in the study and with Medtronic MiniMed, Inc. Subject contact information may be provided to the Jaeb Center if it is necessary to contact the subject to resolve any problems with the study device system.

CHAPTER 6: STATISTICAL CONSIDERATIONS

The approach to statistical analyses and sample size are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

6.1 Primary Efficacy Analysis

The null hypothesis is that there will be no difference in the percent time in range (defined as sensor glucose 70-180 mg/dL) overnight comparing the two treatments nights: predictive low glucose suspend plus hyper minimization (PLGS + HM) or PLGS-only.

The primary analysis in this randomized trial will be a comparison of percent time in range overnight between the two treatments arms. A single percentage calculated for each subject by pooling all CGM readings from the PLSG+HM nights will be compared with the corresponding percentage obtained by pooling all of the data from PLGS-only nights for the same subject. All CGM readings regardless of the amount of data will be weighted equally in the pooled percentage regardless of how they distribute across nights.

Mean (SD) or median (IQR) for % time in range will be tabulated separately by treatments. A repeated measures regression model with an unstructured covariance structure will be fit for percent time in range to compare the two treatments at the subject level. The model will adjust for the mean bedtime CGM glucose as a covariate. If residual values from the regression model have a skewed distribution then a log(x+0.005) transformation, an alternate transformation, or a nonparametric analysis based on ranks will be performed. All p-values will be two-sided.

6.2 Secondary Efficacy Analyses

- Mean overnight sensor glucose
- Glucose standard deviation and coefficient of variation
- Percent of sensor measurements below 50, 60, and 70 mg/dl
- Area under the curve 70 mg/dl and low blood glucose index
- Percent of sensor measurements above 180, 250, and 300 mg/dl
- Area under the curve 180 mg/dl and high blood glucose index
- Percent of sensor measurements between 70 and 140 mg/dl
- Percentage of nights with events of sensor glucose below 50, 60, and 70 mg/dl continuously for more than 0, 10, 25, 30, 60, and 120 minutes; and cumulatively for more than 30, 60, 120, and 180 minutes
- Percentage of nights with events of sensor glucose above 180, 250, and 300 mg/dl continuously for more than 0, 30, 60, and 120 minutes; and cumulatively for more than 60, 120, and 180 minutes
- Mean morning blood glucose (subject-level data) and percent of morning with blood glucose below 50, 60, 70, between 70 and 180, and above 180, 250, and 300 mg/dl (night-level data)
- Amount of total (manual, automatic, combined) and insulin boluses

Analyses for the continuous secondary outcomes will parallel that described above for the primary outcome.

For binary outcomes at the night level (e.g., percentage of nights with at least one CGM value <60 mg/dl), a repeated measures mixed effects logistic regression to account for the correlation from the same subject (by using a spatial power structure for the nights order) and adjusting for the baseline

(bedtime) blood glucose will be fit to compare intervention versus control nights. Only nights with at least 4 hours of CGM values will be included in these analyses. All p-values will be two-sided.

An exploratory analysis for the primary outcome will be done by subject's Tanner Stage (I, II, III, or IV).

6.3 Safety Analyses

Safety principally will be evaluated by comparing the PLGS+HM versus PLGS-only nights:

- Episodes of DKA and episodes of severe hypoglycemia at any time. Each event will be described based on when the previous/current randomization night and when the previous pump shut off or automatic bolus occurred.
- All other reported adverse events.

6.4 Additional Tabulations

Additional metrics to be tabulated by treatment groups without a formal statistical test:

- Mean bedtime blood glucose (subject-level data)
- Mean sensor glucose for up to 12 hours post system deactivation.
- Percentage of sensor glucose values below 50, 60, and 70 mg/dl for up to 12 hours after system deactivation
- Percentage of sensor glucose values between 70 and 180 mg/dl for up to 12 hours after system deactivation
- Percentage of sensor glucose values above 180, 250, and 300 mg/dl for up to 12 hours after system deactivation
- Change in HbA1c from clinical trial baseline to study completion visit
- Any changes in pump settings from the baseline visit at the 21 and 42 day follow up visits.

Additional tabulations and figures will include:

- Demographics and clinical characteristics at baseline
- Flowchart showing any dropouts prior and post randomization along with number of eligible subjects and nights by treatment arm.
- Number of subjects who did not complete the study and reasons for discontinuation.
- Number of intervention and control nights per subject.
- Participants listing with summary outcomes (age, gender, race, T1D duration, A1c at enrollment and final visit, # control and intervention nights, PSO total duration, total automated insulin, pooled time below 70, in range, and above 180 mg/dl during the control and intervention nights.
- Distribution of number of nights required to achieve 42 study nights.
- Among intervention nights:
    a. Percentage of nights with PSO, automated insulin, both, or neither.
    b. Among nights with PSO, distribution of total duration overall and by time of night.
    c. Among nights with automated insulin, distribution of total insulin including % ≥4 units overall and by time of night.
    d. Among nights with sensor nadir <60 mg/dl, percent of nights with automated insulin boluses and total insulin prior to nadir.
- Among control nights:
    a. Percent of nights with PSO, and those that would have had an automated insulin, both, or neither.
    b. Among nights with PSO, distribution of total duration overall and by time of night.
    c. Hyperglycemia minimizer (HM) operating characteristics:

i. Sensitivity defined by percentage of nights with a CGM reading ≥140 mg/dl that would have triggered an automated insulin delivery within 2 hours prior to the first such reading.
ii. Distribution of the timing of the automated delivery that would have occurred prior to the first CGM reading ≥140 mg/dl.
iii. False positive rate defined as percent of nights with automated delivery that would have occurred with no CGM reading ≥140 mg/dl within 2 hours following the first such delivery.

- Scatterplot of sensor glucose values vs. rate of drop at the time of 1st shutoff by treatment group and overall.
- Scatterplot of sensor glucose values vs. rate of increase at the time of 1st automated bolus for intervention nights.
- Distribution of session duration by intervention and control nights.
- All instances of blood ketone ≥0.6mmol/l during or immediately following a night, by treatment group.
- Percent of available CGM data during sessions by treatment group and overall.
- Percent time insulin dosing (intervention nights) and suspension components (control or intervention nights)were inactive because no CGM reading was available in the prior 20 minutes
- Percent of automated insulin boluses requested but not delivered (no bolus within the subsequent 5-minute period) for intervention nights.
- Percent of nights in each treatment group with at least one instance of each of the different automated monitoring alert types (Low CGM, etc.)
- Sensor performance metrics during sessions (bias, RAD, ISO) by different reference (meter) glucose groups (cut points 70, 120, 180), treatment group, and overall.
- Modal overnight CGM plot with median line and IQR bands for both control nights and intervention nights by hour of day/session.
- Modal overnight total insulin plot (combined basal and bolus insulin) with median line and IQR bands for both control nights and intervention nights by hour of day/session.

6.5 Considerations in Analyses

The primary analysis will follow the intention to treat principle with each night included in the treatment group assigned by randomization. All randomized nights with any sensor data available and regardless of the amount of data will be included in the primary efficacy and safety analysis, while only randomized nights with at least 4 hours of sensor glucose data will be included in the night-level efficacy analyses.

6.6 Sample Size

Data from a previous pump shut-off study (6) which parallels the design of the currently planned study were used to estimate sample size. This study also had multiple nights per subject and with randomization of treatment on a night level within subject. The main differences in eligibility criteria between the previous study and the planned study are:

- HbA1c <8.5% for previous study vs HbA1c <10.0% for current study
- Age 3-<15 for previous study vs age 6-<15 for current study

Data were limited to subjects 6 to <15 years of age and to intervention nights from the previous study which utilized the same PLGS treatment as the control treatment in the planned study (pump shut-off without hyperglycemia minimization). Data were also limited to nights with at least 4 hours of sensor data. This resulted in a dataset of 1620 nights from 76 subjects.

A repeated measures regression model was fit with the CGM measured % time in range as the dependent variable. The model accounted for correlated data from multiple nights from the same subject. Extrapolating the resulting variance and correlation estimates to a scenario of 42 nights per subject (half assigned to each treatment) resulted in an equivalent SD of 9.0% at the subject level.

The following sample sizes were estimated assuming a normal distribution for the nighttime % in range, a type I error = 5%, and a 2-sided test with null hypothesis stating that the difference is zero. Sample sizes are given for the above point estimate of SD=9.0% and for a smaller SD (8.0%) and a larger SD (10.0%).

Required sample size[a] for different combinations of SD, power, and treatment effect. Shaded row corresponds to the estimated SD = 9.0%.

SD	Power	Treatment Effect (% CGM values in range)		
		5%	**7.5%**	**10%**
8.0%	**80%**	N=23	N=12	N=8
	85%	N=25	N=13	N=8
	90%	N=29	N=15	N=9
9.0%	**80%**	N=28	N=14	N=9
	85%	N=32	N=15	N=10
	90%	N=37	N=18	N=11
10.0%	**80%**	N=34	N=16	N=10
	85%	N=38	N=18	N=12
	90%	N=44	N=21	N=13

[a] – Does not account for dropout or noncompliance. Would typically add 10% - 15% to these numbers.

Currently, N=30 subjects are planned to be enrolled. Assuming a SD of 9.0%, this would give 90% power to detect a difference as small as 5.5%.

6.7 Extension Phase Outcome Measures

Only a subset of subjects are expected to participate in the 4-week extension phase. The settings of the system may be modified at the end of week 1, 2 and 3 as defined in protocol for each subject.

The analyses for the extension phase will be mainly exploratory. Mean (SD) or median (IQR) for % time in range of 70-180 mg/dl (primary outcome) will be tabulated for weeks 1, 2, 3, and 4 and boxplots will be generated.

The primary analysis will be a comparison at subject level between percentages time in range 70-180 mg/dl from week 1 to week 4. A single percentage calculated for each subject by pooling all CGM readings from the first week nights will be compared with the corresponding percentage obtained by pooling all of the data from the fourth week nights for the same subject. All CGM readings regardless of the amount of data will be weighted equally in the pooled percentage regardless of how they distribute across nights. At least 2 nights per week will be required in order to be included in analysis.

Mean (SD) or median (IQR) for % time in range of 70-180 mg/dl will be tabulated separately by the two weeks. A repeated measures regression model with an unstructured covariance structure will be

fit for % time in range to compare the two weeks at the subject level. The model will adjust for the mean bedtime BG glucose across all sessions during the week as a covariate. If residual values from the regression model have a skewed distribution then a log(x+0.005) transformation, an alternate transformation, or a nonparametric analysis based on ranks will be performed. All p-values will be two-sided.

Although this phase of the study is exploratory, some approximate power calculations were performed. It is possible that the SD for time in range may be smaller during the extension phase if the controller successfully improves time in range during the randomized phase. It is not clear by how much the SD may be affected. It is also not clear how many of the N=30 subjects will consent to participate in the extension phase. The following table gives estimates for the statistical power under different scenarios for the number of participants N, the true treatment effect, and SD for CGM time in range.

Estimated Statistical Power for different combinations of number of participants N, SD, and treatment effect.

SD	N	Treatment Effect (% CGM values in range)		
		5%	**7.5%**	**10%**
7.0%	**15**	73%	97%	>99%
	20	85%	99%	>99%
	25	92%	>99%	>99%
8.0%	**15**	61%	92%	99%
	20	75%	97%	>99%
	25	85%	99%	>99%
9.0%	**15**	51%	85%	97%
	20	65%	94%	99%
	25	76%	97%	>99%

In addition to the above-mentioned model, a repeated measures model with unstructured covariance will be fit for % time in range to see if there is any trend over all 4 weeks, while adjusting for the mean bedtime BG during all sessions of the week as a covariate. At least 2 nights per week will be required in order to include the week in this analysis.

Additional analyses that parallel the above two analyses (week 1 vs 4 and over all 4 weeks) may include:

- Mean overnight sensor glucose
- Glucose standard deviation and coefficient of variation
- Percent of sensor measurements below 50, 60, and 70 mg/dl
- Area under the curve 70 mg/dl and low blood glucose index
- Percent of sensor measurements above 180, 250, and 300 mg/dl
- Area under the curve 180 mg/dl and high blood glucose index
- Percent of sensor measurements between 70 and 140 mg/dl
- Mean morning blood glucose
- Amount of total (manual, automatic, combined) and insulin boluses

Safety will be evaluated by tabulating any episodes of blood ketone ≥0.6mmol/l, DKA, SH, or any other reported AE by each one of the fourth weeks along with any changes in the system settings for that week/subject.

CHAPTER 7: DATA COLLECTION AND MONITORING

7.1 Case Report Forms and Device Data

The main study data are collected through a combination of electronic case report forms (CRFs) and electronic device datafiles obtained from the study software and individual hardware components (CGM/pump and blood glucose and blood ketone meters). These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

7.2 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

APPENDIX: BACKGROUND RESEARCH

1.1 Hypoglycemia in Type 1 Diabetes

The Diabetes Control and Complications Trial (DCCT) convincingly demonstrated that glucose control in the close-to-normal range ("tight" glycemic control), through intensive insulin management and frequent blood glucose monitoring, reduced the likelihood of eye, kidney, nerve and cardiovascular complications of T1D. (7; 8) Unfortunately, the DCCT study also showed that intensive treatment increased the incidence of severe hypoglycemia by three times compared with the standard treatment group, with the increased risk being even greater in adolescents than in adults. (7; 9)

Nocturnal hypoglycemia, often asymptomatic, is common even with the use of insulin pumps or long-acting insulins such as glargine. In a study conducted by the Diabetes Research in Children Network (DirecNet), the incidence of nocturnal hypoglycemia (glucose ≤60 mg/dL (3.3 mmol/L) in children with T1D was 48% on nights following afternoon exercise and 28% on nights after no exercise. (10) In another study, adult subjects who did not have a snack became hypoglycemic (<70 mg/dL (3.9 mmol/L)) during 57% of nights with an average duration of hypoglycemia of over 2.5 hours. (11)

With respect to severe hypoglycemic events, in the DCCT more than half of such events occurred during sleep hours. (12) Other studies also have shown a greater incidence of severe nocturnal hypoglycemic events in T1D. Davis et al found 75% of hypoglycemic seizures in children to occur during sleep. (1) Sovik reported that among patients under age 40 years who died over a 10-year period, 6% of the deaths were due to "dead-in-bed" syndrome (13), which in many cases likely was the result of severe nocturnal hypoglycemia. Buckingham et al documented four episodes of seizures occurring during the night in which CGM demonstrated that there were 2 ¼ to 4 hours of hypoglycemia preceding each seizure. (14)

The availability of CGM systems has allowed determination of the incidence of nocturnal hypoglycemia in the home environment. In a randomized trial evaluating daily CGM use over a 6-month period in children and adults, (15) 216 subjects used a CGM device for 25,473 nights. The glucose level was ≤70 mg/dL (3.9 mmol/L) on 25% of nights, ≤60 mg/dL (3.3 mmol/L) on 15% of nights and ≤50 mg/dL (2.8 mmol/L) on 8% of nights (unpublished data). Similar or even higher frequencies of nocturnal biochemical hypoglycemia have been found in other studies. (16-21)

One of the important potential benefits of real-time CGM is the ability of these devices to alarm for hypoglycemia. However, patients often do not awaken when the CGM device alarms as shown in prior studies in which 71% of youth did not respond to hypoglycemic alarms during the night. (3) An example of a CGM tracing of a 17 year old with T1D who had a seizure during the night while wearing a real-time CGM is shown in Figure 1. Note the alarms for 2 ¼ hours before her seizure.

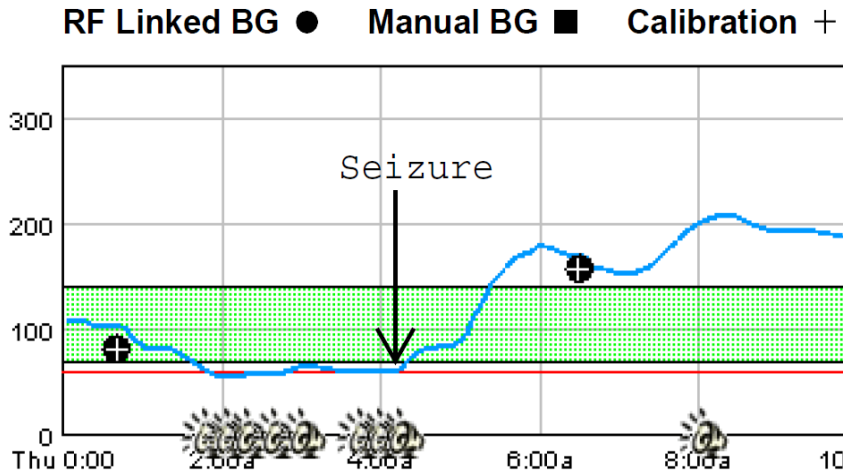


Figure 3: Alarm "bell" along time axis at bottom of graph indicates alarming (vibratory and then audio).The sensor values are in blue. The lowest level reported by the sensor is 40 mg/dL (2.2 mmol/L) (lower limit of blue line).

1.2 Prior Studies with Prototype Systems

1.2.1 Background

Temporarily suspending an insulin infusion is associated with little risk of significant ketosis or acidosis. Previous studies using systems unrelated to the current work (10; 22-24) have demonstrated that turning off an insulin pump for two hours or more does not result in diabetic ketoacidosis (DKA). With 3 hours of continuous pump suspension the mean serum β-hydroxybutyrate level increased from ≈0.4 mM/L at 2 hours to ≈0.6 mM/L after 3 hours of pump suspension in 8 subjects (24), and there was an additional ≈50 mg/dL (2.8 mmol/L) increase in the plasma glucose. In a study by Castillo (25), the mean serum β-hydroxybutyrate level increased from ≈0.3 mM/L at 2 hours to ≈0.5 mM/L after 3 hours of pump suspension in 5 subjects who were hypoglycemic (≈35 mg/dL (1.9 mmol/L)) at the time of pump suspension.

In a study by Attia (26), the mean serum β-hydroxybutyrate level increased from ≈0.35 mM/L at 2 hours to ≈ 0.45 mM/L after 3 hours of pump suspension in 8 subjects. Finally, in a study by Krzentowski (27) the mean serum β-hydroxybutyrate level increased from ≈0.35 mM/L at 2 hours to ≈0.5 mM/L after 3 hours of pump suspension in 8 subjects. The serum ketone values and glucose values are given as approximate values, since they were read off published graphs in these articles. Since the system will initially not be allowed to suspend insulin delivery for more than 3 hours in a given night, and since there will be a ½ hour period of insulin delivery if the pump has been suspended for more than 2 hours within a 2 ½ hours, significant problems with ketosis >1 mM/L or ketoacidosis are not foreseen. In these studies the serum glucose generally increased 50-90 mg/dL (2.8-5.0 mmol/L) with 3 hours of pump suspension, and this should not impose a significant risk of hyperglycemia.

1.2.2 CGM Studies

The investigators have extensive experience with research studies involving CGM and hypoglycemia. The DirecNet studies have provided important information about the frequency of nocturnal hypoglycemia. In an inpatient study with a crossover design of 50 children with T1D, hypoglycemia (glucose ≤60 mg/dL (3.3 mmol/L)) occurred during 48% of nights following afternoon exercise and 28% of nights after no exercise. (10) In an outpatient study of 57 children with T1D (30 using an insulin infusion pump (28) and 27 using multiple daily insulin injections

(MDI) therapy (29)), 4.4% of glucose values were ≤70 mg/dL (3.9 mmol/L), 2.6% ≤60 mg/dL (3.3 mmol/L), and 1.4% were ≤50 mg/dL (2.8 mmol/L).

In the JDRF randomized trial evaluating daily CGM use over a 6-month period in children and adults, Stanford and Colorado were two of the 10 clinical centers and the Jaeb Center was the Coordinating Center. (15) Table 1 below shows several different nocturnal hypoglycemia outcomes for the 216 subjects who used a CGM device for 25,473 nights. Note that this amount of nocturnal hypoglycemia occurred despite the use of hypoglycemic alarms on the CGM devices.

Table 1: Nocturnal hypoglycemia documented by CGM readings during 25,473 nights in the JDRF randomized clinical trial (unpublished data)

	% Of Nights Below Threshold		
	With a glucose reading	20 minutes consecutively	60 minutes consecutively
≤70 (3.9)	25%	18%	9.7%
≤60 (3.3)	15%	9.6%	4.6%
≤50 (2.8)	7.6%	4.5%	2.0%

In this trial, the incidence of hypoglycemia was similar in adults and children 8 to 14 years old and was slightly higher in 15 to 24 year olds. The frequency of hypoglycemic nights was higher in all age groups when HbA1c was <7.0% compared with ≥7.0%.

The DirecNet Navigator Study and the JDRF CGM RCT both demonstrated that daily use of real-time CGM with the current generation of sensors is feasible. In the DirecNet studies of children, the mean days per week wearing the CGM device were 5.7 days for CSII subjects (28) and 5.0 days for MDI subjects. (29) In the JDRF CGM RCT, use was high in both adults and children over the six months of the trial, though higher in adults averaging 6.3 days per week in adults and 5.2 days per week in children (unpublished data).

1.2.3 Pilot Study to Test Algorithms to Predict Daytime Hypoglycemia and to Study the Safety of Stopping Insulin Infusion for 90 minutes to Prevent Hypoglycemia

At Stanford and Colorado, 22 subjects with T1D (mean age 20 years, range 6-38) were admitted to the Stanford or Univ. of CO CTRC on two occasions during the day. (30) On the first admission the basal insulin infusion was gradually increased over several hours until the venous blood glucose was <60 mg/dL (3.3 mmol/L). On the second admission, the increase in basal insulin infusion rates used in the first visit was duplicated and either a linear prediction (LP) or a statistical prediction (SP) algorithm (31) was used to predict hypoglycemia.

When the prediction alarm occurred, the insulin pump was turned off manually for 90 minutes to determine whether this would prevent hypoglycemia. The subjects were followed for an additional two hours to determine if there was rebound hyperglycemia or ketonemia following the 90 minute pump suspension.

Hypoglycemia was avoided in 60-80% of pump suspension events, depending on the active algorithm and its configuration. Following pump suspension there was no rebound hyperglycemia; the highest glucose during the two hours after the pump was restarted was 139 mg/dL (7.7 mmol/L) and no subjects developed clinically significant ketonemia (three subjects developed transient

chemical ketonemia of 0.7 to 1.0 mmol/L) during or following pump suspension. These studies indicated that discontinuing basal insulin was safe and did not result in rebound hyperglycemia.

1.2.4 Assessment of a Protocol to Induce Nocturnal Hypoglycemia

In order to assess the effectiveness of the hypoglycemic prediction and pump shut off algorithms in preventing nocturnal hypoglycemia, a systematic method for creating nocturnal hypoglycemia was developed: the basal infusion rate of the subjects was systematically increased with the goal of inducing hypoglycemia (blood glucose <60 mg/dL (3.3 mmol/L)) by 5 AM on at least 80% of nights. Changes in the pump basal insulin infusion rate were based on a subject's current glucose level and rate-of-change in glucose. The basal rate was not increased more frequently than every 90 minutes. This allowed 60 minutes to determine the full effect of the previous change in basal rate, and then the last 30 minutes (from 60 to 90 minutes) represented the new glucose rate of change. The insulin infusion rate was adjusted using the guidelines in Table 2; however if the glucose level was <70 mg/dL (3.9 mmol/L), then the maximum increase in the glucose infusion rate was limited to 15%.

Table 2: Guidelines for increasing basal insulin infusion rate overnight to achieve hypoglycemia

Time to Predicted Hypoglycemia	Additional % Change to current basal insulin infusion
5 AM to 6 AM	0
6 AM to 7 AM	10%
7AM to 8 AM	15%
8 AM to 9AM	20%
> 9 AM	25%

Basal rate changes were based on a percent increase above a subject's current basal rate at the time the increase was needed. This means that if a subject's programmed basal rate increased (per home basal pattern) at 3 AM, this increase would be included, since the changes were based on a percentage (not absolute value) of the infusion rate.

Fifteen subjects were studied in the Univ. of CO and the Stanford CTRCs using this protocol (32), and all but one became hypoglycemic (blood glucose ≤60 mg/dL (3.3 mmol/L)) (Table 3). The one subject who did not become hypoglycemic was in poor diabetes control (HbA1c of >14%) at the time of admission and was insulin resistant.

Table 3: Results from applying consistent guidelines for increasing insulin dosage to create nocturnal hypoglycemia

Age (years)	DM Duration (years)	BG at Study Start (mg/dL)	Hours to Hypoglycemia	Final % Increase in Basal Insulin	Lowest Laboratory Serum Glucose mg/dL (mmol/L)	Lowest Navigator Glucose mg/dL (mmol/L)
27	17	159	4	150%	57 (3.2)	59 (3.3)

14	12	84	6.5	175%	51 (2.8)	70 (3.9)
22	21	103	1.25	150%	41 (2.3)	68 (3.8)
30	20	172	6.25	175%	43 (2.4)	49 (2.7)
25	10	105	6.5	160%	42 (2.3)	42 (2.3)
12	7	77	7.5	175%	50 (2.8)	64 (3.5)
20	9	151	2.25	100%	44 (2.4)	82 (4.5)
25	8	215	no hypo	200%	78 (4.3)	47 (2.6)
18	10	108	7.75	170%	56 (3.1)	59 (3.3)
18	17	68	1.25	100%	45 (2.5)	66 (3.7)
12	11	182	1.5	100%	41 (2.3)	67 (3.7)
38	22	168	8.75	240%	59 (3.3)	62 (3.4)
18	4	119	6.75	175%	54 (3.0)	69 (3.8)
12	3	87	0.25	100%	46 (2.5)	64 (3.5)
18	8	128	6.5	175%	60* (3.3)	58 (3.2)

**subject was symptomatic with diaphoresis and shakiness with a glucose <67 mg/dL (3.7 mmol/L) for 3 hours and requested the study be stopped when his glucose was 60 mg/dL (3.3 mmol/L).*

1.2.5 G080103 Nocturnal Studies to Assess 5 Algorithms to Predict Hypoglycemia with a Pump Shut Off for 90 minutes

In the next set of experiments, induced hypoglycemia at night—when counterregulatory hormone production is lower than during the day—was studied rather than daytime hypoglycemia. (33) Based on previous daytime studies, it was clear that a single algorithm alarm was not sufficiently effective in preventing hypoglycemia.

1.2.5.1 Theoretical Background

The prediction of hypoglycemia based on continuous subcutaneous glucose monitoring (CGM) technology is complicated by the time-lag between the blood glucose and subcutaneous sensor signal, sensor noise and sensor calibration bias. The advantages of Kalman filtering techniques, based on optimal estimation theory, in separating random sensor noise from deterministic blood glucose changes to best predict hypoglycemic events has been shown. (34; 35) The effect of tuning parameters (prediction horizon and hypoglycemic threshold) on the sensitivity and specificity of the alarm predictions has also been shown. (34) At Stanford a statistical based algorithm which uses multiple statistical linear predictions with regression windows between 5 and 75 minutes and prediction horizons of 0 to 20 minutes was developed. (31) The regressions provide standard deviations, which are mapped to predictive error distributions using their averaged statistical correlation. These error distributions give confidence levels that the CGM reading will drop below a hypoglycemic threshold. In order to improve hypoglycemia prediction multiple hypoglycemia prediction algorithms were combined into a voting strategy. (36) The current voting scheme utilizes five algorithms. Briefly, the individual alarm algorithms are:

1) Modified Linear Prediction Alarm (LP) – This alarm uses a 15 minute linear extrapolation and uncertainty threshold based on the standard deviation of the glucose measurements in the previous 15 minutes.
2) Kalman Filtering – A Kalman Filter is used to obtain an estimate of glucose and its rate of change, which are then used to make predictions of future glucose levels. The filter is tuned to trade off between the probabilities that a measured glucose change is real versus the result of signal noise. (37)

3) Adaptive Hybrid Infinite Impulse Response Filter (HIIR) – An Infinite Impulse Response Filter updates parameters adaptively using the CGM signal. The HIIR filter considers a bandwidth of past data to update the filter parameters.
4) Statistical Prediction (SP) – Multiple empirical, statistical models are used to estimate future glucose values and their error bounds. From these a probability of hypoglycemia is generated and thresholded to produce an alarm. (31)
5) Numerical Logical Algorithm (NLA) – Feeds a three point calculated rate of change and the current value into logical expressions to detect impending hypoglycemia. NLA provides insensitivity to sensor signal dropouts and easy tuning.

The five algorithms can be "tuned" to: 1) their hypoglycemic threshold (the predicted sensor glucose to trigger an alarm: with a range of 70-90 mg/dL (3.9-5.0 mmol/L)); 2) their prediction horizon (the length of time the algorithm is looking into the future to predict hypoglycemia: with a range of 35–55 minutes into the future); and 3) how many of the algorithms need to alarm (one to five out of five) before the pump is shut off (a voting system).

1.2.5.2 Initial Studies Requiring Three Votes

Five hypoglycemia prediction algorithms and the voting scheme were submitted to the FDA and an investigational device exemption (IDE) received to begin studies in July of 2008. Cessation of insulin delivery from the pump when three of the five algorithms were activated as a result of decreasing Navigator CGM glucose values was initially studied. Ten subjects completed overnight studies using the three vote system. (32)

The goal was for the pump suspensions to prevent the glucose level from decreasing to below 60 mg/dL (3.3 mmol/L) on 80% of nights; however only 60% of nights were considered successful (Table 6). It should be noted that multiple pump suspensions in a single study night were permitted if the algorithms continued to predict hypoglycemia, and on a per-event basis were successful in avoiding hypoglycemia 71% of the time.

In order to determine if some algorithms were much more successful than others, data was analyzed to determine which algorithms were either first, second or third in predicting hypoglycemia (Table 4).

Table 4: Distribution of Algorithms which were the first, second or third to predict hypoglycemia

Alarm	% of First Alarms	% of Second Alarms	% of Third Alarms
Statistical Prediction	60	13	13
Numerical Logical	33	20	27
HIIR	7	20	27
Kalman	0	33	33
Linear Prediction	0	7	0

The linear prediction algorithm was the least likely to predict hypoglycemia; otherwise all of the algorithms played a significant role in contributing to the vote.

The time between the point at which two algorithms predicted hypoglycemia and three algorithms predicted hypoglycemia was assessed (Table 5).

Table 5: Time between requiring a vote of 1, 2, or 3 algorithms to trigger a pump shut off

	Mean ± SD	Range
Minutes between 1st and 2nd Algorithms	16 ± 18	0 – 68
Minutes between 2nd and 3rd Algorithms	12 ± 15	0 – 52

1.2.5.3 Subsequent Studies Requiring Only Two Votes

Since the time delay between the second and third algorithm was often significant and could have contributed to a reduced rate of hypoglycemia avoidance, the decision was made to study the effect of requiring only two algorithms to trigger cessation of insulin delivery. A total of 22 subjects were studied using this voting scheme, including 5 subjects previously studied with three alarms and 17 new subjects. (32) Two of these subjects were studied on two occasions, resulting in a total of 24 study nights with the two-alarm voting system. Results are summarized in Table 6.

Although a 75% success rate on a per-night basis did not quite meet the study goal of 80%, an 84% success rate was achieved when hypoglycemia avoidance effectiveness was assessed on a per-suspension basis.

Table 6: Results of the three alarm and two alarm voting systems

No. algorithms needed to trigger pump suspension	No. of subjects	No. of study nights	% of nights without hypoglycemia	No. of pump suspension events*	% of pump suspension events without hypoglycemia
3 of 5	10	10	60%	17	71%
2 of 5	22	24	75%	37	84%

* An event is an episode of predicted hypoglycemia resulting in a pump suspension.

1.2.5.4 Post-Suspension Pump Restart Strategies and Rebound Hyperglycemia Risk

In parallel with the assessment of different algorithm settings for pump suspension, different approaches for restarting the insulin pump following a suspension event were explored. The initial approach of suspending the pump for 90 minutes carried forward from prior daytime investigations confirming that 90-minute suspensions would not cause rebound hyperglycemia.

However, because multiple pump suspension events in a single night were permitted in prior nocturnal studies, an interest developed in limiting the time the pump remained suspended once glucose was past the nadir, was above a minimum threshold level, and showed a strong positive rate of change. Therefore an initial revision of the IDE was submitted to the FDA modifying the protocol to allow earlier resumption of basal insulin delivery under certain conditions. After further assessment of these modified restart rules, another revision was submitted to allow a more aggressive restart while also extending the maximum allowed pump shutoff period from 90 minutes to 120 minutes. Refer to Table 7 for an overview of the different restart rules used during the series of nocturnal studies.

Table 7: Insulin pump restart strategies evaluated during nocturnal studies

Pump	Maximum	Min post-nadir	Min post-nadir BG	No. of	Avg.	Max. peak

Restart Strategy	suspension duration	BG for early restart	ROC for early restart	study nights	peak YSI* mg/dL (mmol/L)	YSI* mg/dL (mmol/L)
1	90 minutes	N/A (no early restarts)	N/A (no early restarts)	15	162 (9.0)	275 (15.3)
2	90 minutes	80 mg/dL (4.4 mmol/L)	+0.5 mg/dL/min (+0.03 mmol/L/min)	11	145 (8.0)	217 (12.0)
3	120 minutes	70 mg/dL (3.9 mmol/L)	+0.4 mg/dL/min (+0.02 mmol/L/min)	7	155 (8.6)	210 (11.7)

* Average and maximumYSI peak values presented here may be somewhat low, because subjects were not all observed for 120+ minutes following the final pump restart of a study night.

There is insufficient data to characterize the safety of any particular suspension/restart strategy in a statistically meaningful way, but there is no evidence that any of the strategies used in prior inpatient studies presented a significant risk of dangerous rebound hyperglycemia for subjects. This result is consistent with the prior work described above.

1.2.6 G100335 Inpatient Feasibility Studies Using Medtronic Hardware

1.2.6.1 Inpatient Feasibility Assessment of Prototype System with Revel/Sof-sensor Components

An initial inpatient feasibility study (G100335, "Feasibility Assessment of Prototype Nocturnal Hypoglycemia Reduction System") was performed with subjects 18-45 years old. The goal of this inpatient study was to assess the performance of a revised hypoglycemic prediction algorithm using the Medtronic Paradigm REAL-Time Revel Insulin Pump and Continuous Glucose Monitoring System prior to launching a follow-up outpatient safety study.

The control algorithm used in these inpatient studies was a simplified version of the controller described above. The Kalman filter component was improved and shown via retrospective data analysis to perform as well by itself as the previously-studied controllers that had incorporated both the Kalman and other algorithm components. Adjustable algorithm parameters were set to the following values during this study, based on retrospective analysis of previous inpatient admissions described above:

- **H**, hypoglycemia prediction horizon for Kalman filter: **70 minutes**
- $\mathbf{g_{off}}$, predictive threshold for hypoglycemia: **80 mg/dl**
- $\mathbf{g_{on}}$, predictive threshold for pump restart after suspension: **100 mg/dl**

A total of 16 subjects were studied in the U.S. As anticipated, the modified algorithm worked successfully with the Medtronic hardware: hypoglycemia, defined as a reference blood glucose reading ≤60 mg/dL, was avoided in 73% of study nights (11 of 15). (38) One of the nights could not be evaluated because the subject's blood glucose remained elevated the entire night.

Table 8: Performance Metrics for 15 Subjects in G100335 Feasibility Assessment of Prototype System with Revel/Sof-sensor

Subject	Hypo occurred?	Closest glucose at	Closest glucose at	Longest suspension	Last glucose	Nadir glucose	Peak glucose

		start of longest suspension (mg/dl)	end of longest suspension (mg/dl)	time (min)	(mg/dl)	(mg/dl)	(mg/dl)
1	No	96	81	107	138	81	286
2	Yes	80	85	60	134	52	256
3	No	143	134	87	145	128	234
4	No	217	226	50	68	68	352
5	No	163[a]	163[a]	41	265	131	265
6	No	95	73	120	105	73	181
7	No	115	79	96	97	69	283
8	No	123	113	120	222	91	222
9	No	107	102	102	92	68	208
10	Yes	100	86	120	114	53	252
11	No	120	96	97	172	83	191
12	No	65	105	60	74	65	158
13	Yes	119	102	96	100	55	151
14	No	99	80	80	127	80	174
15	Yes	82	67	98	197	53	283
Overall (mean)	27%	122[b]	114[b]	87[b]	137[b]	77	233

[a] Same measurement is closest to both start and end of suspension
[b] Mean for nights without hypoglycemia
Reference metrics from 10:00 pm until end of study

1.2.6.2 Inpatient Feasibility Assessments of Prototype System with Veo/Enlite Components

Canada Veo/Enlite Study

A small companion study to the G100335 investigation described above was performed in London, Ontario, Canada with subjects 18-45 years old to assess the functionality of the algorithm when paired with the Medtronic Veo pump and Enlite CGM sensor.

A total of four patients were studied as inpatients during daytime studies to induce hypoglycemia; aside from daytime rather than overnight admissions, the design of the Canadian study was the same as the G100335 study. The adjustable algorithm parameters were set to the same values described above. Study outcome measures—all related to basic system functionality rather than hypoglycemia prevention given the small sample size—were all satisfied:

1. One or more pump suspensions were performed for each subject whose CGM glucose readings dropped to 80 mg/dL (approximately 4.44 mmol/L) or lower during the admission
2. No pump suspension events occurred at times in which, in the investigator's opinion, it was completely unfeasible for CGM glucose readings to drop below 80 mg/dL (approximately 4.44 mmol/L) within 35 minutes

3. Each pump suspension event was followed by a pump restart event within 120 minutes if CGM glucose readings trended upward and rose above 100 mg/dL (approximately 5.55 mmol/L) within that time period
4. At no point did pump suspension and restart events produce a cumulative suspension time or more than 120 minutes in any 150 minute period, or more than 180 minutes over the entire admission
5. No significant system malfunctions were observed relating to software communication with the Veo or algorithm execution

U.S. Veo/Enlite Study

Following the Canada study, an IDE supplement to G100335 was submitted to extend the U.S. study to include 12 additional subjects 18-45 years old. These subjects used the Veo/Enlite hardware rather than the Revel/Sof-sensor hardware to drive the control algorithm during their nocturnal admissions and wore additional passive Enlite and Sof-sensor CGM sensors, but otherwise the study protocol was unchanged. Algorithm parameter values were slightly different than those described above; more conservative values (less aggressive pump suspension) had been shown to be safe and effective during the final portion of the G110055 outpatient study described below, so these values were used in the extended inpatient study:

- **H**, hypoglycemia prediction horizon for Kalman filter: **30 minutes**
- $\mathbf{g_{off}}$, predictive threshold for hypoglycemia: **80 mg/dl**
- $\mathbf{g_{on}}$, predictive threshold for pump restart after suspension: **N/A due to override below**
- $\mathbf{ROC_{over}}$ (new parameter), whether rising CGM can trigger a pump restart even if predicted glucose not yet above restart threshold: **On**
- $\mathbf{ROC_{trump}}$ (new parameter), whether rising CGM parameter "trumps" low threshold (i.e. can trigger a pump restart even if the current glucose is below the low glucose threshold): **On**
- $\mathbf{T_{max}}$ (new parameter), High glucose threshold above which suspension is forbidden: **230 mg/dl**
- $\mathbf{\Delta CGM_{max}}$ (new parameter), maximum CGM delta absolute value above which suspension is forbidden: **40 mg/dl**

A total of 12 subjects were studied in the U.S. As with the Canada study, the system worked successfully with the newer Medtronic hardware, with no unexplained system malfunctions or inappropriate algorithm behavior. Hypoglycemia, defined as a reference blood glucose reading ≤60 mg/dL, was observed more frequently (5/12 admissions, or 42%) than with the previous 16 subjects. This increased incidence of hypoglycemia may have been the result of the less aggressive algorithm parameter settings in conjunction with the artificial context of hypoglycemia induced by increased basal insulin delivery.

1.2.7 G110055 Outpatient Feasibility and Safety Study of Prototype System

An outpatient feasibility and safety study (G110055, "Reduction Of Nocturnal Hypoglycemia By Using Predictive Algorithms And Pump Suspension - An Outpatient Pilot Feasibility and Safety Study") was performed with subjects 18 years old or older prior to the currently proposed investigation (39). The goal of this study was to gain experience in the use of a similar device system in a home setting by 20 subjects over approximately 21 days to obtain feasibility and initial safety data.

A total of 20 subjects were enrolled in the study. Nineteen of 20 successfully provided up to 21 nights of randomized nights of system use ≥4 hours for a combined total of 375 nights of randomized system use.

As an objective of this pilot study was to evaluate and refine the control algorithm, the data were reviewed periodically during the study with the pre-stated goal of determining whether any changes should be made in the control algorithm. After the first 105 nights of the study (algorithm 1), the frequency of pump suspension was higher than expected and mean morning fasting blood glucose was higher following intervention nights compared with control nights. The algorithm was then modified (algorithm 2) to reduce the hypoglycemia prediction horizon from 70 minutes to 50 minutes, to suspend the pump only when the CGM glucose value was $\leq$ 230 mg/dl, not suspend if there was not a drop of $\geq$40 mg/dl in consecutive CGM readings, and to resume insulin delivery at the first rise in sensor glucose following a suspension (see Table 9). After a review of data from 156 nights using algorithm 2, the hypoglycemia prediction horizon was reduced further (algorithm 3) from 50 minutes to 30 minutes.

The study demonstrated that a predictive low glucose suspend system could be safely implemented overnight. There were few instances of morning ketonemia (see Table 10) and no cases of ketoacidosis or the need to change therapy as a result of mild ketosis. Although the study was not designed to statistically evaluate the success of the algorithm in reducing hypoglycemia, the algorithm appeared to be successful in reducing nocturnal hypoglycemia ($\leq$70 mg/dl) by 40% and the number of nights with prolonged hypoglycemia $\leq$60 mg/dl for more than one hour was reduced by 60% with active intervention.

Table 9: G100055 Distribution of Pump Suspension and Duration per Night

	Intervention		
	Algorithm 1 (N=5 Participants)	Algorithm 2[a] (N= 12 Participants)	Algorithm 3[a] (N= 9 Participants)
# Intervention Nights	67	108	77
# Nights with Pump Suspension	52 (78%)	84 (78%)	41 (53%)
# Pump Suspensions Per Night			
Median (Q1, Q3)	2 (1, 3)	1 (1, 3)	1 (0, 2)
Range	[0, 7]	[0, 8]	[0, 8]
0 shutoffs	22%	22%	47%
1 – 2 shutoffs	43%	47%	31%
3 – 4 shutoffs	31%	19%	12%
5 – 8 shutoffs	3%	11%	10%
Mean Glucose at First Shutoff[b]	139 (37)	121 (29)	113 (33)
Shutoff Duration Per Night (minutes)[b]			
Median (Q1, Q3)	85 (45, 128)	70 (35, 108)	55 (25, 105)
Range	[5, 180]	[5, 175]	[5, 185]
5 – 30 min	21%	24%	32%
31 – 60 min	12%	20%	24%
61 – 120 min	37%	39%	22%
121 – 185 min	31%	17%	22%

a- Hypoglycemia prediction horizon shortened from 70 minutes to 50 minutes to 30 minutes; new rule restarts insulin pump with first positive change in sensor glucose following a suspension

b- Restricted to nights with pump suspension

Table 10: G100055 Safety and Efficacy Measures Across Algorithms

	Algorithm 1		Algorithm 2		Algorithm 3	
	Control (N=5 Participants)	Intervention (N=5 Participants)	Control (N=10 Participants)	Intervention (N=12 Participants)	Control (N=8 Participants)	Intervention (N=9 Participants)
# Nights	38	67	48	108	37	77
# CGM measurements per night *median (IQR)*	103 (82, 110)	103 (88, 111)	86 (75, 96)	86 (74, 96)	91 (82, 103)	89 (77, 102)
Mean Bedtime BG *mg/dl*	166 (51)	155 (46)	139 (45)	148 (47)	152 (41)	157 (44)
Mean Overnight Sensor Glucose *mg/dl*	145 (42)	158 (34)	123 (40)	137 (36)	133 (37)	148 (42)
% of nights with CGM values ≤70/≤60 mg/dl[a]						
> 0 min	26%/24%	19%/12%	33%/25%	19%/11%	30%/22%	16%/8%
> 30 min	24%/16%	13%/6%	31%/17%	15%/8%	22%/14%	10%/4%
> 60 min	21%/11%	10%/3%	25%/15%	11%/5%	14%/3%	8%/3%
> 120 min	11%/3%	0%/0%	15%/4%	5%/3%	8%/0%	3%/0%
% of nights with AUC 70/60 mg/dl						
> 0.00	26%/24%	18%/9%	33%/21%	18%/10%	27%/19%	14%/5%
> 2.00	11%/0%	4%/0%	15%/6%	6%/2%	14%/0%	4%/0%
> 10.00	0%/0%	0%/0%	2%/0%	1%/0%	0%/0%	0%/0%
% of CGM values 71-180 mg/dl *median (IQR)*	76% (46%, 99%)	71% (51%, 91%)	91% (68%, 100%)	90% (65%, 100%)	94% (69%, 100%)	89% (50%, 100%)
% of nights with CGM values >180/>250 mg/dl[a]						
> 0 min	63%/29%	78%/24%	29%/6%	56%/15%	49%/8%	60%/21%
> 30 min	55%/18%	72%/18%	23%/6%	46%/8%	35%/5%	52%/14%
> 60 min	47%/16%	64%/9%	21%/4%	38%/6%	32%/3%	40%/12%

> 120 min	34%/8%	54%/3%	17%/2%	27%/2%	22%/3%	32%/4%
> 240 min	24%/3%	19%/3%	10%/0%	16%/1%	14%/0%	23%/0%
% of nights with AUC 180/250 mg/dl						
> 0.00	63%/29%	78%/24%	29%/6%	56%/15%	49%/8%	60%/21%
> 2.00	47%/13%	63%/10%	19%/6%	36%/4%	30%/5%	40%/9%
> 10.00	34%/8%	37%/3%	10%/2%	19%/1%	16%/0%	29%/4%
> 20.00	11%/3%	6%/1%	6%/0%	5%/0%	5%/0%	14%/1%
# Nights with food intake for low treatment	7 (18%)	5 (7%)	9 (19%)	6 (6%)	2 (5%)	4 (5%)
Mean Morning BG *mg/dl*	125 (53)	158 (52)	138 (63)	151 (57)	133 (57)	144 (48)
% of mornings with BG ≤70/ ≤60 mg/dl	11%/8%	4%/1%	4%/0%	4%/1%	11%/5%	3%/1%
% of mornings with BG 71-180 mg/dl	71%	63%	77%	70%	68%	71%
% of mornings with BG >180/>250 mg/dl	18%/3%	33%/3%	19%/8%	26%/6%	22%/3%	26%/1%
# of mornings with blood ketone >0.6 mmol/L[b]	0	0	1 (2%)	3 (3%)	0	1 (1%)
# of mornings with urine ketones ≥15 mg/dl[c]	1 (3%)	0	0	7 (7%)	0	0

a – For each night, the time spent below or above a threshold was recorded and placed into 1 of 5 categories. The table gives the % nights in each category.

b – 4 blood ketone measurements were missing from 1st algorithm group.

c – 10 urine ketone measurements were missing (2 missing from 1st algorithm group, 8 missing from 2nd algorithm group).

1.2.8 G120069 Outpatient Feasibility and Efficacy Study of Prototype System

A larger, randomized, in-home feasibility and efficacy study (G120069, "Reduction Of Nocturnal Hypoglycemia By Using Predictive Algorithms And Pump Suspension - An Outpatient Pilot Feasibility and Efficacy Study") was subsequently conducted with subjects 15-45 years old. The goal of this study was to evaluate the effectiveness and safety of the system studied previously to assess safety only, and to include younger subjects by lowering the minimum age for eligibility from 18 to 15 years old.

The control algorithm used in this efficacy study was identical to "Algorithm 3" from the final stage of the G100055 safety study described above. Night-level randomization ensured that the system was active on half the study nights and inert otherwise. A total of 49 subjects were enrolled across three clinical sites, with 45 subjects participating in the randomized portion of the study. These 45 individuals completed a total of 1,912 nights of system use, 942 being intervention nights and 970 control nights.

Use of the system was again shown to be safe (Table 11), with morning blood glucose levels slightly higher on intervention nights and a similar frequency of levels above 250 mg/dl (6% versus 6%) and similar frequency of morning ketosis (0.1% versus 0.3%). There were no serious adverse events in either arm.

Use of the system was also shown to be effective at reducing nocturnal hypoglycemia (Table 11). Cumulative exposure to hypoglycemia as measured with the AUC was reduced by 81% and episodes of prolonged overnight hypoglycemia (≤60 mg/dl for more than 2 hours) were reduced more than threefold; significant benefits were also seen with other measures of hypoglycemia exposure.

Table 11: G120069 Safety and Efficacy Measures

	Control Arm N=45	Intervention Arm N=45	P-value
# Nights	970	942	
Bedtime Measures			
Bedtime sensor glucose *mg/dl median (IQR)*	144 (109, 192)	143 (110, 189)	
Bedtime blood glucose *mg/dl median (IQR)*	152 (114, 197)	144 (115, 195)	
Overnight Measures Using CGM Sensor			
# measurements per night	96 (84, 110)	96 (85, 107)	
Hypoglycemia Outcomes			
% nights with ≥1 value			
≤50 mg/dl	19%	10%	<0.001
≤60 mg/dl*	**33%**	**21%**	**<0.001**
≤70 mg/dl	45%	32%	<0.001
% nights with ≥2 consecutive values ≤60 mg/dl	31%	19%	<0.001
% nights with ≥5 consecutive values ≤60 mg/dl	25%	14%	<0.001
Participant time below 60 mg/dl per 8 hr[a] *minutes median (IQR)*	23 (11, 45)	7 (3, 12)	<0.001
Participant time below 50 mg/dl per 8 hr[a] *minutes median (IQR)*	10 (4, 25)	2 (0, 4)	<0.001

Participant overnight area under the curve 60 mg/dl per 8 hr[a] *median (IQR)*	215 (88, 482)	40 (18, 96)	<0.001
Participant LBGI *median (IQR)*	2.28 (1.45, 3.52)	0.92 (0.69, 1.63)	<0.001
Hyperglycemia Outcomes			
% nights with ≥1 value			
>180 mg/dl	57%	59%	0.17
>250 mg/dl	20%	20%	0.93
>300 mg/dl	5%	6%	0.37
>400 mg/dl	0	0	–
Participant time above 250 mg/dl per 8 hr[a] *minutes median (IQR)*	12 (5, 19)	10 (4, 19)	0.78
Participant overnight area under the curve 250 mg/dl per 8 hr[a] *median (IQR)*	236 (83, 772)	219 (72, 666)	0.98
Participant HBGI *median (IQR)*	4.17 (2.99, 5.30)	3.99 (2.50, 5.73)	0.95
Overall Control Outcomes			
Overnight Mean Glucose *mg/dl median (IQR)*	125 (98, 163)	132 (110, 163)	<0.001
Percentage of glucose values 71-180 mg/dl *median (IQR)*	75% (46%, 93%)	82% (54%, 99%)	<0.001
Morning Measures			
Morning blood glucose *mg/dl*[b] *median (IQR)*	129 (96, 173)	144 (114, 186)	<0.001
% mornings with blood glucose			
≤60 mg/dl	4%	<1%	<0.001
≤70 mg/dl	9%	2%	<0.001
71-180 mg/dl	70%	70%	0.87
>180 mg/dl	21%	27%	<0.001
>250 mg/dl	6%	6%	0.71
% mornings with blood ketone >1.0 mmol/L[c]	0.3%	0.1%	0.62[d]
% mornings with urine ketones ≥15 mg/dl[e]	2%	3%	0.10

* Bold indicates pre-specified primary outcome

a- For each patient, time below and above a threshold and area under a curve was divided by total time and multiplied by 8 hours

b- 1 morning blood glucose measurement in the control arm was missing

c- 9 blood ketone measurements in the control arm and 10 blood ketone measurements in the intervention arm were missing

d- P-value computed using permutation test because parametric analysis had convergence issue.

e- 12 urine ketone measurements in the control arm and 12 urine ketone measurements in the intervention arm were missing

1.2.9 G130074 Outpatient Efficacy Study in Children

A large, randomized, in-home efficacy study with a study protocol very similar to G120069 was performed with subjects aged 3 to 14 (G130074, "Outpatient Reduction Of Nocturnal Hypoglycemia By Using Predictive Algorithms And Pump Suspension in Children"). The goal of this study was to determine whether the safety and efficacy of the system used in the prior study extended to this younger population.

The control algorithm used in this study was unchanged from the previous study. Night-level randomization again ensured that the system was active on half the study nights and inert otherwise.

A total of 45 subjects were expected to complete the clinical trial phase of the study, with approximately half the subjects in a "pubertal" age range (11 to 14) and half in a "prepubertal" age range (3 to 10). Data analysis is still ongoing at the time of this submission.

1.2.10 G140072 Pump Suspension with Hyperglycemia Minimization Inpatient Feasibility Study

A pilot CRC-based safety and feasibility study was conducted in subjects aged 15 to 45 (G140072, "Pump Suspension with Hyperglycemia Minimization Nocturnal Inpatient Safety and Feasibility Study"). The objective was to gain experience with, and assess the safety of, the modified algorithm to be used in the currently-proposed in-home study. As described in section 1.2 of the main study protocol document above, this algorithm doses insulin to minimize hyperglycemia overnight in addition to suspending the pump if hypoglycemia is projected.

A total of 28 overnight CRC admissions occurred (Table 12), most with an unbolused bedtime snack but some with a manual pump suspension of up to 120 minutes, so that the system's response to predicted and actual hyperglycemia could be assessed. The major safety outcome was avoidance of hypoglycemia caused by excessive automated insulin dosing in response to the challenges. The protocol design permitted adjustments to key parameters of the algorithm in case of persistently poor performance, such that the algorithm settings at the end of the study were expected to be appropriate for in-home use.

After the first three admissions included some overcorrection for hyperglycemia and low blood glucose values in the morning, the insulin dosing component was made less aggressive by raising the hyperglycemia correction target from 125 mg/dL to 150 mg/dL. This new target level resulted in satisfactory correction behavior for the remainder of the study.

Communication between system components was problematic at various points, but modifications prior to the final 10 admissions resulted in a system that typically dosed at least 90% of the insulin recommended by the control algorithm and was judged satisfactory to proceed to in-home testing.

Table 12: PHM1 Study Admission List and Key Results

#	PtID	Age	Ins (U/ kg· day)	Ins (U/ day)	A1c	Challenge Type	Hyper Corr Target (mg /dl)	Low BG (mg/ dl)	End BG (mg/ dl)	Cum Algo Ins (U)	% Ins dosed[1]	Comment
1	PHM1-001-0002	21	0.64	58	9.2	Snack	125	208				
2	PHM1-001-0001	23	0.70	57	7.2	Suspend	125	67				
3	PHM1-001-0003	18	0.80	67	7.5	Snack	125	57				
	***** SYSTEM REENGINEERED TO AVOID OVERDOSE HAZARDS; HYPER CORRECTION TARGET CHANGED FROM 125 mg/dl to 150 mg/dl***											
4	PHM1-002-0001	23	0.59	42	8.7	Snack	150	171				
5	PHM1-002-0002	15	0.79	42	8.5	Snack	150	156				
6	PHM1-002-0002	15	0.79	42	8.5	Suspend	150	99				
7	PHM1-002-0003	17	0.86	74	7.4	Suspend	150	104				
	***** SYSTEM FURTHER REENGINEERED TO AVOID OVERDOSE HAZARDS PER FDA REQUIREMENT***											
8	PHM1-002-0005	37	0.46	32	7.3	Snack	150	71				
9	PHM1-002-0006	25	0.81	49	7.4	Snack	150	117				
10	PHM1-002-0005	37	0.46	32	7.3	Suspend	150	91				
11	PHM1-002-0006	25	0.81	49	7.4	Snack	150	96				
12	PHM1-002-0001	23	0.59	42	8.7	Snack	150	194				
13	PHM1-002-0004	16	0.98	89	8.9	Snack	150	107				
	***** SYSTEM REARCHITECTED TO AVOID UNPLANNED SUSPENSION AND IMPROVE USABILITY; RESTARTED ADMISSIONS NOVEMBER 12***											
14	PHM1-002-0007	16	0.90	60.6	8.0	Snack	150	90	105	0.10	100%	
15	PHM1-002-0009	15	1.03	51.3	9.2	Snack	150	152	268	0.00	N/A	Session aborted due to CGM time issue
16	PHM1-002-0007	16	0.90	60.6	8.0	Snack	150	80	80	1.32	65%	
17	PHM1-002-0008	19	0.54	40.8	7.3	Snack	150	152	161	0.88	81%	
	***** FINAL MODIFICATION TO ADD 4-MINUTE WINDOW TO IMPROVE DOSING ABILITY***											
18	PHM1-002-0009	15	1.03	51.3	9.2	Snack	150	82	88	1.55	100%	
19	PHM1-002-0010	17	0.73	47.8	8.9	Snack	150	80	80	0.75	100%	
20	PHM1-002-0003	17	0.86	74.5	7.4	Snack	150	83	166	0.45	72%	
21	PHM1-002-0011	33	0.44	30.1	6.2	Snack	150	176	206	3.35	76%	
22	PHM1-002-0004	16	0.98	89.5	8.9	Snack	150	132	150	5.65	91%	
23	PHM1-002-0008	19	0.54	40.8	7.3	Snack	150	120	135	1.32	98%	
24	PHM1-002-0012	41	0.37	23.6	6.7	Snack	150	65	102	0.10	100%	
26	PHM1-001-0006	16	0.66	42.0	7.0	Snack	150	86	110	0.08	100%	
27	PHM1-001-0007	18	0.99	65.0	7.8	Snack	150	82	82	5.55	100%	
28	PHM1-001-0008	15	0.87	53.0	7.1	Snack	150	70	97	0.80	100%	

[1] Note: an algorithm-recommended bolus was classified as not dosed if there was no successful dosing event within 5 minutes of the occurrence of an "inability to deliver a bolus due to communications issues" event

1.2.11 G150078 Reduction of Nocturnal Hypoglycemia and Hyperglycemia in the Home Using Predictive Algorithms, Pump Suspension, and Insulin Dosing (PHM2)

A larger, randomized, in-home feasibility and efficacy study was subsequently initiated with subjects 15-45 years old. The goal of this study was to evaluate the effectiveness and safety of the system studied previously in the CRC to assess safety only, and to include younger subjects by lowering the minimum age for eligibility from 18 to 15 years old.

Night-level randomization ensured that the insulin dosing portion of the algorithm was active on half the study nights and inert otherwise so that only predictive pump shutoff was running. A total of 33 subjects were enrolled across three clinical sites, with 30 subjects participating in the randomized portion of the study. These 30 individuals have completed a total of 1,126 nights of system use with at least four hours of CGM data to date, 575 intervention nights and 551 control nights. There have been no adverse events related to the study device to date.

Investigators are blinded to outcomes from the main clinical trial phase until completion of this study. The DSMB for the currently proposed study has reviewed a series of full data packets from this ongoing PHM2 study and have judged it safe and appropriate to proceed with the remainder of the study. We will obtain DSMB and FDA approval to move to the proposed study in children and younger adolescents before initiating the proposed study.

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