Title of Protocol: PRECISION Study: A Prospective, Multicenter Evaluation of Precision, Compression, Accuracy and Updated Algorithm of a Novel Continuous Implanted Glucose Sensor

Protocol Number: CTP-0031

Protocol Version: 04

Effective Date: 29 September 2017

Senseonics, Incorporated

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Confidential Information

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PRECISION Clinical Study Protocol (CTP-0031)

Signed and Dated Electronically

_____ _____

Katherine Tweden, Vice President, Clinical Sciences Date

09/28/2017

_____ _____

David Y. He, Statistical Consultant Date

PROTOCOL SIGNATURE PAGE

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this protocol and all applicable regulatory requirements. Modifications to the clinical investigation are acceptable only with a mutually agreed upon protocol amendment as approved by the sponsor, regulatory bodies and Institutional Review Board/ Ethics Committee. I agree to await Institutional Review Board/ Ethics Committee approval of the protocol, informed consent, and sponsor approval before initiating the study, and to obtain consent from subjects prior to their enrollment in the study. I agree to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

Confidential

This document contains confidential information belonging to Senseonics, Inc. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

_____ _____

Investigator's signature Date of signature

SYNOPSIS

Title of Protocol	PRECISION Study: A Prospective, Multicenter Evaluation of Precision, Compression, Accuracy and Updated Algorithm of a Novel Continuous Implanted Glucose Sensor
Sponsor	Senseonics, Inc.
Investigational Device	Senseonics Continuous Glucose Monitoring (CGM) System (the "System")
Reference Instrument	Reference Glucose Analyzer (bedside, YSI 2300 STAT PLUS® Glucose and Lactate Analyzer, Yellow Springs Instruments, Yellow Springs, OH, USA).
Calibration Standard	FDA-cleared Blood Glucose Meter (Subject SMBG Meter)
Study Purpose	The purpose of this clinical investigation is to evaluate the precision and accuracy of the Senseonics Continuous Glucose Monitoring System (Senseonics CGM System) measurements when compared with reference standard measurements. Compression of the sensor site and use of a new algorithm will also be evaluated. The investigation will also evaluate safety of the Senseonics CGM System usage.
Target Indication for Use	The Senseonics CGM System is a glucose monitoring device intended to continually measure interstitial fluid glucose levels in individuals with diabetes for the operating life of the sensor. The Senseonics CGM System is intended to be used: • To provide real-time glucose readings directly to the user. • To provide glucose trend information. • To provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).
Study Design Summary	This is a non-randomized, prospective, single-arm, multi-center study, enrolling adult subjects with diabetes mellitus in the United States at up to 4 sites. The investigation will include both clinic visits and home use of the Senseonics CGM System. Subjects will have one or two Sensors inserted in the upper arms by trained Investigators. The accuracy of the system will be evaluated during clinic visits, comparing Sensor glucose with laboratory reference values. For qualifying subjects, during the clinic visits, there are planned hyperglycemia and hypoglycemia challenges, as described in protocol Section 5. All diabetes care decisions will be based on plasma glucose values, rather than System CGM results.

Visit Schedule:

- **Visit 1 Screening Visit**. Following informed consent process, screening evaluation will determine subject eligibility for enrollment. Visit lasting approximately 2 hours. Visit includes screening medical and diabetes history, examination and laboratory assessments.

- **Visit 2 Sensor Insertion Visit** (Day 0, visit window: Visit 1 +0-30 Days). Sensors will be inserted by Investigator in the upper arms. A minimum of 6 and a maximum of 9 subjects will receive one sensor. Remaining subjects will receive two sensors, one in each arm. Subject receives training on study and devices. In addition for a group of subjects, 3 blood draws post-insertion will be done to measure dexamethasone levels. Visit lasting approximately 2-6 hours.

- **Sensor Accuracy Visits.** The following visits include Sensor accuracy assessment with reference laboratory glucose comparison, Sensor calibration with BG meter, and safety assessments including blood draws to measure dexamethasone levels. Protocol Section 4 describes the procedure details, including hyperglycemia challenges and hypoglycemia challenge for eligible subjects.
  - **Visit 3** (Day 1 ± 0 Day). Visit lasting approximately 19 hours.
  - **Visit 4** (Day 7 ±1 Day). Visit lasting approximately 18 hours.
  - **Visit 5**(Day 14 ±1 Day). Visit lasting approximately 18 hours.
  - **Visit 6** (Day 30 ±7 Days). Visit lasting approximately 14 hours.
  - **Visit 7**(Day 60 ±7 Days). Visit lasting approximately 14 hours.
  - **Visit 8** (Day 90 -3/+7 Days). Visit lasting approximately 15 hours.
    Following evaluation of Sensor accuracy, Sensors are removed at end of visit.

- **Visit 9 Follow-up Visit.** Sensor Site Assessment is performed approximately 10 days after Sensor removals (- 3/ +7 day window) to assess Sensor sites. At this visit, if there is a concern by investigator about healing of sensor site, subject will return in approximately 10 days and followed until resolution.

Home Use: Subjects will follow their usual diabetes care routine as per their medical team recommendations while wearing the System. All diabetes management decisions by the subject and health care team will be made based on standard of care with blood glucose monitoring, and not based on Senseonics CGM glucose values. Subjects will be advised to wear the Transmitter over the Sensor for data collection, except during transmitter charging, bathing or water activity.

	Subjects will calibrate the CGM using the study-provided Subject SMBG Meter a minimum of two times per day according to Instructions for Use (Four times per day during Initialization Phase). Subject will use the same study-provided BG meter for monitoring their diabetes care, and this meter will be downloaded during the clinic visits. Subjects will be requested to check the BG meter glucose for all diabetes care decisions at a minimum 4-7 times per day. **Clinic Visits**: Blood samples, meter BG, and Sensor glucose values will be collected. Diabetes care decisions during the visit will be made based on blood glucose determinations, rather than Senseonics CGM System results. During sampling period blood sample glucose measurements will be performed and collected for laboratory glucose reference analysis approximately every 15 minutes, and more frequently (approximately every 5 minutes) during periods of hypoglycemia and hyperglycemia as described in the protocol. <u>Safety Assessments and Management</u> As described in Section 7.1, there will be trained staff and an emergency cart available at the site at all times. Safety guidelines will be utilized for subject care during periods of hyperglycemia (including monitoring blood ketones) and hypoglycemia. A physician or nurse practitioner will be available at all times during hypoglycemia and hyperglycemia challenges. The sensor insertion sites will be assessed at each clinic visit. A review and documentation of adverse events occurring in the clinic and during home use will be on-going. Laboratory tests will be monitored as per protocol for safety assessment. Additional details of the study design and safety assessments and management are described in the protocol. Blood draws for Dexamethasone measurement will be made at Screening and on Visits 2-8. A subset of a minimum of 6 and a maximum of 9 subjects will also have blood draws for dexamethasone measurement at days 3-6 of sensor use to identify possible blood draw time points during the first week of sensor wear for the remaining subjects.

Estimated Study Duration of Study and Subject Participation	Enrollment Period: Approximately 2 months Individual Subject Participation: Approximately 4.5 months Duration of Study: Approximately 6 months
Study Sites	Up to 4 investigative sites located in the United States.
Subject Population	The subject population consists of adult subjects with diabetes mellitus. Based on sample size calculations, approximately 44 adult subjects will be enrolled and approximately 36 will be inserted with the CGM Sensor in the investigation.
Inclusion Criteria	Male and Female Subjects meeting all of the following inclusion criteria will be included in this study: 1. Adult subjects, age ≥18 years 2. Clinically confirmed diagnosis of diabetes mellitus for ≥1 year 3. Subject has signed an informed consent form and is willing to comply with protocol requirements
Exclusion Criteria	Subjects meeting any of the following exclusion criteria at the time of screening will be excluded from this study: 1. History of severe hypoglycemia in the previous 6 months. Severe hypoglycemia is defined as hypoglycemia resulting in loss of consciousness or seizure 2. History of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months 3. Female subjects of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year) who are lactating or pregnant, intending to become pregnant, or not practicing birth control during the course of the study. 4. A condition preventing or complicating the placement, operation, or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition. 5. Symptomatic coronary artery disease; unstable angina; myocardial infarction, transient ischemic attack or stroke in the past 6 months; uncontrolled hypertension (systolic>160 mm Hg or diastolic >100 mm Hg at time of screening); current congestive heart failure; history of cardiac arrhythmia (benign PACs and PVCs allowed). Subjects with asymptomatic coronary artery disease (e,g, CABG, stent placement or angioplasty) may participate if negative stress test within 1 year prior to screening and written clearance from Cardiologist documented. 6. Hematocrit <30% or >55% 7. History of hepatitis B, hepatitis C, or HIV 8. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study 9. History of adrenal insufficiency

	10. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); glucocorticoids (excluding ophthalmic or nasal). This exclusion does include the use of inhaled glucocorticoids and the use of topical glucocorticoids (over sensor site only); antibiotic for chronic infection (e.g. osteomyelitis, endocarditis) 11. A condition requiring or likely to require magnetic resonance imaging (MRI) 12. Known topical or local anesthetic allergy 13. Known allergy to glucocorticoids 14. Any condition that in the investigator's opinion would make the subject unable to complete the study or would make it not in the subject's best interest to participate in the study. Conditions include but are not limited to psychiatric conditions, known current or recent alcohol abuse or drug abuse by subject history, a condition that may increase the risk of induced hypoglycemia or risk related to repeated blood testing. Investigator will supply rationale for exclusion 15. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period 16. The presence of any other active implanted device (as defined further in protocol) 17. The presence of any other CGM sensor or transmitter located in upper arm (other location is acceptable)
Investigation Objectives	<u>Effectiveness Objective</u>: To determine accuracy of the Senseonics CGM System measurements through approximately 90 days post-insertion. An interim analysis will be conducted on all subjects after completion of Visit 6 (day 30 accuracy visit). <u>Safety Objective</u>: To demonstrate safety of the Senseonics CGM System through 90 days post-insertion or sensor removal and follow-up by measuring the incidence of device-related and insertion/removal procedure-related serious adverse events during the investigation.
Endpoints	<u>Effectiveness Endpoint</u>: The effectiveness endpoint will be mean absolute relative difference (MARD) for paired Sensor and reference measurements through 90 days post-insertion for reference glucose values from 40-400 mg/dL. This endpoint will be evaluated descriptively. Neither inferential analysis nor hypothesis testing will be performed An interim analysis will be conducted on all subjects after completion of Visit 6 (day 30 accuracy visit).

	Safety Endpoint: Incidence of device-related or sensor insertion/removal procedure-related serious adverse events through 90 days post-insertion or sensor removal and follow-up.
Other Safety Endpoints	1. Incidence of all device-related or sensor insertion/removal procedure-related adverse events in the clinic and during home use. 2. Incidence of all adverse events in the clinic and during home use. 3. Incidence of hospitalizations due to hypoglycemia, hyperglycemia or ketoacidosis occurring during home use. 4. Incidence of reported hypoglycemic and hyperglycemic events occurring during home use.

ABBREVIATIONS

AE	Adverse Event
BG	Blood Glucose
BG Meter	Blood Glucose Meter (also known as SMBG Meter)
β-HOB	β-hydroxybutyrate or “ketones,” also abbreviated B-HOB
BMI	Body Mass Index
CD	Compact disc
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CRO	Contract Research Organization
DCF	Data Clarification Form
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EKG	Electrocardiogram (also commonly abbreviated as ECG)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c or A1C
HCT	Hematocrit
HIV	Human Immunodeficiency Virus
HHD	Hand Held Device
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
MARD	Mean absolute relative difference
MAD	Mean absolute difference
MDI	Multiple Daily Injections
MMA	Mobile Medical Application
MRD	Mean relative difference
PARD	Percent absolute relative difference
PI	Principal Investigator
POC	Point of Care
SAE	Serious Adverse Event
SMBG	Self-Monitoring Blood Glucose
SQ	Subcutaneous
UADE	Unanticipated Adverse Device Effect
USB	Universal Serial Bus
YSI	Yellow Springs International (Blood glucose analyzer)

1 INTRODUCTION, IDENTIFICATION OF THE INVESTIGATIONAL DEVICE, AND RATIONALE

In spite of recent improvement in therapies, diabetes mellitus continues to be a difficult medical condition to treat. The challenge remains to achieve desired glycemic control and to prevent both the short-term consequences (severe hypoglycemia and DKA) and long-term complications (retinopathy, neuropathy, nephropathy and cardiovascular problems). The monitoring of blood glucose by the patient with diabetes is one of the key tools of diabetes self-care. The current standard glucose monitoring regimen for patients with diabetes involves using a small portable meter to obtain a capillary fingertip glucose measurement multiple times a day. According to the International Society of Pediatric and Adolescent Diabetes (ISPAD), "successful application of intensified diabetes management with multiple injection therapy or insulin infusion therapy requires frequent self-monitoring of blood glucose (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan."[1] Despite this diagnostic procedure and therapeutic interventions, due to the nature of diabetes glucose values may fluctuate widely throughout the day. In addition, as the BG meter value shows only a point in time glucose level, even patients who monitor frequently, may miss significant hypoglycemic and hyperglycemic excursions. Continuous glucose monitoring (CGM), which measures interstitial glucose levels, has been developed recently and has been shown to be associated with improved glycemic control in adults with type 1 diabetes. Current commercially available CGM devices require the repeated, frequent insertion of a sensor by the patient.

Senseonics, Inc. a medical device manufacturer headquartered in Germantown, Maryland, USA, is developing a new CGM System intended for measuring interstitial fluid glucose levels in adults with diabetes mellitus. The Senseonics CGM System measures interstitial fluid glucose levels continuously and is implanted under the skin by a trained clinician. Unlike commercially available transcutaneous continuous glucose monitoring devices with short operating lives (up to 7 days), the Senseonics Sensor is intended to be inserted subcutaneously with no sensor part protruding from the skin, and the operating life is intended to be up to 90 days or until the end of life indicator is reached.

This clinical trial is being carried out to assess the safety and efficacy of the Senseonics CGM System. It is intended that the results of this study will support the targeted indication as described in Section 1.1 below, providing quantification of accuracy and demonstrate safety in clinic and home use settings over the operating life of the Sensor.

1.1 Names, Intended Use, and Description of Study Device

The study investigational Device is the Senseonics CGM System ("System").

The Senseonics Continuous Glucose Monitoring System is a glucose monitoring device intended to continually measure interstitial fluid glucose levels in individuals with diabetes for the operating life of the sensor. The Senseonics Continuous Glucose Monitoring System is intended to be used:

- To provide real-time glucose readings directly to the user
- To provide glucose trend information
- To provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

The Senseonics CGM System consists of:

1. Glucose Sensor, (approximately 3.5 mm [0.138”] diameter x 18.3 mm [0.720”] length) which has a ring that elutes the steroid dexamethasone
2. Battery-powered external Transmitter (“Transmitter”, Gen1/Gen2)
3. Mobile Medical Application (MMA) for display of glucose information that runs on a Handheld Device (HHD).

Accessories to the system include:

1. Blunt dissector for creating a pocket under the skin
2. Insertion tool used to place the Sensor into the pocket.
3. Transmitter accessories (power supply, adhesive patches)

Senseonics’ continuous glucose monitoring system has been branded for commercial use as the Eversense Continuous Glucose Monitoring (CGM) System. System components may be branded as Senseonics or as Eversense. The use of the system in this clinical study is outside the current commercial indications for use.

1.1.1 Description

The Senseonics CGM Sensor uses a selective, fully reversible binding between glucose and a unique fluorescent indicator macromolecule that is grafted on the surface of the Sensor. The fundamental recognition reaction is a reversible condensation of the cis-diol groups of glucose with the bis-boronate moiety of an indicator. Glucose binding by the indicator macromolecule results in an increase in fluorescence intensity. Glucose signal transduction is accomplished by measuring the fluorescence intensity modulation using the Sensor's optical system.

The Senseonics System Transmitter powers the Sensor and receives signals from the Sensor across the skin. The Sensor does not contain a battery or other stored power source; instead it is powered discretely, as needed, by a simple inductive magnetic link between the Transmitter and Sensor. Signals carrying glucose concentration data are superimposed upon the magnetic power link between the two components. This results in "passive" telemetry, rather than an "active" radio frequency (RF) transmission, between the Sensor and Transmitter. Between readings, the Sensor remains electrically dormant and fully powered down. At each query (automatically set for approximately every five minutes, with a duration of approximately 100 milliseconds), the Transmitter sends power (via magnetic link) to activate the sensor, and then uses this same magnetic link to capture the reading. Finally, the Transmitter calculates and stores the measured glucose value for transmission to the Mobile Medical Application.

Components of the Senseonics CGM System are traced by serial number and/or lot number. The Sensor, Sensor holder, insertion tool, and blunt dissector are provided sterile. Sterilized components also have an expiration date. The device is labeled in compliance with regulatory language requirements identifying it as investigational. The Instructions for Use are provided with each shipment.

Insertion of the Sensor is a minimally invasive procedure and clinical investigators representing the intended use population (Endocrinologists, Internists, General and Family Practitioners) will be appropriately trained in the procedure prior to insertion or removal of the Sensor. Training and qualifications of investigators will be documented.

Transmitters will be provided for single-subject use in this clinical trial.

1.1.2 Calibration

The primary Senseonics CGM System will be calibrated by the Subjects according to the Eversense CGM User Guide, using the study-provided, commercially available BG Meter (Subject SMBG Meter), according to the SMBG meter manufacturer instructions. The

calibration process automatically moves through three phases: Warm Up, Initialization, and Daily Calibration:

- Warm Up is the first 24 hours after Sensor insertion. During this period, Glucose information is not calculated. No calibration is performed.
- Initialization can be performed a minimum of 24 hours after Sensor insertion. Following the Warm Up phase, the entering of four successful calibration BG readings within 24 hours is required for successful completion of Initialization. Glucose information will begin to be calculated after the second calibration is entered successfully.
- Daily Calibration requires 2 successful calibrations per day, a minimum of 10 and maximum of 14 hours apart.

If the Subject fails to wear the Transmitter for more than 24 hours, or is unable to enter a successful calibration, then glucose information will not be calculated and the Subject will re-enter the Initialization phase.

The secondary Senseonics CGM System will not require calibration and will have the ability to collect and log data only, and it will not calculate or store glucose information.

1.2 Summary of Pre-clinical and Clinical Experience

Bench testing and animal testing have been conducted on the Senseonics CGM System to characterize performance, evaluate biocompatibility and demonstrate proof of principle in primates. Results of these tests are presented in the Report of Prior Investigations.

Clinical experience has included healthy volunteers and people with type 1 and 2 diabetes. As of February 2017, the Senseonics CGM System has been tested in two feasibility studies in the US. Other initiated Competent Authority/FDA and EC/IRB-approved feasibility studies include studies in the UK (Manchester), India (Mumbai, Pune), Romania (Bucharest Study I, II and III), Belgium (Brussels), South Africa (Cape Town), US (Set-Point Study), Canada and Sweden (HOUSE). Two pivotal studies, PRECISE Study (in the EU) and PRECISE II Study (in the US) were also conducted. As of February 2017, a total of 556 subjects have been inserted with 983 sensors with days in-vivo totaling 102,665 days.

These studies demonstrated that the Senseonics CGM System provided reliable interstitial fluid glucose readings for periods of up to approximately 180 days when compared to laboratory blood glucose analyzer measurements, with no noted safety issues. Detailed presentation of methods and results for each investigation are presented in the Report of Prior Investigations.

2 STUDY OBJECTIVES

2.1 Effectiveness

The effectiveness objective is to determine the accuracy of the Senseonics CGM System through 90 days post-insertion for reference glucose values from 40-400 mg/dL. The exploratory objectives are to determine other relevant Senseonics CGM System performance measures during the period of Sensor use and are detailed further in Section 11.3, along with plans and analysis details on the effectiveness endpoint. An interim analysis will be performed and data submission will be made based on the sensor performance data accrued through the day 30 visit (Visit 6).

2.2 Safety

The safety objective is to demonstrate safety of the Senseonics CGM System through 90 days post-insertion by measuring the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAEs) during the investigation. The other safety objectives are to evaluate the incidence of all procedure-related or device-related adverse events (AEs) in clinic and home use, and to evaluate the incidence of all adverse events, regardless of relatedness, in clinic and home use. The safety endpoints and their respective analysis are detailed further in Section 11.2.

3 STUDY DESCRIPTION

3.1 Study Population

The study population includes adults with diabetes mellitus.

3.2 Inclusion and Exclusion Criteria

3.2.1 Inclusion Criteria

Male and Female Subjects meeting all of the following inclusion criteria will be included in this study:

1. Adult subjects, age ≥18 years
2. Clinically confirmed diagnosis of diabetes mellitus for ≥1 year.
3. Subject has signed an informed consent form and is willing to comply with protocol requirements

3.2.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria at the time of screening will be excluded from this study:

1. History of severe hypoglycemia in the previous 6 months. Severe hypoglycemia is defined as hypoglycemia resulting in loss of consciousness or seizure

2. History of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months
3. Female subjects of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year) who are lactating or pregnant, intending to become pregnant, or not practicing birth control during the course of the study
4. A condition preventing or complicating the placement, operation or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition
5. Symptomatic coronary artery disease; unstable angina; myocardial infarction, transient ischemic attack or stroke within 6 months; uncontrolled hypertension (systolic>160 mm HG or diastolic >100 mm Hg at time of screening); current congestive heart failure; history of cardiac arrhythmia (benign PACs and PVCs allowed). Subjects with asymptomatic coronary artery disease (e.g. CABG, stent placement or angioplasty) may participate if negative stress test within 1 year prior to screening and written clearance from Cardiologist documented.
6. Hematocrit <30% or >55%
7. History of hepatitis B, hepatitis C, or HIV
8. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study
9. History of adrenal insufficiency
10. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); glucocorticoids (excluding ophthalmic or nasal). This exclusion does include the use of inhaled glucocorticoids and the use of topical glucocorticoids (over sensor site only); antibiotics for chronic infection (e.g. osteomyelitis, endocarditis)
11. A condition requiring or likely to require magnetic resonance imaging (MRI)
12. Known topical or local anesthetic allergy
13. Known allergy to glucocorticoids
14. Any condition that in the investigator's opinion would make the subject unable to complete the study or would make it not in the subject's best interest to participate in the study. Conditions include, but are not limited to, psychiatric conditions, known current or recent alcohol abuse or drug abuse by subject history, a condition that may increase the risk of induced hypoglycemia or risk related to repeated blood testing. Investigator will supply rationale for exclusion
15. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period
16. The presence of any other active implanted device*

17. The presence of any other CGM sensor or transmitter located in upper arm (other location is acceptable)

* An example of an active implanted device includes, but is not limited to an implantable defibrillator. Passive implantable devices are allowed. An example of a passive implantable device includes, but is not limited to, a cardiac stent.

3.3 Study Design

3.3.1 Overview

This is a non-randomized, prospective, single-arm, multi-center study, whereby approximately 44 subjects will be enrolled and 36 subjects will be inserted in the United States at up to 4 sites. The investigation will include both clinic visits and home use of the Senseonics CGM System. The subjects will have one or two Sensors inserted by trained Investigators. The Sensors will be inserted in the upper arms of the subjects. The accuracy of the Senseonics CGM System will be evaluated during clinic visits comparing Sensor glucose values and plasma glucose values measured on a bedside glucose analyzer. For qualifying subjects, during the clinic visits, there will be planned hyperglycemia and hypoglycemia challenges, as described in Section 5.12. Effects of compression/sensor dropout will be evaluated during the designated overnight periods.

In this study, including the clinic and home settings, all diabetes care decisions will be based on SMBG blood glucose values and clinical standard of care, rather than Senseonics CGM System results.
This study will not be randomized. Subjects will be selected consecutively (i.e., selecting every subject in the order they present at the site) among those who meet the inclusion/exclusion criteria.

The Subject visit schedule includes 9 visits over a period of approximately 4.5 months (inclusive of visit windows from screening visit through follow-up visit).

A subset of a minimum of 6 and a maximum of 9 subjects will have blood samples drawn daily for the first 7 days of sensor wear for additional dexamethasone screening and to determine blood draw time points during the first week of sensor wear for the remaining subjects. These subjects will only have one sensor inserted in the left arm, which will be linked to the Gen 1 transmitter. Remaining subjects will have 2 sensors inserted, one in each arm, with the left sensor linked to a Gen 1 transmitter, and the right sensor linked to the Gen 2 transmitter. These subjects may be required to make additional visits for dexamethasone screening between visits 3 and 4.

The study is anticipated to take approximately 6 months, including the enrollment period.

3.3.2 Justification for Clinical Investigation Design

The design of the clinical investigation was developed following a review of current published clinical studies evaluating the accuracy of continuous glucose monitors.[2, 3, 4] In addition, the recommendations of the following standards and guidelines were considered in the clinical investigation design:

- CLSI. Performance Metrics for Continuous Interstitial Glucose Monitoring: Approved Guideline. CLSI Document POCT05-A. Wayne, PA. Clinical and Laboratory Standards Institute. 2008.[5]
- ISO. In-vitro Diagnostic Test Systems-Requirements for Blood Glucose Monitoring Systems for Self-Testing in Managing Diabetes Mellitus. ISO 15197. Geneva. International Organization for Standardization. 2013.[6]
- FDA. Content of Premarket Submissions for Management of Cybersecurity in Medical Devices. Guidance. 2014.[7]
- FDA. The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems. Draft Guidance. 2011.[8]
- FDA. Design Considerations for Pivotal Clinical Investigations for Medical Devices. Guidance 2013.[9]

The operational components of the investigation are consistent with:

- US Code of Federal Regulations (21 CFR Part 812)
- ICH GCP E6

Potential for bias during this investigation has been minimized by design of a well-controlled study, expected conduct under the terms of an approved study protocol, use of specific inclusion and exclusion criteria, careful definitions for study procedures and outcomes and prospectively defined methods of data analysis, and careful selection of investigators and investigative sites.

3.3.3 Overview of Visit Schedule:

- **Visit 1 Screening Visit**. Following the informed consent process, the screening evaluation will determine subject eligibility for sensor insertion. This visit will last approximately 2 hours. Screening will include medical and diabetes history, physical examination and laboratory assessments including EKG.
- **Visit 2 Sensor Insertion Visit** (Day 0, +0 to 30 Days after Visit 1). Sensors are inserted by Investigator in the upper arms. Subject training on study and devices. Visit lasting approximately 2 to 3 hours. Designated subjects for dexamethasone testing have only 1 sensor inserted, and will be required to stay up to 6 hours. Depending on the results from this subset, all following subjects may be required to stay up to 6 hours for this visit.

- **Sensor Accuracy Visits**. The following visits include Sensor accuracy assessment with bedside reference comparison, Sensor calibration with Subject SMBG Meter, and safety assessments. Procedure details are described in Section 4 of the protocol.
    - Visit 3 (Day 1 ± 0 Day). Visit lasting approximately 19 hours.
    - Visit 4 (Day 7 ±1 Days). Visit lasting approximately 18 hours.
    - Visit 5 (Day 14 ±1 Days). Visit lasting approximately 18 hours.
    - Visit 6 (Day 30 ±7 Days). Visit lasting approximately 14 hours
    - Visit 7 (Day 60 ±7 Days). Visit lasting approximately 14 hours
    - Visit 8 (Day 90 -3/+7 Days). Visit lasting approximately 15 hours.

  Following evaluation of Sensor accuracy, the Sensors are removed at the end of this visit. (Note: Sensor removals may also be performed at an unscheduled visit and will not be considered a protocol deviation)
- **Visit 9: Follow Up Visit** (10 days after Sensor removal, -3/ +7 day window). Sensor insertion/removal sites are assessed for healing. At this visit, if there is a concern by investigator about healing of sensor sites, the subject will return in approximately 10 days and followed until resolution. Visit length will be approximately 30 minutes.

4 STUDY METHODS, PROCEDURES AND CLINIC VISITS

Each visit is described in detail in this section.

Visit Number	**1**	**2**	**3**	4	**5**	**6**	**7**	**8**	**9**
Visit Type	Screening	Sensor Insertion and Training	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit and Sensor Removal	Follow-up Sensor Site Assessment
Study Day and Window		Day 0 (+0 to 30 Days after Visit 1)	Day 1 (±0 Day)	Day 7 (± 1 Days)	Day 14 (±1 Days)	Day 30 (±7 Days)	Day 60 (±7 Days)	Day 90 (-3/+7 days)	10 Days Following Sensor Removal (-3/+7 days)
Anticipated Length of Visit	2 Hours	2 to 6 Hours	19 Hours	18 Hours	18 Hours	14 hours	14 hours	15 hours	30 Minutes
Informed Consent Process	X								
Screening history, exam, labs to assess Inclusion/Exclusion	X								
Sensor Insertion		X							

Visit Number	**1**	**2**	**3**	4	**5**	**6**	**7**	**8**	**9**
Device Training		X							
Urine pregnancy	X	X	X	X	X	X	X	X	
IV Catheter			X	X	X	X	X	X	
Approximate length of time to collect blood Samples			16 Hours	16 Hours	16 Hours	12.5 Hours	12.5 Hours	12.5 Hours	
Dexamethasone blood draw (4.0 mL)[2]	X	X	X[3]	X[3]	X[3]	X	X	X	
HCT	X		X	X	X	X	X	X	
A1C (2.0 mL)	X					X	X	X	
Fingerstick blood glucose and ketones per protocol			X	X	X	X	X	X	
Download Transmitter and BG Meters			X	X	X	X	X	X	
Assess changes in medications and Adverse Events		X	X	X	X	X	X	X	X
Assess Sensor site			X	X	X	X	X	X	X
Hypoglycemia and Hyperglycemia Challenge			X	X	X	X[1]	X[1]	X[1]	
Sleep Assessment				X	X				
Questionnaire								X[4]	
Sensor Removal								X	
Approximate Samples for glucose analysis			89 (13 hrs @4 per, 3 hrs @ 12 per)	89 (13 hrs @4 per), 3 hrs @ 12 per	89 (13 hrs @4 per), 3 hrs @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	
Maximum Estimated Blood Draw Volume	6	12	97	97	97	65	65	65	Total=504

1 Only hypoglycemia challenge or hyperglycemia challenge, depending on glucose level

2 Designated subjects will have 3 samples drawn at visit 2. A subset of subjects will have daily blood samples drawn for the first 7 days of sensor wear

for dexamethasone assessment. Remaining subjects may have an additional blood sample drawn during the first 7 days TBD based on the results from the subset.
3 Subjects will have 2 blood samples drawn for dexamethasone assessment, one at the beginning of the visit, and one at the end.
4 Subjects will be asked to complete a questionnaire at the end of sensor wear period.

Visit Details

4.1 Visit 1 – Screening/Enrollment

Subjects will be enrolled into the study following informed consent. Screening evaluation will determine subject eligibility for sensor insertion. No study-specific procedures may be performed prior to informed consent signature. The Screening Visit is anticipated to last approximately 2 hours. The visit will occur within 30 days before the Sensor Insertion Visit (V2).

The Screening Visit includes performing/collecting the following information:

- Demographics- including age, gender at birth, race/ethnicity, dominant hand, and BMI.
- Diabetes History- including type of diabetes, date of diagnosis or length of diabetes, history of DKA and severe hypoglycemia, current treatment (type of insulin and type of insulin delivery (injections or insulin pump), insulin doses, and when applicable: basal rates, correction factors, glucose targets, insulin duration, insulin to carbohydrate ratios, sliding scales).
- Current and Past Medical History- including concomitant medications.
- Physical examination and vital signs- including height, weight, blood pressure, pulse, temperature, assessment of potential sensor insertion sites, assessment of venous access for repeated blood draws.
- EKG- an EKG will be performed with the results kept in the subject records.
- Laboratory

  Blood samples (approximately 6 ml total) will be drawn for the following laboratory tests. All samples will be collected and processed as described in the operations manual:

  - Hemoglobin A1C
  - Dexamethasone

4.1.1 Point of care testing

- Urine pregnancy test- for females of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year)
- Hematocrit (using local lab or point of care testing device)

4.2 Visit 2 – Sensor Insertion/Training

4.2.1 Subject Admission

The subject will arrive at the clinic during the day, at an appropriate time to allow for sensor insertion to occur a minimum of 24 hours before the planned day 1 (Visit 3) study activities, and the following tests will be performed to confirm eligibility:

- Female subjects of childbearing capacity will undergo a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented.
- The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- If all admission criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit.

  The subject will be asked about any adverse events or changes to medications since the last study visit.

4.2.2 Device preparation

All Study devices will be time synchronized and checked for function as described in section 5.3.

4.2.3 Sensor Insertions

Each subject will have the Sensors inserted at Visit 2 (Day 0); above the elbow of their arms. The study team will prepare the Sensor insertion site appropriately. The hair at the insertion area may be clipped in order to ensure appropriate visualization of the insertion site. The Sensor will be prepared by qualified personnel (Sponsor personnel or trained investigative staff).

A trained study clinician will insert the Sensor into the subcutaneous tissue using appropriate technique described in the Eversense CGM Sensor Insertion and Removal Instructions and the Study Operations Manual. The training and qualifications of the clinician performing the insertion procedure will be documented. The location of each Sensor will be documented.

Subjects will be advised that they may take over the counter pain medication if needed for any discomfort after the insertion process. No medication, including medication-containing creams and patches is to be applied over the sensor insertion site.

Subjects will be advised to keep the area dry for 24-48 hours. Subjects will be advised to change the dressing approximately 48 hours post insertion and they will check that the healing process is going as expected (minor redness, no swellings, no increased temperature, no increased pain and no sign of infection). After 48 hours subjects will be advised to change the dressing as required until the wound is closed. Cleaning can be done with normal saline in the clinic, but at home they can use tap water from a running tap.

Identification of the Sensor, Transmitter and accessories will be recorded (part number, serial number, lot number, and expiration date as applicable).

After sensor insertion, the transmitters will be worn briefly (approximately 20 minutes) to ensure proper operation of the system (confirmation of system operation).

4.2.4 Dexamethasone blood draw

Blood samples for dexamethasone measurement will be drawn as follows:

- Designated subset of subjects
  - Approximately 30-60 minutes after sensor insertion is complete
  - 2 additional samples, timing to be specified, within approximately 4 hours of the sensor insertion.
- All remaining subjects
  - One sample drawn based on analysis of dexamethasone from subset group.

All samples will be collected and processed as described in the operations manual.

4.2.5 Device disbursement

Subjects will be assigned the following devices:

- Senseonics Continuous Glucose Monitoring (CGM) Systems consisting of-
  - One Gen 1 Transmitter and accessories (charger, adhesive patches)- PRIMARY- Displays glucose
  - One Gen 2 Transmitter and accessories (charger, adhesive patches)- SECONDARY - Does not display glucose (subjects inserted with one sensor only will not use this system)
  - Handheld Device (1 per Subject) running the Mobile Medical Application (MMA)
  - Eversense CGM User Guides

- A widely-used, commercially available FDA-approved self-monitoring blood glucose (SMBG) meter and associated supplies-
  - BG meter strips
  - Lancets
  - control solution
  - Instructions for Use

4.2.6 Subject training

Subjects will be issued one or two transmitters as applicable. Gen 1 and Gen 2 transmitters will be visually distinguishable from each other to ensure matching to the correct limb. Subjects participating in the subset for additional dexamethasone testing will only be issued the Gen 1 transmitter. Each transmitter is linked to a specific sensor as described in the Eversense CGM User Guide. Subjects will be issued a hand held device which will be used for entering calibration information into the Gen 1 transmitter only. The Gen 2 transmitter worn on the opposite arm will have the ability to collect and log data only and will not calculate and store glucose information.

The subject will be given instructions on how to contact study staff for 24 hours per day to report any study- related problems. The subject will be instructed to contact the study staff for prolonged hyperglycemia, severe hypoglycemia, or if he/she experiences nausea, vomiting, or abdominal pain within 48 hours after discharge. The subject will be instructed to contact the study staff for any problems related to the sensor sites, including fever, pain, redness, itching, discharge, warmth or swelling at the sensor insertion sites. If infection is experienced, standard medical practice and administration of antibiotics as required should be followed until resolution. Subjects will be further instructed to advise the investigator if new medications have been prescribed or started, or if any hospitalizations or significant medical changes have occurred.

The subject will be instructed on the proper use and quality control of the Subject SMBG Meter including the number and timing of fingersticks expected during each day (approximately 7 times per day (before meals, approximately 2 hours after meals, and at bedtime)).

The subject will be instructed on the proper use of the Transmitter and Mobile Medical Application (refer to the Eversense CGM User Guides). The transmitter will be worn over the sensor at all times (except while charging, bathing or during any other water activities) starting approximately 24 hours post insertion. Subjects will be prompted to calibrate the sensor using fingerstick measurements (a minimum of 2 each day, approximately 12 hours apart) using the Subject SMBG meter.

Training may continue at Visit 3, or as needed.

4.2.7 Discharge

Discharge will occur upon completion of confirmation of system operation and subject training. The site will document any adverse events that may have occurred during the visit.

When subjects leave the clinic after completing the sensor insertion/training visit, they will NOT bring the transmitters or study-supplied meter home with them. Transmitters and study-supplied meters will remain at the site overnight and issued to the subject for home use at visit 3. Subjects may take the HHD home with them overnight in order to pair with their home wifi, and to familiarize themselves with the MMA.

4.2.8 Estimated Total Blood Volume

The total amount of blood will not exceed 12 ml plus fingersticks taken during the visit.

4.2.9 Estimated Visit Duration

The total duration of the inpatient visit is approximately 2-6 hours.

4.3 Subset of subjects for dexamethasone analysis

A designated subset of a minimum of 6 and a maximum of 9 subjects across the study will return on days 3-6 for blood draws (~ 4 mL each) for dexamethasone analysis. These samples are in addition to the samples collected at visit 3 on days 1 and 2 and at visit 4 on days 7 and 8 (as described below).

Dexamethasone results from these subjects will be used to determine whether and when the remaining subjects will need to come in for an additional blood draw for dexamethasone measurement. This may occur within several hours of sensor insertion (at the end of Visit 2), or during the first 7 days post sensor insertion.

4.4 Sensor Accuracy (Sampling) Visit 3 – Day 1 (± 0 Days)

Approximate visit duration - 19 hours
Approximate sampling duration – 16 hours

Approximate visit timeline:

Approximate time	Activity	~Time relative to first IV sample
~16:00	Admission and First Calibration	T=0 -2:00
~16:30	Blood draw for dexamethasone	T=0 -1:30
~17:00	Fingerstick	T=0 -1:00
~17:15-17:45	Period for glucose stabilization	T=0 -0:45 - -0:15
~18:00	First IV blood sample drawn/ second calibration	T=0 0:00
~18:00 – 0:00	For qualifying subjects, hyperglycemia challenge to achieve hyperglycemia to goal glucose >350 mg/dL. • Sampling @ 5 min when glucose ≥ 325 mg/dL, with a target duration of 1 hour. • Challenge may be stopped once 12 samples ≥325 mg/dL are collected.	T=0 0:00 – +6:00
19:00	Fingerstick	T=0 0:00 - +1:00
~20:00	Third calibration	T=0 0:00 - +2:00
21:00	Fingerstick	T=0 0:00 - +3:00
~22:00	Fourth calibration	T=0 0:00 - +4:00
~23:00	Fingerstick	T=0 0:00 - +5:00
~0:00	Fingerstick	T=0 0:00 - +6:00
~0:00-07:00	Overnight period • Overnight period. Sampling q 15 min when glucose is > 75 mg/dL and < 325 mg/dL. Q 5 minutes when outside this range.	T=0 +6:00 - +13:00
~07:00	CGM system calibration	T=0 +13:00

Approximate time	Activity	~Time relative to first IV sample
~07:00-10:00	For qualifying subjects, hypoglycemia challenge to achieve hypoglycemia target <60 mg/dL. • Sampling q 5 min when glucose ≤ 75mg/dL. • Target 24 YSI values <75 mg/dL, including 6 YSI values <60 mg/dL at q 5 min before rescue. • Subjects fed low glycemic morning meal and YSI data collection discontinued once challenge is concluded. • Hourly fingersticks from 07:00 to 11:00.	T=0 +13:00 - +16:00
~08:00	Fingerstick	T=0 +13:00 - +14:00
~09:00	Fingerstick	T=0 +13:00 - +15:00
~10:00	Fingerstick	T=0 +13:00 - +16:00
~10:00-11:00	Discharge preparation	T=0 +16:00 - +17:00
~10:30	Blood draw for dexamethasone	T=0 +16:30
~11:00	Discharge	T=0 +17:00

4.4.1 Device preparation

All Study devices will be time synchronized and checked for function as described in section 5.3.

4.4.2 Medications and Medical Supplies

Medications and medical supply status will be checked as described in Section 5.2.

4.4.3 Meals

Other than during glucose challenges, subjects will be allowed to eat, drink and continue his/her diabetes treatment regimen throughout the admission. Specific information regarding subject meals is described in Section 5.13.

4.4.4 Subject Instructions prior to admission

Prior to admission, subjects should take their medications and food as follows:

- Subjects participating in hyperglycemia challenge soon after admission should not take subcutaneous bolus insulin approximately 3 hours prior to the challenge. Subjects should take their normal dose and timing of basal insulin. If challenge subjects need to eat or take insulin for safety reasons, they should inform study staff of this information on arrival to the clinic.

- If subjects blood glucose is <150 mg/dL they should be instructed to eat a snack prior to coming to the clinic, and be given specific instructions how to modify basal infusion until they arrive at the study site. Subjects may receive guidance from study staff trained in diabetes treatment regarding insulin and carbohydrate intake prior to the visit.

4.4.5 Subject Admission

The subject will arrive at the clinic during the day, no later than approximately 16:00 and the following tests will be performed to confirm eligibility for participation in visit 3:

- Hematocrit will be assessed using local lab or Point of Care testing device. Subject must be within reference range to participate in accuracy (sampling) visit.
- Female subjects of childbearing capacity will perform a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented.
- The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- The study team will confirm that the subject brought his/her personal insulin and insulin pump or injection supplies (as applicable) and required medications. The subject will continue to use his/her diabetes treatment regimen throughout the admission. The subject will be rescheduled if he/she did not bring his/her required medications or appropriate medications are not available at the clinic.
- Clinical staff to confirm that the transmitters and hand held device are in communication and functioning.
- If all admission readiness criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit. NOTE: If rescheduling is required, Clinicians should make every effort to reschedule the visit within 1-3 days from the originally scheduled visit. Rescheduling of Visit 3 for safety reasons will not be considered a protocol deviation.

4.4.6 Adverse events

Upon admission subject will be asked about any adverse events or changes to medications since the last study visit. Adverse events will be documented on the appropriate eCRF.

4.4.7 Dexamethasone blood draw

Blood sample will be drawn at the beginning of the visit, and again at the end of the visit prior to discharge for dexamethasone measurement. All samples will be collected and processed as described in the operations manual.

4.4.8 Ketone testing

On arrival to the clinic, subject blood ketones should be evaluated from capillary blood using the ketone meter. If ketones are ≥0.6 mmol/L, ketone testing should be repeated as described in Section 5.8 and subjects should be treated for ketones following ketone treatment guidelines Section 7.1.5.

4.4.9 SMBG testing

During in-clinic days, subjects should continue testing blood sugar using the study-supplied Subject SMBG Meter following the study visit timeline (hourly, except during overnight period).

4.4.10 IV placement

Intravenous (IV) access appropriate for blood drawing and potential intravenous rescue (such as dextrose or glucagon) will be established following the IV placement guidelines (Section 5.9)

4.4.11 Blood sampling for glucose measurement

Once IV access has been established, blood will be sampled for bedside reference glucose every 5-15 minutes per the Blood Sampling guidelines (Section 5.9).

4.4.12 Hyperglycemia Challenge

For qualifying subjects, a hyperglycemia challenge will be conducted to achieve a glucose goal of >350 mg/dL. Sampling interval will be q 5 min when glucose ≥325 mg/dL for a target of 1 hour before rescue. For those subjects not following a basal/bolus routine on MDI or CSII, glucose control will be free range. Details regarding conduct of the hyperglycemia challenge can be found in Section 5.12.

4.4.13 Hypoglycemia Challenge

For qualifying subjects, a hypoglycemia challenge will be conducted to achieve a glucose goal of ≤60 mg/dL. Sampling interval will be q 5 min when glucose ≤ 75 mg/dL for a target of 2 hours before rescue. For those subjects not following a basal/bolus routine on MDI or CSII, glucose control will be free range. Details regarding conduct of the hypoglycemia challenge can be found in Section 5.12.

4.4.14 Observation subjects

Subjects with gastroparesis or those subjects unable to participate in glucose challenges will participate in the sampling sessions using free range glucose control.

4.4.15 Discharge instructions

The discharge procedure will occur upon completion of ~approximately 16 hours of IV blood sampling. Discharge instructions are detailed in Section 5.14.

4.4.16 Estimated Total Blood Volume

Approximately 89 blood samples will be obtained throughout the course of the visit in addition to the blood sample required for dexamethasone analysis and fingersticks taken. The maximum estimated amount of blood estimated for the visit is 97 ml.

4.4.17 Estimated Visit Duration

The total duration of the inpatient visit is approximately 19 hours. The study time may be extended for glucose stabilization prior to discharge.

4.5 Sensor Accuracy (Sampling) Overnight Visits

Visit 4 – Day 7 Accuracy (Sampling) Visit (±1 Day)
Visit 5 – Day 14 Accuracy (Sampling) Visit (±1 Day)

Approximate visit duration – 18 hours
Approximate sampling duration – 16 hours

Approximate visit timeline:

Approximate time	Activity	Time relative to first IV sample
~17:00	Admission	T=0 -1:00
~17:15-17:45	Period for glucose stabilization and CGM calibration	T=0 -0:45 - -0:15
~17:30	Blood draw for dexamethasone, prior to YSI sampling	
~18:00	First IV blood sample drawn	T=0 0:00
~18:00 – 0:00	• For qualifying subjects, hyperglycemia challenge to achieve hyperglycemia to goal glucose >350 mg/dL. • Sampling @ 5 min when glucose ≥ 325 mg/dL, with a target duration of 1 hour. • Challenge may be stopped once 12 samples ≥325 mg/dL are collected.	T=0 0:00 – +6:00
~19:00	Fingerstick blood glucose	T=0 +1:00
~20:00	Fingerstick blood glucose	T=0 +2:00
~21:00	Fingerstick blood glucose	T=0 +3:00

Approximate time	Activity	Time relative to first IV sample
~22:00	Fingerstick blood glucose	T=0 +4:00
~23:00	Fingerstick blood glucose	T=0 +5:00
~0:00	Fingerstick blood glucose	T=0 +6:00
~0:00-07:00	• Overnight period. Sampling q 15 min when glucose is > 75 mg/dL and < 325 mg/dL. Q 5 minutes when outside this range.	T=0 +6:00 - +13:00
~07:00	Fingerstick blood glucose and sensor calibration	T=0 +13:00
~07:00-10:00	For qualifying subjects, hypoglycemia challenge to achieve hypoglycemia target <60 mg/dL. • Sampling q 5 min when glucose ≤ 75 mg/dL. • Target 24 YSI values <75 mg/dL including 6 YSI values <60 mg/dL at q 5 min before rescue. Subjects fed low glycemic morning meal and YSI data collection discontinued once challenge is concluded.	T=0 +13:00 - +16:00
~08:00	Fingerstick blood glucose	T=0 +14:00
~09:00	Fingerstick blood glucose	T=0 +15:00
~10:00	Fingerstick blood glucose	T=0 +16:00
~10:00-11:00	discharge preparation	T=0 +16:00 - +17:00
~10:30	Blood draw for dexamethasone after YSI sampling complete.	T=0 +16:30
~11:00	Discharge	T=0 +17:00

The following procedures/instructions will be followed for accuracy (sampling) visits at Visits 4 and 5:

4.5.1 Pre-visit phone call

One to two days prior to the Accuracy (Sampling) Visit, site personnel will contact the subject to ensure the subject is in compliance with study device wear. Subjects will also be advised if they are scheduled for a glucose challenge and will be given appropriate instructions regarding pre-visit medications and meals.

4.5.2 Device preparation

All Study devices will be time synchronized and checked for function as described in section 5.3

4.5.3 Medications and Medical Supplies

Medications and medical supply status will be checked as described in Section 5.2.

4.5.4 Meals

Specific information regarding subject meals is described in Section 5.13. Food and drink will be controlled as required.

4.5.5 Subject Instructions prior to admission

Prior to admission, subjects should take medications and meals as usual as follows:

- Subjects participating in hyperglycemia challenge soon after admission should not take subcutaneous bolus insulin approximately 3 hours prior to the challenge. Subjects should take their normal dose and timing of basal insulin. If challenge subjects need to eat or take insulin for safety reasons, they should inform study staff of this information on arrival to the clinic.

- If subjects blood glucose is <150 mg/dL they should be instructed to eat a snack prior to coming to the clinic, and be given specific instructions how to modify basal infusion until they arrive at the study site.

4.5.6 Subject Admission

The subject will arrive at the clinic during the day, no later than approximately 17:00 and the following tests will be performed to confirm eligibility for participation in visits 4 and 5:

- Hematocrit will be assessed using local lab or Point of Care testing device. Subject must be within reference range to participate in accuracy (sampling) visit.
- Female subjects of childbearing capacity will perform a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented. The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- The study team will confirm that the subject brought his/her personal insulin and insulin pump or injection supplies (as applicable) and regular medications. The subject will continue to use his/her diabetes treatment regimen throughout the admission. The subject will be rescheduled if he/she did not bring his/her regular medications or appropriate medications are not available at the clinic.
- Clinical staff to confirm that the subject is wearing the transmitters and that the transmitters and hand held device are in communication and functioning.

- The subject will be rescheduled if he/she did not bring his/her Transmitters and cannot make them available during the visit.
- If all admission readiness criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit.

4.5.7 Adverse events

Upon admission subject will be asked about any adverse events or changes in medication since the last study visit. The sensor insertion site will be examined. Adverse events including those associated with the insertion site will be documented on the appropriate eCRF.

4.5.8 Dexamethasone blood draw

Blood sample will be drawn at the beginning of the visit and prior to discharge for Dexamethasone measurement. All samples will be collected and processed as described in the operations manual.

4.5.9 Ketone testing

On arrival to the clinic, subject blood ketones should be evaluated from capillary blood using the ketone meter. If ketones are ≥0.6 mmol/L, ketone testing should be repeated as described in Section 5.8 and subjects should be treated for ketones following ketone treatment guidelines Section 7.1.5.

4.5.10 SMBG testing

During in-clinic days, subjects should continue testing blood sugar using the study-supplied Subject SMBG Meter following the visit schedule (hourly except during overnight period).

4.5.11 IV placement

Intravenous access appropriate for blood drawing and potential intravenous dextrose or other medically necessary and appropriate rescue will be established following the IV placement guidelines (Section 5.9).

4.5.12 Blood sampling for glucose measurement

Once IV access has been established, blood will be sampled for bedside reference glucose every 5-15 minutes per the Blood Sampling guidelines (Section 5.9).

4.5.13 Calibration (Visits 4 & 5)

Subjects/clinicians will calibrate the system during the time period for glucose stabilization and will calibrate again approximately 12 hours later. The morning calibration reminder, adjusted through use of the HHD and mobile medical application will be set to approximately 12 hours after the evening calibration entry.

4.5.14 Glucose Challenges

Qualifying subjects will participate in hyperglycemia and hypoglycemia challenges during the times indicated in the visit timeline table. The intention of the hypoglycemia and hyperglycemia challenge is to safely manipulate the subject's blood glucose levels so that sensor performance can be evaluated over a wider range than might otherwise be observed. Details regarding the glucose challenges can be found in Section 5.12.

4.5.15 Observation subjects

Subjects with gastroparesis or those subjects unable to participate in glucose challenges will participate in the sampling sessions using free range glucose control.

4.5.16 Sleep Assessment

Designated subjects will be inserted with two sensors, one in each upper arm. Each subject will spend two overnights in the clinic where they will be instructed to sleep on one side for situations in which compression of the sensor site may occur during sleep. "Sensor drop-out," if a phenomenon of the Senseonics CGM System, will be identified during these periods. Sleep position will not be documented.

4.5.17 Discharge instructions

The discharge procedure will occur upon completion of IV blood sampling. Please refer to section 5.14 for discharge instructions.

4.5.18 Estimated Total Blood Volume

Approximately 89 blood samples will be obtained throughout the course of the respective visits in addition to the blood sample required for dexamethasone analysis and fingersticks taken. The maximum estimated amount of blood estimated for each visit is 97 ml.

4.5.19 Estimated Visit Duration

The total duration of the inpatient visit is approximately 18 hours. The study time may be extended for glucose stabilization prior to discharge.

4.6 Sensor Accuracy (Sampling) Daytime Visits

Visit 6 – Day 30 Accuracy (Sampling) Visit (±7 Days)
Visit 7 – Day 60 Accuracy (Sampling) Visit (±7 Days)
Visit 8 – Day 90 Accuracy (Sampling) Visit (-3/+7 Days)

	Approximate Visit	Approximate Sampling
Visit 6 (Day 30 ±7 Days)	14 hours	12.5 hours
Visit 7 (Day 60 ±7 Days)	14 hours	12.5 hours

Visit 8 (Day 90 -3/+7 Days)	15 hours	12.5 hours

Approximate visit timeline:

Approximate time	Activity	Time relative to first IV sample
~07:00	Admission	T=0 -1:00
~07:15-07:45	Period for glucose stabilization and CGM calibration	T=0 -0:45 - -0:15
~08:00	First IV blood sample drawn	T=0 0:00
~08:00 – 13:00	For qualifying subjects, hypoglycemia challenge to achieve hypoglycemia target <60 mg/dL. • Sampling q 5 min when glucose ≤ 75 mg/dL. • Target 24 YSI values <75 mg/dL including 6 YSI values <60 mg/dL at q 5 min before rescue. • Subjects fed low glycemic meal.	T=0 0:00 – +5:00
~08:00 – 13:00	• Alternatively, for qualifying subjects, hyperglycemia challenge to achieve hyperglycemia to goal glucose >350 mg/dL. • Sampling @ 5 min when glucose ≥ 325 mg/dL, with a target duration of 1 hour. • Challenge may be stopped once 12 samples ≥325 mg/dL are collected.	T=0 0:00 – +5:00
~08:00 – 13:00	For those subjects not following a basal/bolus routine on MDI or CSII, glucose control will be free range.	T=0 0:00 – +5:00
~09:00	Fingerstick blood glucose	T=0 +1:00
~10:00	Fingerstick blood glucose	T=0 +2:00
~11:00	Fingerstick blood glucose	T=0 +3:00
~12:00	Fingerstick blood glucose	T=0 +4:00
~13:00	Fingerstick blood glucose	T=0 +5:00
~13:00-16:00	Recovery Period with meal/bolus and glucose stabilization	T=0 +5:00 - +8:00
~16:00-19:30	Free range glucose control	T=0 +8:00 - +11:30
~14:00	Fingerstick blood glucose	T=0 +6:00
~15:00	Fingerstick blood glucose	T=0 +7:00

Approximate time	Activity	Time relative to first IV sample
~16:00	Fingerstick blood glucose	T=0 +8:00
~17:00	Fingerstick blood glucose	T=0 +9:00
~18:00	Fingerstick blood glucose	T=0 +10:00
~19:00	Fingerstick blood glucose	T=0 +11:00
~19:30-20:30	Discharge preparation period	T=0 +11:30 - +12:30
~20:00	Blood draw for dexamethasone	T=0 +12:00
~20:30	Last IV blood sample drawn	T =0 + 12:30
21:00	Discharge	T=0 +13:00

The following procedures/instructions will be followed for accuracy (sampling) daytime visits at days 30, 60 and 90:

4.6.1 Pre-visit phone call

One to two days prior to the Accuracy (Sampling) Visit, site personnel will contact the subject to ensure the subject is in compliance with study device wear. Subjects may also be advised of the scheduled challenge type and will be given appropriate instructions regarding pre-visit medications and meals.

4.6.2 Device preparation

All Study devices will be time synchronized and checked for function as described in section 5.3.

4.6.3 Medications and Medical Supplies

Medications and medical supply status will be checked as described in Section 5.2.

4.6.4 Meals

Specific information regarding subject meals is described in Section 5.13. Food and drink will be controlled as required.

4.6.5 Subject Instructions prior to admission

Prior to admission, subjects should take morning medications and meals as usual as follows:

- If challenge subjects need to eat or take insulin for safety reasons, they should inform study staff of this information on arrival to the clinic.
- Subjects participating in hypoglycemia challenges should arrive fasted for 6 hours and should not take subcutaneous bolus insulin 3-4 hours previous to the challenge. Subjects should take their normal dose and timing of basal insulin.
- If subjects blood glucose is <80 mg/dL they should be instructed to eat a snack prior to

coming to the clinic, and be given specific instructions how to modify basal infusion until they arrive at the study site. Subjects may receive guidance from study staff trained in diabetes treatment regarding insulin and carbohydrate intake prior to the visit.

- Subjects should consume the food they would normally consume to treat or prevent hypoglycemia at the blood glucose level they feel is appropriate.

A clinician trained in the treatment of diabetes should also discuss and make recommendations about each subject's insulin regimen for the remainder of the day to prevent post-visit rebound hypoglycemia which can occur 12 hours later.

4.6.6 Subject Admission

The subject will arrive at the clinic during the day, no later than approximately 07:00 am and the following tests will be performed to confirm eligibility for participation in visits 6, 7 and 8:

- Hematocrit will be assessed using local lab or Point of Care testing device. Subject must be within reference range to participate in accuracy (sampling) visit.
- Female subjects of childbearing capacity will perform a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented.
- The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- The study team will confirm that the subject brought his/her personal insulin and insulin pump or injection supplies (as applicable) and regular medications. The subject will continue to use his/her diabetes treatment regimen throughout the admission. The subject will be rescheduled if he/she did not bring his/her regular medications or appropriate medications are not available at the clinic.
- Clinical staff to confirm that the subject is wearing the transmitters and that the transmitters and hand held device are in communication and functioning.
- The subject will be rescheduled if he/she did not bring his/her Transmitters and cannot make them available during the visit.
- If all admission readiness criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit.

4.6.7 Adverse events

Upon admission subject will be asked about any adverse events or changes in medication since the last study visit. The sensor insertion site will be examined. Adverse events including those associated with the insertion site will be documented on the appropriate eCRF.

4.6.8 Ketone testing

On arrival to the clinic, subject blood ketones should be evaluated from capillary blood using the ketone meter. If ketones are present, ketone testing should be repeated as described in Section 5.8 and subjects should be treated for ketones following ketone treatment guidelines Section 7.1.5.

4.6.9 SMBG testing

During in-clinic days, subjects should continue testing blood sugar using the study-supplied Subject SMBG Meter following the schedule for each visit (hourly except during overnight). For home use periods, it is requested that subjects test approximately 7 times per day (before meals, 2 hours after meals, and at bedtime). Subjects should test their blood sugar using the study supplied Subject SMBG Meter at least 2 times per day while participating in the study.

4.6.10 IV placement

Intravenous access appropriate for blood drawing and potential intravenous DW10 rescue will be established following the IV placement guidelines (Section 5.9)

4.6.11 Blood sampling for glucose measurement

Once IV access has been established, blood will be sampled for bedside reference glucose every 5-15 minutes per the Blood Sampling guidelines (Section 5.9).

4.6.12 Calibration (Visits 6, 7 & 8)

Subjects/clinicians will calibrate the system during the time period for glucose stabilization and will calibrate again approximately 12 hours later. The morning calibration reminder, adjusted through use of the HHD and mobile medical application will be set to approximately 12 hours after the evening calibration entry.

4.6.13 Glucose Challenges

Qualifying subjects will participate in hyperglycemia or hypoglycemia challenges during the times indicated in the visit timeline table. The intention of the hypoglycemia and hyperglycemia challenge is to safely manipulate the subject's blood glucose levels so that sensor performance can be evaluated over a wider range than might otherwise be observed. Details regarding the glucose challenges can be found in Section 5.12.

4.6.14 Observation subjects

Subjects with gastroparesis or those subjects unable to participate in glucose challenges will participate in the sampling sessions using free range glucose control.

4.6.15 Dexamethasone blood draw

Blood sample will be drawn at the end of the visit prior to discharge for Dexamethasone measurement. All samples will be collected and processed as described in the operations manual.

4.6.16 Discharge instructions

The discharge procedure will occur upon completion of IV blood sampling. Please refer to section 5.14 for discharge instructions.

4.6.17 Estimated Total Blood Volume

Approximately 59 blood samples will be obtained throughout the course of the respective visits in addition to the blood sample required for dexamethasone analysis and fingersticks taken. The maximum estimated amount of blood estimated for each visit is 65 ml.

4.6.18 Estimated Visit Duration

The total duration of the inpatient visit is approximately 14-15 hours. The study time may be extended for glucose stabilization prior to discharge.

4.7 Visit 8, Day 90 Sensor Removal

Sensors will be removed after glucose sampling is complete approximately 90 days post insertion, or when the designated time for Sensor removal is reached. If designated time for sensor removal is reached prior to Visit 8, the sensor will be removed at the subject's next scheduled visit or at an unscheduled visit. All Visit 8 procedures will be performed as applicable. Removal of the sensor may also be scheduled after Visit 8 if more convenient for subject and clinicians (but no longer than 100 days post insertion) provided that the Subject's transmitters and HHD have been taken from the Subject at the conclusion of Visit 8. Sensor removal before or after Visit 8 will not be considered a protocol deviation provided that removal is performed prior to 101 days post insertion and Visit 8 removal procedures/activities are followed. Subjects will be asked to complete a questionnaire regarding their experiences at the end of sensor wear period.

Blood samples will be drawn prior to sensor removal for Dexamethasone measurement. All samples will be collected and processed as described in the operations manual.

Prior to Sensor removal, the Investigator will assess the Sensor location, including by process of palpation. The Sensor will be removed following the procedure in the Eversense CGM Sensor Insertion and Removal Instructions and the Study Operations Manual.

The removed Sensors will be handled in compliance with institution/regulatory requirements for biomedical waste, and will be returned following Senseonics instructions, using the provided Biohazard Return Kit.

4.8 Visit 9 –Follow-up Visit (10 days following sensor removal. Window: sensor removal date +7 to 17 Days)

The healing of the Sensor sites will be evaluated at this planned final visit. If Sensors are removed at a time other than Visit 8, the Follow-up Visit will occur in approximately 10 days after Sensor removal.

If there is a concern by the investigator about healing of the Sensor sites, the subject will be asked to return in approximately 10 days, and followed until resolution. Any adverse event would be reported.

Subject will exit the study after the Follow-up Visit is completed as above. Subjects will continue to follow their diabetes care routine according to their health care provider recommendations.

5 GENERAL CONSIDERATIONS FOR STUDY VISITS

5.1 Definition of Enrollment

A subject is considered enrolled in the clinical trial after he or she has provided informed consent.

Subjects who fail one or more of the eligibility criteria are considered screen failures. Subjects who withdraw consent or are withdrawn by the investigator after enrollment and prior to the first Sensor insertion attempt are “withdrawn prior to Sensor insertion” and are withdrawn from the study without data acquisition. A listing of screen failures and “withdrawals prior to Sensor insertion” subjects including the reason for study exit will be reported.

Subjects who begin a first Sensor insertion procedure (defined as injection of local anesthetic) remain enrolled in the study and will be analyzed as evaluable subjects per the description of study populations in Section 11 Statistical Methods.

5.2 Medications and medical supplies

All medications and medical supplies required for the Clinical Research Center (CRC) hypoglycemia and hyperglycemia treatment protocols will be readily available at the time of subject treatment including a code cart. The subject will be rescheduled if he/she did not bring his/her required medications or appropriate medications are not available at the clinic.

5.3 Device setup

5.3.1 Device Calibration

Prior to subject blood sampling, the CRC study equipment (YSI glucose analyzer, ketone meter and study-supplied Subject SMBG Meter) will be checked for proper function and the appropriate quality controls will be run per the manufacturer's guidelines and/or Study Operations Manual, as appropriate.

5.3.2 Time sync

At each study visit the date and time on all study devices (i.e. study clocks, laptop(s), Subject SMBG Meter, Reference instrument and Senseonics Continuous Glucose Monitoring System) will be synchronized at the start of the visit to the Official US Time using www.time.gov or to an equivalent atomic clock. The details of the time and date synchronization are described in the Study Operations Manual.

The study devices do not all automatically adjust for daylight savings time. Subjects should not adjust the study device times on their own – they should wait until someone at the clinic can adjust the time so any offsets can be documented in order to reconcile the data.

5.3.3 Downloading devices

The study issued Subject SMBG meter and the sensor transmitters will be downloaded at the end of each sensor accuracy visit (visits 3-8) or at any unscheduled visit as appropriate. Sensor transmitter data will also be uploaded to a data management system to monitor calibration compliance.

5.4 Measurement Devices – Maintenance/Control Testing

At device disbursement or as appropriate, study equipment (bedside YSI glucose analyzer, ketone meter and study-supplied (SMBG) meter) will be checked for proper function and the appropriate quality controls will be run per the manufacturer's guidelines.

5.4.1 Bedside YSI

The primary instrument for plasma glucose measurements is the YSI glucose analyzer (2300 Stat Plus Glucose & Lactate Analyzer, Yellow Springs Instruments, Yellow Springs, OH, USA). Manufacturer instructions for operation, calibration, quality control, and maintenance will be followed.

5.4.2 Subject SMBG Meter

The study will supply and use a widely-used, commercially available FDA-approved self-monitoring blood glucose (SMBG) meter and strips. Control solution testing of the meter/strips will be verified with the control solution(s) specific to the meter and strips. The tested control solutions must read within the established range on the glucometer strips per

manufacturer labeling in order to be used in the study. Manufacturer instructions for operation and quality control will be followed. Subjects will be advised to perform control solution testing each time a new package of strips is deployed, or any time the subject suspects improper performance of the meter.

5.4.3 Ketone meter

The study will supply and use an FDA-approved self-monitoring ketone meter and strips (Abbott Precision Xtra or similar), which will measure β-hydroxybutyrate (β-HOB). Ketone meters will remain at the clinical site (not disbursed to the subject). Calibration of the ketone meter will be verified with the control solution(s) specific to the meter and strips. The tested control solutions must read within the established range on the strips per manufacturer labeling in order to be used in the study. Manufacturer instructions for operation and quality control will be followed.

5.5 Senseonics Continuous Glucose Monitoring (CGM) System Calibration

The Senseonics Continuous Glucose Monitoring (CGM) System will be calibrated and maintained per Eversense CGM User Guide. After the initialization period (approx. 30 hours after sensor insertion), the system enters the Daily Calibration phase. For this study, subjects should follow the recommendations below:

5.5.1 At home

During periods of home use, it is recommended to calibrate the Senseonics CGM System using SMBG values from the study-supplied meter two times per day. Calibration is best done when glucose is neither rapidly rising nor falling. Subjects can set morning and evening daily calibration reminders and Subjects will be periodically prompted by the Senseonics CGM System until a calibration point is entered.

5.5.2 In clinic

During the in-clinic sampling sessions, subjects will be instructed to calibrate at the start of the sampling session and then approximately 12 hours later unless in the initialization phase.

5.6 Use of Study Devices for Diabetes Treatment

For the duration of the study, all diabetes care decisions will be based on reference blood glucose values or SMBG as appropriate, rather than Senseonics CGM System results.

5.7 Fingersticks

During the study, while at home and in the clinic, it is requested that all subjects test their blood sugar using the study supplied SMBG meter approximately 7 times per day (before meals, 2 hours after meals, and at bedtime). Subjects should test their blood sugar using the study supplied Subject SMBG Meter at least 2 times per day while participating in the study.

All fingersticks for capillary blood glucose testing will be preceded by hand washing (with soap, warm water and a dry towel), or by using an alcohol swab and allowing the area to air dry.

5.8 Ketones

Ketone (β-hydroxybutyrate (β-HOB)) measurements will be made using a study supplied FDA-approved self-monitoring ketone meter and strips as described in 5.4.3. Subject blood ketones should be evaluated from capillary or venous blood using the ketone meter while in the clinic for sensor insertion and accuracy (sampling) visits at the following times:

- On arrival to and at discharge from the clinic
- Glucose ≥300 mg/dL (measure approximately within 20 minutes of the first glucose reading >300 mg/dL and repeat approximately every 60 minutes until < 300mg/dL)
- Ketones ≥0.6 mmol/L (repeat approximately every 60 minutes until < 0.6 mmol/L)
- Subject has nausea, vomiting or abdominal pain regardless of glucose level.

Treatment guidelines for ketones can be found in section 7.1.5.

5.9 IV/Blood Draw Guidelines

5.9.1 IV Placement/Setup

IVs for blood sampling may be placed in the arm or hand. IV Access will be maintained during the sampling portion of the study for blood sampling and for the treatment of severe hypoglycemia or hyperglycemia during the study. If an IV fails, a reasonable effort should be made to replace it.

It is advised that sites use a heating pad in order to help keep IV sampling sites patent and improve blood flow.

Sites will be advised to use a dual stopcock closed-loop or single stopcock blood-wasting technique, as long as site personnel are cognizant of the following:

- The single-stopcock technique has a lower risk of diluted samples, but sites must take care not to exceed the protocol total blood loss limit of 475 ml in any 8-week period.
- Please note that when calculating waste volume to consider the volume of saline in the system that is drawn when clearing the line. This could include the extension set (0.2 ml), stopcock (0.2ml), and cannula (0.1 ml). Therefore a 1.5 ml “waste” draw actually contains 1.0 ml blood.

5.9.2 Timing of blood sampling

Blood will be sampled every 5-15 minutes, dependent on the value of the previous sample according to the following ranges:

- BG ≥ 325 mg/dL: every 5 minutes (+/- 2 minutes)
- BG >75 mg/dL and < 325 mg/dL: every 15 minutes (+/- 2 minutes)
- BG ≤75 mg/dL: every 5 minutes (+/- 2 minutes)

Additional samples may be drawn for YSI glucose analysis as needed for patient safety or to recheck a suspected erroneous value (e.g. dilute sample).

In the event of loss of IV access or loss of functional YSI and need for continued subject monitoring, glucose measurements will be made on capillary whole blood using the Subject SMBG meter as needed. These values will not be included in the study data set, but will only be used for subject treatment decisions.

Samples missed due to loss of IV access or loss of functional YSI will not be considered protocol deviations.

5.9.3 Sample volume

Approximately 1.0 ml IV blood samples will be collected (after saline is cleared from sampling apparatus) in sample containers with an appropriate anticoagulant additive (BD Microtainer K2E tubes (REF 365955) or Sarstedt Monovette with K2E (REF 06.1664.001) or similar) for analysis.

5.9.4 Centrifuge

Centrifuge sample to sufficiently separate the plasma, approximately 30 seconds in StatSpin Express 2 (or similar) centrifuge (8500 rpm).

Samples centrifugation should begin as soon as possible after the blood draw (within a maximum of 3 minutes). Spun samples should be prepared, as defined in the Study Operations Manual.

*More detailed guidelines are included in the Study Operations Manual.

5.10 Sensor Replacement

For subjects with one sensor (participating in the subset), if sensor failure is suspected, sensor will not be replaced.

For subjects with two sensors, suspect failure of the primary sensor (the sensor for which calibration fingersticks are entered), the secondary sensor in the contralateral arm will become the primary sensor. Subjects will be instructed to replace the Gen 2 transmitter with

the Gen 1 transmitter in the contralateral arm. The suspect failed primary sensor will not be replaced and will be removed at the end of the study. Subjects will proceed with the next regularly scheduled visit. For the suspect failure of the secondary sensor, the sensor will be removed at the end of the study and not replaced.

5.11 Sponsor Presence at Visits

One or more technical representatives of the sponsor may be present during clinic visits under supervision of the Clinical Investigator.

5.12 Glucose challenges

The intention of the hypoglycemia and hyperglycemia challenge is to safely manipulate the subject's blood glucose levels so that sensor performance can be evaluated over a wider range than might otherwise be observed. The intentions are to induce the following:

Hypoglycemia challenge

Range	Duration (approximate)	Estimated number of paired points per subject per challenge
<60 mg/dL	30 minutes	7
<75 mg/dL	120 minutes (including 30 minutes <60 mg/dL)	25

Hyperglycemia challenge

Range	Duration (approximate)	Estimated number of paired points per subject per challenge
>325mg/dL	60 minutes	13
>180 mg/dL	120 minutes (including 60 minutes >325 mg/dL)	17

It is the intent of this protocol to induce a hyperglycemic protocol upon admission to the clinic for visits 3, 4 & 5. Subjects participating in hyperglycemia challenge soon after admission should not take subcutaneous bolus insulin approximately 3-4 hours prior to the challenge. Subjects should take their normal dose and timing of basal insulin. If challenge subjects need to eat or take insulin for safety reasons, they should inform study staff of this information on arrival to the clinic.

5.12.1 Subject eligibility

Subjects with gastroparesis will not be eligible to participate in glucose challenges. Subjects not on insulin therapy will not be expected to undergo hypoglycemic challenges. Eligible subjects will be required to participate in glucose challenges.

5.12.2 Challenge periods (Visits 3, 4 & 5)

Subject blood glucose level as measured by the first blood glucose sample reading will determine whether or not the subject will begin the hyperglycemia challenge. If blood glucose is <180 mg/dL the glucose sampling period may be delayed until blood glucose is brought into range.

5.12.3 Determining which challenge to choose (Visits 6, 7 & 8)

Subject BG level as measured by the first blood glucose sample reading will determine whether or not the subject will participate in the hypoglycemia or hyperglycemia challenge on that study day, according to the following table:

Glucose level	Challenge
<180 mg/dL	Hypoglycemia challenge
≥180 mg/dL	Hyperglycemia challenge

5.12.3.1 Hyperglycemia Challenge Guidelines

Glucose level	Insulin administration	Glucose administration (challenge initiation)	Duration* (Approx.)	Safety
<180 mg/dL	None. Glucose sampling period may be delayed until blood glucose is brought into range (>180 mg/dL).	Administer carbohydrates to gradually bring blood glucose into range (>180 mg/dL).		
180 mg/dL to 325 mg/dL	None	Administer meal of known carbohydrate content (and SQ insulin if appropriate, see mixed meal examples in the table in 5.11), targeting glucose level of 350 mg/dL based on subject's insulin/carbohydrate ratio. Do not withhold insulin >2-3 hours.	2 hours (including approx, 60 minutes 325-400 mg/dL)	Check/treat for ketones if subject BG >300mg/dL. Treat ketones according to the Hyperglycemia and Ketone Treatment Section 7.1.5

Glucose level	Insulin administration	Glucose administration (challenge initiation)	Duration* (Approx.)	Safety
>325mg/dL to 400 mg/dL	After approximately 60minutes in this range and achieving the targeted number of points, administer SQ fast-acting insulin targeting 120 mg/dL based on subject's insulin sensitivity ratio. Insulin may not be delivered or repeated unless approximately 3 hours after previous dose.	None	60 minutes	Check/treat for ketones if subject BG >300 mg/dL. Treat ketones according to the Hyperglycemia and Ketone Treatment Section 7.1.5
>400 mg/dL	Administer SQ fast-acting insulin targeting 120 mg/dL based on subject's insulin sensitivity ratio. Insulin may not be delivered or repeated unless 3 hours after previous dose.	None		Check/treat for ketones if subject BG >300 mg/dL. Treat ketones according to the Hyperglycemia and Ketone Treatment Section 7.1.5

*Once Hyperglycemia challenge durations have been met (120 minutes >180 mg/dL including 60 minutes >325 mg/dL), the challenge should be ended by administering SQ fast-acting insulin targeting 120-150 mg/dL based on subject's insulin sensitivity ratio. Once the subjects' BG is normal, glucose control will be free range. If additional carbohydrates are required to reach challenge goals, they may be administered.

5.12.3.2 Hypoglycemia challenge guidelines

Glucose level	Insulin administration (challenge initiation)	Glucose administration	Duration* (Approx.)	Safety
<60 mg/dL	None	After 30 minutes and targeted points achieved, treat	30 minutes	If subject is unable to ingest glucose orally, IV

Glucose level	Insulin administration (challenge initiation)	Glucose administration	Duration* (Approx.)	Safety
		hypoglycemia using glucose tablets (15 g. and check in 15 minutes, repeat) until BG >60 mg/dL		dextrose may be used. Glucagon will be available for emergency.
60 – 75 mg/dL	None	None	120 minutes (including 30 minutes below 60 mg/dL)	
> 75 but <180 mg/dL	SQ fast-acting insulin to be delivered targeting 60 mg/dL based on subject's insulin sensitivity ratio. Bolus insulin may not be delivered or repeated unless 3 hours after previous dose.	None		

*Once Hypoglycemia challenge durations have been met (120 minutes <75 mg/dL including 30 minutes <60 mg/dL), the challenge should be ended by inducing a controlled raising of the subject's BG to the normal range (75-120 mg/dL) using glucose tablets or food. Once the subjects BG is normal, glucose control will be free range.

5.13 Example Meal Choices

The following meal choices are examples that may be used during clinic visits 3-8.

Meal Choice 1	Description	Portion Size	Carbohydrate (g) per portion	Sugar (g) per portion	Protein (g) per portion	Fat (g) per portion	Fiber (g) per portion
6" sub roll or flat bread Acceptable substitute: 2 large slices of whole grain sandwich bread	Ex: Subway wheat roll or multigrain flatbread	71g	40	5	7	2	5
4 oz. ham, turkey, chicken, beef (this would be "double	Subway or similar deli cuts	112g	4	1	28	2-8g depending upon choice	0

Meal Choice 1	Description	Portion Size	Carbohydrate (g) per portion	Sugar (g) per portion	Protein (g) per portion	Fat (g) per portion	Fiber (g) per portion
meat" for subway 6" sub)							
1 oz. cheese	Ex: Swiss, monteray jack, provolone, American, cheddar	28g	0	0	6	10	0
Lettuce, 2-3 slices tomato Additional vegetables or small salad acceptable	-	41	2	0	0	0	1
1 Tbsp mayonnaise, 2 T lite mayo or 1 Tbsp oil	Varies	15	0	0	0	12	0
1 1/2 oz. chips – whole grain if possible	Ex: Sunchips at Subway	43	29	3	4	9	3
1 ½ oz cookie - **OR-**	Ex: Choc Chip at Subway	45	30	18	2	10	1
Medium piece of fresh fruit or equivalent	Ex: 2 packages of Subway apple slices, 8" banana	Varies	30	26	0	0	4
Water or other zero calorie beverage	Ex: water, diet coke	8-16 oz.	0	0	0	0	0
			105	27-35	45-47	35-51	10-13

Meal Choice 2	Description	Portion Size	Carbohydrate (g) per portion	Sugar (g) per portion	Protein (g) per portion	Fat (g) per portion	Fiber (g) per portion
6 oz. Grilled Chicken	Ex: Applebee's "Create Your Masterpiece Menu" Grilled Chicken Breast	168g or 6 oz.	2	0	42	4	0
9 oz baked potato – seasoned 2 tsp butter or margarine	Ex: Applebees "Choice of Sides" Baked Potato	252g or 9 oz.	41	0	6	24	3
Steamed broccoli – seasoned lightly with butter, margarine or oil	Ex: Applebees "Choice of Sides" Steamed Broccoli	84g	2	0	2	8	3

Meal Choice 2	Description	Portion Size	Carbohydrate (g) per portion	Sugar (g) per portion	Protein (g) per portion	Fat (g) per portion	Fiber (g) per portion
Dinner Roll – 2 oz.	Ex: Applebee's kid's sized burger roll	56g	30	4	5	1	0
1 tsp butter or margarine (for roll) – optional	-	1tsp	0	0	0	9	0
Medium piece of fresh fruit or equivalent	1 8" banana 2 c. melon	Varies	30	26	0	0	4
			105	30	55	38-46	10

Low Glycemic Breakfast*	Description	Portion Size	Carbohydrate (g) per portion	Sugar (g) per portion	Protein (g) per portion	Fat (g) per portion	Fiber (g) per portion
2 slices whole grain toast	Preferably Whole grain	28g	30	4	5	-	4
1 tsp butter or margarine	-	1 tsp	0	0	0	9	0
2 Scrambled Eggs or 3 Egg Whites – prepared with up to 1 tsp. fat Optional: Cheese/veggies mixed into eggs	-	2 eggs ¼ c.	0 1	0 0	14 2-7	5-8 0-5	0 0
Coffee – if desired	Limit to 10 oz. for caffeine	10 oz.	0	0	0	0	0
Non-calorie sweetener	-	User preference	-	-	-	-	-
Up to 2 Tbsp milk or cream	Milk can be whole, 1%, 2% or skim	2T	Negl.	0	Negl.	0-4g	0
			30-31	4	21-28	14-34	4

*Overall Guidelines: Limit Carbohydrate to 30g. No fruit juice, no milk beyond any used in coffee. Fruit acceptable up to 15g portion.

5.14 Discharge instructions – Sensor accuracy visits

The discharge procedure will occur upon completion of visit related activities. Blood glucose (either SMBG or YSI) and ketone measurements will be assessed. If the glucose level is<75 mg/dL or ≥300 mg/dL, corrective action will be taken by the investigator as below:

- If plasma glucose is <75 mg/dL, carbohydrates or other medically necessary and appropriate interventions will be administered to raise the glucose to ≥75 mg/dL.
- If plasma glucose is >300 mg/dL, fingerstick ketones will be checked and the Inpatient Hyperglycemia and Ketone Treatment guidelines will be followed.

The subject will be discharged once plasma glucose is:

- 100-300 mg/dL and stable or rising in this range for 2 consecutive glucose measurements at least 15 minutes apart, and ketone is ≤0.6 mmol/L; or
- >75-100 mg/dL and rising for 2 consecutive glucose measurements at least 15 minutes apart, and ketone is ≤0.6 mmol/L.
- Subjects should not be released if BG is <100 mg/dL and not rising.
- Site will document any adverse events that may have occurred during the visit.

**These measurements should be taken after approximately 60-90 minutes since the last administration of fast-acting bolus insulin.*

Additional inpatient time for BG stabilization will not be considered an adverse event or protocol deviation.

Subjects will be provided a standard meal or snack as necessary during the last hour of visit prior to release to prevent post-discharge hypoglycemia. Snacks will be available in the clinic for subjects to take with them on the ride home.

A clinician trained in the treatment of diabetes should also discuss and make recommendations about each subject's insulin regimen for the remainder of the day to prevent post-visit rebound hypoglycemia which can occur 12 hours later.

5.15 Photograph/Videography

The procedure for inserting or removing the sensors may be photographed and/or recorded on video after receiving subject authorization in writing. Only the area immediately nearby the sites will be photographed and/or recorded and subjects will not be identifiable.

6 CLINICAL LABORATORY EVALUATIONS AND ESTIMATED BLOOD VOLUMES

Standard clinical laboratory analysis equipment, procedures and quality control will be used for all laboratory evaluations in this clinical trial. Blood samples will be drawn at Visits 1 through 8 (or sensor removal as appropriate) for laboratory dexamethasone measurement. Additionally designated subjects across the study will have blood samples drawn for dexamethasone

measurement 3 times on the insertion date, and on each day between visits 3 and 4. Samples for hemoglobin A1C measurement will also be collected at Visit 1, 6, 7 and 8. Hematocrit will be assessed using local lab or Point of Care testing device.

Total Estimated Blood Loss

Maximum estimated blood loss over the study is 504 mL.

7 SUBJECT SAFETY, STOPPING RULES, AND STUDY EXIT

7.1 Diabetes and Safety Considerations during Clinic Visits

Diabetes care in the Clinic Visit will be the responsibility of the Investigator and appropriately delegated staff. As diabetes self-management is an integral part of diabetes care, the Investigator may work closely with the Study subject, when appropriate, to determine the best approach, however the ultimate responsibility lies with the Investigator.

7.1.1 Medical oversight

There will be staff trained in emergency response, and there will be an EKG and emergency cart available at the site at all times. Site-specific safety guidelines will be utilized for subject safety management during periods of hyperglycemia (including monitoring blood ketones) and hypoglycemia. Study staff (MD, DO, or NP who has experience in diabetes management) will also be immediately available at all times during hypoglycemia and hyperglycemia challenges. A nurse, nurse practitioner, or physician will be at the bedside or on the unit throughout the entire visit.

7.1.2 Sensor Site

The sensor insertion sites will be assessed (visually, as well as by palpation, and by eliciting Subject history) at each clinic visit, and the Subject will be instructed to call the clinic if signs or symptoms of irritation or infection (increased temperature, pain, redness, warmth, swelling, or purulence) are observed at any time. Sensor site infections are to be treated with antibiotics, either topical or oral.

At any time during the study if the study physician determines that there is an infection at the sensor insertion site that has not responded to treatment within 3 days, study procedures other than safety procedures will be stopped, and the sensor will be removed. In the event of an insertion site infection and sensor removal, the subject will be withdrawn from the study and not replaced.

7.1.3 Other Considerations and Safety Assessments

- An assessment and documentation of adverse events occurring in clinic and during home use will be on-going.

- Urine pregnancy testing (for women of childbearing potential) will be performed at the start of visits 1 through 8 with study exit as described in section 7.2.4 if the Subject is pregnant.
- Subjects will arrive at Clinic Visits, having followed their usual diabetes care, including insulin dosing and food.
- Subjects must not be afebrile in the 24 hours prior to Clinic Visits 2-8.
- IV access is required during Clinic Visits 3 through 8. In the event of loss of IV access, glucose measurements may be made using Subject SMBG meter or alternate sampling method for subject care. Investigator may determine when further attempts at IV access will cease.
- In order to prevent adverse effects that may occur as a result hyperglycemia challenge, unlimited sugar free oral fluids should be provided to subjects to prevent dehydration secondary to hyperglycemia.
- "Insulin stacking" should be avoided. No bolus insulin (SQ or IV) should be administered less than approximately 3 hours after a previous SQ fast-acting insulin bolus dose or less than approximately 1 hour after a previous IV fast-acting insulin bolus dose (unless necessary to treat DKA, in which case, IV fast-acting bolus insulin may be administered less than 3 hours after a previous SQ fast-acting insulin bolus dose as per the protocol of the institution).

7.1.4 Hypoglycemia

The Subject will be asked to alert the study team anytime he or she experiences symptoms of hypoglycemia (i.e., shakiness, dizziness, sweating, headache, moodiness, difficulty concentrating, or the Subject's usual symptoms of hypoglycemia). The symptoms will be confirmed by Subject SMBG Meter and/or YSI.

Intravenous access is to be maintained during the Clinic Visit and available for hypoglycemia treatment as indicated. Glucagon by injection and IV dextrose will be available at the site and may be used as clinically indicated. A heating pad or heating chamber may be used during the session to minimize potential for occlusion or to enable the insertion of the port.

YSI and/or Subject SMBG meter BG will be checked every 5 minutes until glucose >75 mg/dl.

7.1.4.1 Guidelines for treatment for hypoglycemia

During hypoglycemia challenge or monitoring period, site will follow section 5.12 hypoglycemia challenge table. Subject safety prevails and Investigator may treat for hypoglycemia when clinically indicated.

Subjects will be treated for hypoglycemia as appropriate according to the following table:

Glucose level	Glucose administration	Safety
<60 mg/dL	Treat hypoglycemia as appropriate using oral carbohydrates such as glucose tablets or juice (~15 g. and check glucose in 15 minutes minimum, repeat) until BG >60 mg/dL	If subject is unable to ingest glucose orally, IV dextrose (~2-3 mL/kg D10 intravenous or up to 30 ml D50%) may be used. Glucagon will be available for emergency.
60 – 75 mg/dL	Treat hypoglycemia as appropriate using oral carbohydrates such as glucose tablets or juice (~10 g. and check glucose in 15 minutes minimum, repeat) until BG >60 mg/dL	

- Glucose <60 mg/dL will be treated orally with fast acting carbohydrate as tolerated by the subject and as needed until a glucose level of ≥75 mg/dL is achieved.
- Risk for severe hypoglycemia is defined as any of the following situations:
    - Glucose <50 mg/dL
    - The subject is unable to cooperate with oral treatment of hypoglycemia
    - The glucose is dropping at a rate that may not respond adequately to oral treatment
    - The subject experiences symptoms of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior)
    - The subject experiences symptoms of severe hypoglycemia (i.e. hypoglycemic seizure or loss of consciousness)

- In the event that there is NO intravenous access and the subject is at risk for severe hypoglycemia (as defined above), the subject will be treated with 1 mg of glucagon subcutaneously or intramuscularly.
    - The drug will be reconstituted and administered per package insert/instructions.
    - Glucagon may be repeated as needed every 20 minutes to achieve glucose level ≥75 mg/dL. Once the subject is able to consume oral treatment, the subject will be treated orally with fast acting carbohydrate as needed until a glucose level of ≥75 mg/dL is achieved. Orange juice and milk will be avoided after glucagon administration.
    - Attempts will be made to reestablish intravenous access.
- The accuracy (sampling) visit will be stopped if the subject experiences a hypoglycemic seizure or loss of consciousness and only safety procedures will be continued. The study physician or nurse practitioner will take control over glucose sampling decisions in order to stabilize the subject's glucose between 100-300 mg/dL and determine the appropriate subject disposition (i.e. home or medical facility).

7.1.5 Hyperglycemia and Blood Ketone Monitoring

The Subject will be asked to alert the study team anytime he or she notes symptoms of hyperglycemia (i.e. thirst, increased urination, or other symptoms). A glucose level will be confirmed by YSI or Subject SMBG meter.

If glucose >400 mg/dl and no symptoms and no ketones, the cause of the hyperglycemia will be investigated and treated as appropriate by the Investigator. Fingerstick blood ketones, using commercially available ketone meter will be monitored if blood glucose ≥300 mg/dl and hourly until resolved.

If blood ketones ≥ 0.6 mmol/L; subject participation in glucose challenges will be stopped for the day. Appropriate care will be provided, including fluids and insulin as determined by Investigator. Standard-of-care troubleshooting for insulin pump users will take place, including change of infusion set if indicated and insulin by injection if indicated.

During hyperglycemia challenge or monitoring period, site will follow section 5.12 hyperglycemia challenge table. Subject safety prevails and Investigator may treat for hyperglycemia when clinically indicated.

7.1.5.1 Treatment Guidelines for Hyperglycemia and Ketones

Subjects will be treated for hyperglycemia according to the following table:

Ketone				
BG		**<0.6**	**0.6-1.5**	**>1.5**
	<300		• Glucose challenge will be stopped • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ insulin targeting 120mg/dL using subject's insulin sensitivity factor	• Accuracy (Sampling) visit will be stopped, only safety procedures will continue • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ insulin targeting 120mg/dL using subject's insulin sensitivity factor
	>300	• Ketone testing will be repeated hourly until BG <300	• Glucose challenge will be stopped • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ insulin targeting 120mg/dL using subject's insulin sensitivity factor • Continue monitoring until BG <300	• Accuracy (Sampling) visit will be stopped, only safety procedures will continue • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ insulin targeting 120mg/dL using subject's insulin sensitivity factor • Continue monitoring until BG <300

- If the subject's glucose is >300 mg/dL or ketone level is ≥0.6 mmol/L on admission, the subject will be stabilized per the procedures above. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and ketone measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team). Blood sample collecting and analysis on YSI will continue during this time.

- Subsequently, glucose >300 mg/dL for >2 hours or glucose ≥400 mg/dL at any time will prompt discontinuation of the Hyperglycemia challenge.

- Ketones will be assessed hourly while the glucose is ≥300 mg/dl or the ketone level is ≥0.6 mmol/L.

- If the glucose is >300 mg/dL and ketone level is <0.6 mmol/L, corrective action will be taken only after it has been approximately 60-120 minutes from the last subcutaneous insulin dose. Specifically, the subject will be asked to bolus with his/her pump or deliver by injection an amount of corrective insulin that will bring him/her to a target glucose of 120 mg/dL.

- If the ketone level is ≥0.6 mmol/L, the cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). Additional insulin may be administered either via insulin syringe or via a new pump site. The amount of insulin administered will be calculated using the subject's insulin sensitivity factor and a target glucose of 120 mg/dL.

- Insulin treatment for hyperglycemia or ketones should be done using the subject's own insulin. In the event that the subject's own insulin appears to be compromised (not having the expected effect on the subject's blood glucose), appropriate insulin (based on the subject's normal insulin type and concentration) provided by the site may be used.

If the ketone level is ≥1.5 mmol/L, the accuracy (sampling) visit will be stopped and the study MD or NP will take control of the subject's insulin dosing. The cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). If the subject's home parameters are not felt to be working adequately due to hyperglycemia, ketonemia, or other factors (e.g. intercurrent illness), the study MD or NP will administer corrective insulin either via insulin syringe or via a new pump site using an ISF determined to be appropriate for the setting and a goal glucose of 120 mg/dL. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and ketone measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).

7.2 Subject Stopping Rules

7.2.1 Stopping challenges

Glucose challenges will be stopped and subject will enter free range glucose control if:

- Subject meets the challenge completion criteria:
    - Hypoglycemia challenge - approximately 120 minutes <75 mg/dL including 30 minutes <60 mg/dL
    - Hyperglycemia challenge – approximately 120 minutes >180 mg/dL including 60 minutes >325 mg/dL
- Subject requests to end the challenge due to discomfort (desires food and/or insulin)
- Subject ketone measurement ≥0.6 mmol/L and glucose is >300 mg/dL

These subjects will be eligible to continue participating in challenges at future accuracy (sampling) visits. Blood sample collecting and analysis on YSI will continue during this time.

7.2.2 Stopping challenges – no reattempt

Glucose challenges will be stopped and subject will enter free range glucose control if:

- Subject develops significant nausea, vomiting, abdominal pain, chest pain, or develops ketoacidosis
- The subject is unable to cooperate with oral treatment of hypoglycemia
- The glucose is dropping at a rate that may not respond adequately to oral treatment
- The subject experiences symptoms of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior)

Subjects may continue to participate in the study, including future accuracy (sampling) visits but only under observation; participation in future glucose challenges will not be allowed.

7.2.3 Stopping accuracy (sampling) visit

During accuracy (sampling) visits, study procedures other than those required for subject safety will be stopped for that day if any of the following occur:

- The subject had a serious adverse event that is deemed either related to study or in the investigator's opinion requires stopping
- Medical intervention is required to treat severe hypoglycemia (seizure, unconsciousness, etc.)
- Adequate intravenous access cannot be maintained
- The YSI and back-up YSI, (if available), stop functioning and neither can be re-established within 2 hours.
- Subject requests to stop
- Investigator determines it is in Subject's best interest to stop the accuracy (sampling) visit

7.2.4 Subject withdrawal

Subjects will be withdrawn from the study if:

- Subject is noted to be pregnant at any Visit.
- The subject may withdraw if he/she had a serious adverse event that is deemed either related to study device or procedures.

- The subject experiences symptoms of severe hypoglycemia (i.e. hypoglycemic seizure or loss of consciousness)
- Subject experiences DKA (related to the use of the study device) during home use
- Subject voluntarily withdraws from study
- There is an infection at the sensor insertion site that has not responded to treatment within 3 days
- Subject needs an MRI and Sensor is removed and not replaced.
- Investigator determines it is in Subject's best interest to withdraw.
- Subject is lost to follow-up
- Subject dies

7.2.5 Study Exit

A Subject's participation is considered complete after Visit 9 (or Follow-up Visit). A Subject may choose to withdraw at any time without adverse effect on their care. The subject will continue with their medical follow-up, according to standard-of- care. The reason for study withdrawal will be documented.

In the event that a subject withdraws from the investigation and is lost to follow-up, the Investigator will make all reasonable efforts to locate a Subject and encourage Subject to return for Sensor removal. If a subject is lost to follow-up, three separate telephone calls should be made to attempt to schedule a follow-up visit or obtain follow-up information. All attempts and contacts should be documented in the source documents. The subject's Primary Care Physician may also be contacted as stated in the Informed Consent Form. If the Subject does not respond to the three telephone calls, then the Investigator will send a certified letter to the Subject. The Subject will be considered lost to follow-up if this communication is unsuccessful.

7.2.6 Replacement of Subjects

Subjects who exit the study prematurely may not re-enter the study, and will not be replaced.

7.3 Study Stopping Rules

Senseonics may choose to suspend or prematurely terminate the investigation for the following reasons:

- Subject safety issue
- Production limitation

- Administrative decision

The Medical Monitor will review adverse events on a scheduled periodic basis as outlined in Section 13.13. In the case of device-related serious adverse events, the Medical Monitor will consult with the Sponsor and Principal Investigator if appropriate to ensure that the necessary steps are taken to protect the safety and well- being of the Subjects.

The study may be suspended for subject safety reasons. If two or more subjects are stopped (subject withdrawal per section 7.2.4) for the same adverse event related to device, and/or insertion/removal procedure, then the associated portion of the study should be suspended to allow for an investigation. For example, if two subjects are stopped due to infections that do not respond to treatment within three days, new sensor insertions should be suspended while the root cause is investigated.

In the event that that study is stopped, the Investigator will promptly inform the Subjects and ensure appropriate therapy and follow-up, including Sensor removal. Additionally the investigator will promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities will be informed according to local regulations.

7.4 Termination of Investigator or Investigational Site

Senseonics reserves the right to terminate an investigator/investigational site for any of the following reasons, which are considered major deviations:

- Failure to secure subject informed consent including protection of personal data prior to enrollment
- Failure to report unanticipated adverse device effects and serious adverse events to Senseonics and to the IRB/ EC within its required reporting time after learning of the event
- Repeated investigational plan deviations
- Loss of or unaccounted for investigational product inventory.

8 RISK AND BENEFIT ANALYSIS

8.1 Potential Benefits

There will be no direct benefit to the subjects participating in the investigation other than the knowledge that they are contributing to the overall advancement of medical and scientific knowledge that may benefit future subjects with similar conditions. The CGM data collected will not be used for any clinical decisions or care.

8.2 Potential Risks

The Senseonics CGM System is investigational and is therefore not considered to be a medical standard. To evaluate the Senseonics CGM system, blood draws for glucose measurements will be performed more frequently than in daily routine. In addition to use of the System, hyperglycemia and hypoglycemia challenges may be performed exclusively for study purposes.

8.2.1 Anticipated Adverse Effects

The following adverse effects could occur in association with insertion, removal, and/or use of the Senseonics CGM System Sensor and/or Transmitter:

- Infection, local or systemic, possibly resulting in sensor removal
- Excessive bleeding during insertion or removal
- Bruising or swelling
- Poor wound healing after insertion or removal
- Keloid and/or scar formation
- Excessive or prolonged pain or discomfort at the Sensor site
- Nerve damage causing tingling, numbness, pain or weakness
- Uncomfortable heating
- Burn
- Electrostatic shock
- Skin irritation and/or redness
- Itch
- Discoloration of skin
- Hematoma formation
- Device migration
- Skin erosion
- Allergic reaction to the device components, local anesthetic, or other medication or materials used in the procedure
- Anxiety and/or nervousness and/or lack of sleep
- Device fragments or particulate matter remaining in the body
- Failure to retrieve device or device left behind
- Difficulty in removing device that may require surgery
- Device malfunctions of the Sensor and/or Transmitter with possible need to remove and/or replace the Sensor and/or Transmitter
- Burning sensation or pain.
- Elevated blood pressure
- Water retention in the tissue, swelling or edema
- Airway spasms

- Shortness of breath
- Circulatory disorders
- Confusion
- Disorientation
- Increased or decreased sensitivity to touch or pain
- Metallic taste
- Sleepiness
- Visual disturbances and/or blurred vision
- Tinnitus
- It is possible that the local anesthetic could cause a reaction other than listed or previously seen.
- Fluid/electrolyte disturbances such as fluid retention
- Muscle weakness
- Osteoporosis
- Peptic ulcer
- Pancreatitis
- Ulcerative esophagitis
- Impaired wound healing
- Headache
- Psychic disturbances and mood swings
- Convulsions
- Glaucoma
- Weight gain
- Nausea and/or vomiting
- Malaise
- Irritability
- Insomnia
- Heartburn
- Hyperglycemia
- Ketosis
- Headaches
- Dizziness, lightheadedness, and/or fainting
- It is possible that the use of the Senseonics CGM system could cause a reaction other than listed or previously seen.
- It has not been determined whether the risks usually associated with injectable dexamethasone apply to the use of dexamethasone elution ring, a highly localized, controlled-release device.
- The dexamethasone ring could cause other adverse events not listed or previously seen.

- Other adverse events typically related to diabetes treatment and diabetes are unknown

8.2.2 Residual Risks Associated with the Investigational Device

Components of the Senseonics CGM System are manufactured under the Quality System provisions of ISO 13485:2003.

Risk analysis has been performed and adequate control put in place as prescribed in relevant provisions of IEC 62304, ISO 14971, and IEC 60601-1, in accordance with the requirements of ISO 13485:2003. Residual risks associated with the device included risks in the categories of electromagnetic and thermal energy, biocompatibility, biologic, chemical and mechanical factors, and user-related error. All identified risks have been reduced as far as possible using various control methods including software revision and re-validation, hardware design modification, packaging and sterilization process validation and labeling revision. The calculated residual risks were determined to be acceptable for conduct of this clinical investigation.

8.2.3 Risks Associated with Participation in the Clinical Investigation

This clinical investigation involves subjects with diabetes mellitus. These subjects may experience hyperglycemia and hypoglycemia as a consequence of their existing condition and medical management (e.g. insulin administration). For this study, hyperglycemia and hypoglycemia will not be reported as adverse events unless meeting criteria of a Serious Adverse Event. Episodes of hyperglycemia and hypoglycemia as documented by the Subject SMBG Meter will be reported in an extra listing separate from the AE listings. Should a known side effect(s) occur to administered medication(s) used in the intervention, such effects will be reported as part of the adverse event description and will not be considered a separate adverse event.

The amount of blood drawn for in-clinic testing during the study is below the acceptable limits of blood donation of approximately 475 mL; hence it does not pose any additional unacceptable risk to the subjects.

This clinical investigation involves the following procedures that present risk: placement of an intravenous catheter, frequent blood sampling, and conduct of hyperglycemia and hypoglycemia challenges at the clinic visits. In addition, Subjects in this study may use an insulin pump or syringes to administer subcutaneous insulin.

The following risks are potentially associated with such procedures:

- Routine administration of insulin may cause hematoma, redness, swelling and itch at the injection site, skin rash, itch, sweating, gastro-intestinal complaints, edema, difficulty breathing, palpitations and drop in blood pressure, and even death.
- Hypoglycemic symptoms requiring medical intervention which may include seizures, neuroglycopenia, coma and even death (including occurrence during home use)
- Insulin administration leading to hypoglycemia include: cold sweating, cool and pale skin, fatigue, nervousness, shakiness, anxiety, weakness, confusion, feeling of numbness, hunger, impairment of vision, problems with concentration, headache, nausea, palpitations, coma, or death.
- Hyperglycemia and diabetic ketoacidosis requiring medical intervention which may include potential complications such as nausea, vomiting, abdominal pain, dehydration, difficulties with breathing, confusion, bad breath, low blood pressure, coma, kidney failure, cardiac arrhythmia, myocardial infarction, cerebral edema, rhabdomyolysis and even death (including occurrence during home use).
- Excessive pain during insertion of the IV catheter
- Multiple sticks due to IV placement
- IV placement failure
- Restricted mobility
- Fainting, dizziness, lightheadedness or low blood pressure in response to blood sampling
- Bleeding during catheter insertion or infusion pump infusion set change
- Bruise formation at catheter site or due to infusion pump use
- Fluid overload due to saline flushes of IV catheter
- Skin redness or scarring due to infusion pump use
- Temporary muscle or nerve irritability, arrhythmia or death due to electrolyte disturbance
- Tissue damage (burn) due to heating devices
- Severe gastro-intestinal distress
- Difficulty breathing
- Cardiovascular symptoms
- Nerve damage
- Rash
- Pain
- Infection, local or systemic
- Blood clots, which may cause inflammation, swelling and pain
- Circulatory disorders, including but not limited to low blood pressure
- Skin irritation or pruritus due to medical adhesive (electrodes, tapes, etc.)
- Infection, inflammation or phlebitis at IV insertion sites or infusion pump infusion set sites
- Edema at the insertion site

- Erythema at the insertion site
- Allergic reaction
- Excessive pain or burning sensation associated with injections
- Headache
- Vasovagal response or fainting
- Anemia due to blood sampling
- Muscle soreness or extremity injury from exercise including weight lifting

Subject may have an X-ray or ultrasound of the sensor site. X-rays may cause damage to cells in the body, which in turn may increase the risk of developing cancer. This increase in risk associated with each X-ray procedure is extremely low but does slowly increase with the increasing number of X-rays tests you have.

Even though there are no known risks of ultrasound imaging, it can produce effects on the body. When ultrasound enters the body, it heats the tissues slightly. In some cases, it can also produce small pockets of gas in body fluids or tissues (cavitation). The long-term effects of tissue heating and cavitation are not known.

8.2.4 Possible Interactions with Concomitant Medical Treatments

Subjects participating in the investigation will be provided with a card advising of the contraindication of magnetic resonance imaging (MRI), and providing contact information of the investigational site.

Subjects must not undergo MRI while the Sensor is inserted or the Transmitter is in place. Both are incompatible with MRI procedures. Serious injury such as internal tissue burn (from the Sensor overheating) or topical skin burn (from the Transmitter overheating) may occur during an MRI and subsequent localized infection may develop as a result of the Sensor overheating.

If an MRI is required for subject care, the Sensor should be removed and the Subject will be withdrawn from the study, according to study stopping rules.

In the event of a situation where MRI is required and it is not possible to remove the Sensor, Subject is advised to have medical staff contact the Sponsor.

8.2.5 Dexamethasone

As it has not been determined whether the risks usually associated with injectable dexamethasone apply to the use of dexamethasone elution ring, a highly localized, controlled-release device, routine blood dexamethasone measurements have been incorporated into the study design.

8.2.6 Electrostatic Shock

The external device (Transmitter) has been tested and passed the Electrostatic Discharge (ESD) test according to IEC 61000-4-2:2008 air and contact immunity test levels in accordance with IEC 60601-1-2:2014 EMC collateral standard. No known damage to the external device or to the overall CGM system has been observed as documented in the EMC report.

8.3 Efforts to Minimize Risk

This investigation will be conducted by investigators who are qualified by training and experience in the treatment of diabetes mellitus and specifically in the execution of hyperglycemia and hypoglycemia challenges. In the event of a clinical emergency, detailed safety plans will be in place at each clinical site for monitoring and the management of clinically significant hypoglycemia and hyperglycemia. A full resuscitation cart with defibrillator, and staff trained in the care of diabetes and cardiac emergencies will be present at site. A nurse, nurse practitioner or physician will be present at the bedside or unit at all times. A study physician or nurse practitioner will be present during the hypoglycemia and hyperglycemia challenge times.

In addition, adequate measures including eligibility criteria limitations, subject screening and pre- visit assessment of the subject's diabetes status have been incorporated into the clinical investigation with the intention of minimizing such risks.

Investigators will be trained in the technique for Sensor insertion and removal. Investigators will examine the insertion site during each in-clinic visit and document any suspected adverse event. Subjects will be instructed to contact the investigator immediately upon any sign of significant irritation or discomfort or evidence of infection as described previously. In addition, an independent medical monitor will review safety related aspects of the investigation including review of serious adverse events and unanticipated adverse device effects.

Furthermore, potential risks associated with participation in this investigation will be minimized and managed in accordance with 21 CFR Part 812, ISO 14155, regulations by local regulatory authorities and requirements of the approving Investigational Review Boards and Ethics Committee(s).

8.4 Risk to Benefit Ratio

The Sponsor believes that any potential risk presented by this investigation has been minimized and that adequate testing, safeguards, and safety monitoring have been incorporated into the investigation to further minimize and mitigate the risks.

The Sponsor believes that the value of the knowledge to be gained by conducting this clinical investigation to demonstrate the safety and accuracy of the Senseonics CGM System outweighs the potential risks posed to participating subjects.

All potential study Subjects will sign an informed consent form and conduct a discussion with delegated investigative personnel concerning the risks and benefits of participating in the clinical trial.

9 ADVERSE EVENTS

The following are definitions and requirements for adverse event monitoring and reporting. The definitions and requirements of local regulations will be followed if different from below.

The name and telephone number of the individual for the Site to contact regarding safety issues is listed in the General Information and Contacts section in the front of the protocol. Subjects will contact the Investigator with any questions or concerns. The Investigator will contact Senseonics with questions regarding recording and reporting of adverse events.

9.1 Adverse Event Definitions

Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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

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

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

Serious Adverse Event (SAE) is defined as an adverse event that:

- Leads to death;
- Leads to a serious deterioration in the health of the Subject that either:
  - Results in life-threatening illness or injury; or
  - Results in a permanent impairment of a body structure or a body function; or
  - Requires inpatient or prolonged hospitalization; or
  - Results in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
- Led to fetal distress, fetal death or congenital abnormality or birth defect;
- Significant medical event.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Anticipated adverse events are AEs that have been identified as possible adverse events related to the investigational device or procedure.

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

Severity

Mild: Awareness of a sign or symptom that does not interfere with the Subject's usual activity or is transient, resolves without treatment and with no sequelae

Moderate: Interferes with the Subject's usual activity and/or requires symptomatic treatment

Severe: Symptom(s) causing severe discomfort and significant impact on the Subject's usual activities and/or requires treatment

Causality: The causal relationship should be determined with respect to the investigational device, the insertion or removal procedure, or other study-related procedures.

None: The event is not associated with the device or procedure. There is no relation between the event and the device or procedure.

Possibly Related: The temporal sequence between the device or procedure and the event is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the Subject's condition. There is a possibility of any relation between the event and the device or procedure.

Related: The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the patient's condition or comorbidities. The event is related or most likely associated with the device or procedure.

Unknown: There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

9.2 Monitoring of Adverse Events

Adverse events (AEs) may be volunteered by Subjects, elicited by Investigator or others, or observed. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device, and/or insertion or removal procedure or other study-related procedure. The Investigator will determine whether or not the event meets the serious criteria. If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the reporting process, including source documentation.

9.3 Adverse Event Reporting

All adverse events (AEs) will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations. Site will follow local IRB reporting requirements for reporting to IRB.

All SAEs must be reported to Sponsor as soon as possible but in no event later than 48 hours after learning of the event. Include Study ID, Study Site, Adverse Event, causal relationship to device and procedure (insertion/removal/other study procedure), seriousness, expectedness, and provide source documentation as soon as available. The AE form of the CRF must be completed within 3 working days of awareness for all SAEs.

All UADEs must be reported to the Sponsor and to the reviewing IRB as soon as possible, but in no event later than 48 hours after the Investigator first learns of the event (21 CFR 812.150(a)(1)). The AE form of the CRF must be completed as soon as possible but no later than 3 working days for all UADEs.

All adverse events classified as possibly related or related to the device or procedure will be reported to Senseonics as soon as possible but no later than 3 days of learning of events.

9.3.1 AE Reporting Period

Adverse events are reported from enrollment until study participation has ended. Adverse events will be followed until resolution, AE has stabilized, or the study has been completed.

9.3.2 Pre-existing Medical Conditions

Pre-existing medical conditions or symptoms reported prior to enrollment will not be recorded as an AE. In the event there is a change in the pre-existing medical condition or symptoms due to the device or study-related procedure, than an AE must be recorded.

9.3.3 Protocol-Specific Reporting Information

For the purpose of this protocol, mild (i.e., clinically non-significant) hypoglycemia and hyperglycemia symptoms or blood glucose values out of the normal range will not be reported as adverse events unless determined to meet the criteria of a Serious Adverse Event.

9.4 Device Deficiencies

All device deficiencies related to the identity, quality, durability, reliability, safety, or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the Sponsor. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10 SOURCE DOCUMENTATION, CASE REPORT FORMS AND DATA MANAGEMENT

Data in this study will be collected on Case Report Forms (electronic or paper) as well as electronic file transfers.

10.1 Source Documents and Case Report Forms

The investigator or his/her designee at each site is responsible for recording investigation-related data onto the CRFs and maintain source documentation supporting the data. Good Clinical Practice in the documentation on source documents and CRFs will be followed. For source documentation or if papers CRFs are used, the data must be legibly written in ink. If changes are required, a single line is to be drawn through the incorrect information, the correct information written in and the change initialed and dated by the individual making the change. The reason for correction may be noted, unless obvious. Pencil, correction fluid or correction tape must not be used and incorrect information must not be obscured (scribbled-out).

The investigator must review, sign, and date the CRFs as indicated on the form or electronically; these responsibilities cannot be delegated to another person. It is the investigator's responsibility to comply with regulatory requirements including, but not limited to, the maintenance of accurate, complete and current records relating to the CRFs.

Data clarification forms (DCFs) may be generated by Senseonics (or designee) or by the monitor during a monitoring visit. DCFs are treated as CRFs and are completed and signed by the investigator or designee.

The Sponsor (or their designee) will review the data against the original source documents and ensure any noted discrepancies are resolved by the investigational site. Subject data

will be compared to information originally recorded on source documents related to the trial (i.e. professional notes, laboratory reports, investigation-specific worksheets, etc.).

Investigation-related information collected on CRFs will be entered into a secure database. The database design and installation will be validated prior to use.

Validation techniques used by Senseonics are consistent with applicable regulations and guidelines. Each database must pass a series of standard tests that demonstrate the usability and correctness of the database system to approved specifications. The test process generates detailed test result logs, which are provided as part of the database documentation.

The details of data review, database cleaning and data querying are described in a Data Quality and Management Plan (DQMP). This plan is updated throughout the investigation as amended data management requirements and investigation-specific data conventions are determined.

A comprehensive EDC User Guideline will be developed for participating investigational sites describing general instructions on CRF completion; this guideline also includes investigation- specific data entry, and query management instructions.

Data entered by investigational sites will be reviewed by the Sponsor or their designee on an ongoing basis to ensure adequate query resolution and identify and query adverse events, protocol deviations, and any other ambiguous data points.

10.2 Glucose Measurement Data Flow Process

10.2.1 Data Logging

The Transmitter is a rechargeable, external device worn over the Sensor insertion site that supplies power to the Sensor. The Transmitter periodically (usually every 5 minutes) reads sensor data and calculates sensor glucose and trends. The information from the Transmitter is then transmitted for display to a handheld device (e.g. Smartphone) via Bluetooth Low Energy with AES-CCM encryption. At any one time, the Transmitter contains all of the data collected since last erasure, extending back in time to the limit of its capacity. Each Sensor reading is recorded with a timestamp. Successive uploads from a subject's assigned Transmitter can be assembled into a cumulative time profile, using these timestamps.

10.2.2 Data Retrieval

Data from Subject Assigned Transmitters will be collected at clinic visits. The data will be downloaded by a data communication device running Senseonics' custom software

application and saved to a file. The file will be uploaded to a 21CFR11 compliant record, utilizing a 21CFR11- compliant third party software application.

The Senseonics' software application will identify the Sensor serial number and ask the user to enter the site ID, subject ID and visit number. The file name will include these identifiers as well as the download date and time. Transmitter data will also be uploaded to a data management system to monitor calibration compliance.

Incomplete or missing data downloads that cannot be used in the analysis or cannot be made available at a future visit would be considered missing data for the purpose of analysis for the corresponding time interval.

10.2.3 Reference Glucose Analyzer Data

Plasma glucose data will be recorded by a YSI Analyzer and recorded on Source Document Forms. This data will be transferred to a 21CFR11-compliant electronic record system. Paper strip records and/or electronic records collected from the YSI Reference Glucose Analyzer will be retained according to GCP. Printouts should be labeled, including a patient identifier, sample number, and operator initials, and either photocopied or scanned.

10.2.4 Blood Glucose Meter Data

Data from the study Subject SMBG Meters will be uploaded at clinic visits and electronically transferred to a 21CFR11-compliant electronic record system.

Incomplete data downloads that cannot be used in the analysis or cannot be made available at a future download would be considered missing data for the purpose of analysis for the corresponding time interval.

During and/or at the conclusion of the investigation, original data from the laptop at the clinical site will be transferred to a 21CFR11-compliant electronic record system. The clinical site will be provided a master CD/USB of the electronic data to meet record retention requirements.

11 STATISTICAL METHODS

11.1 Statistical Analysis Overview

11.1.1 General Considerations

The statistical analysis of the data is focused on assessing performance via downloads and data from the clinic including the Fingerstick Blood Glucose Meter Data (Subject SMBG), the YSI Reference Glucose Data, the Senseonics CGM System Data, and other manual entries (

e.g. Implant Time , Subject Number). Descriptive statistics will be used to summarize all subject Baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, and ranges. Categorical variables will be summarized in frequency distributions.

Statistical analyses will be performed by validated software (e.g., MATLAB and SAS® 9.4). Adequate source document verification and/or audit activities will be utilized to assess the validity of investigation conclusions. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.

11.1.2 Randomization and Data Pooling across sites

Subjects will not be randomized. Subjects will be selected consecutively (i.e., selecting every subject in the order they present at the site) among those who meet the inclusion/exclusion criteria. All subjects will receive sensors and transmitters. The primary effectiveness endpoint (MARD) will be analyzed with data pooling across sites. Site effects will be examined, but only descriptively.

11.1.3 Sensor Evaluation Period

The Senseonics CGM System performance will be evaluated in the period after insertion. The Transmitter will assess the Sensor's signal sensitivity in real time for any premature failure independent of the expected lifetime based on time from insertion. If the measurement of potential degraded response of the Sensor optical system signal drops below a pre-defined percent of its original value and/or systemic patterns in Sensor accuracy to entered calibration points drops below a pre-defined threshold, then the device has reached it end of life (sensor retirement) and will no longer provide glucose readings. This end of life determination marks the end of the accuracy evaluation period for this Sensor. The distribution of times between Sensor insertion and end of life or completion of scheduled study visits, whichever occurs first will be summarized.

11.1.4 Expected Paired Points by Range*

The expected number of paired YSI/sensor points by YSI glucose range are as follows:

YSI range	Each Day 1, 7, 14 16 Hr. Session	Each Day 30,60,90 12.5 Hr. Session	Total
40-60 mg/dL	166	106	815
61-80 mg/dL	446	285	2194
80-120 mg/dL	1128	722	5550
121-160 mg/dL	1078	690	5303
160-200 mg/dL	712	456	3505
201-250 mg/dL	620	397	3052
251-300 mg/dL	290	186	1426

301-350 mg/dL	127	81	623
350-400 mg/dL	65	42	319
		Total paired points	22786

*Estimates based on 66 sensors. Number of YSI values in each range will be approximately half the number of paired points.

11.1.5 Evaluable Data for Analysis

All data will be evaluable for the study safety and effectiveness analysis.

11.1.6 Analysis Populations

Effectiveness Analysis population: The effectiveness analysis and exploratory effectiveness endpoints will be based on all data from all subjects in this investigation with at least one paired glucose reading (one Sensor with one reference glucose). The Senseonics CGM System and reference readings are compared by pairing each reference reading with the first Sensor reading that occurred up to 5 minutes after sample acquisition.

Safety Analysis Population: Safety analysis will be based on all subjects that undergo the sensor insertion in this investigation.

Dexamethasone Analysis Population: The approximately 6 subjects with Sensor's inserted will constitute the dexamethasone analysis population to determine if and when a peak dexamethasone level occurs. Subsequent to determining if and when a peak occurs, all subjects with Sensor's inserted will constitute the complete dexamethasone analysis population.

11.1.7 Dexamethasone Analysis

The peak dexamethasone and the timing that the peak dexamethasone occurs will be analyzed descriptively in the subset of approximately 6 subjects. Subsequent analysis of the dexamethasone levels in all subjects will be analyzed descriptively.

11.1.8 Interim Analysis

A planned interim analysis will be performed after all the subjects have completed Visit 6 (day 30 accuracy visit). Only descriptive statistics will be performed. This interim analysis does not feature any stopping rules and has no impact on the collection of the complete follow-up data through 90 days of Sensor use.

11.1.9 Subject Accountability

A Subject Accountability flow diagram will account for all subjects from informed consent through end of study and includes any early explants or withdrawals (Figure 1 in APPENDIX 1).

11.1.10 Study Demographics Analysis

Descriptive statistics will be provided for demographic variables and other baseline characteristics, such as age, gender, race, BMI, diabetes type, insulin therapy, history of ketoacidosis, and history of hypoglycemia.

11.1.11 Tabulation of Investigational Device Deficiencies

11.1.11.1 Transmitter Deficiencies

A tabulation of all reported transmitter device deficiencies will be presented (Table 1 in APPENDIX 1).

11.1.11.2 Sensor Deficiencies

A tabulation of all reported sensor device deficiencies will be presented (Table 2 in APPENDIX 1).

11.2 Safety Endpoints

The safety endpoint is the incidence of device-related or insertion/removal procedure-related serious adverse events (SAEs) in the clinic and during home use through 90 days post-insertion.

An Adverse Event is considered 'related' if the relatedness is categorized as 'possibly related', or 'related'. The assessment of seriousness and relatedness made by the Medical Monitor will be used for analysis. The numbers of SAEs and the percentage of patients with SAEs will be reported for each SAE type that is observed, identified as device-related, procedure-related or unrelated to the study (Table 3 in APPENDIX 1). The count and proportion of patients experiencing at least one device-related or procedure-related SAE will be presented. No inferential statistical analysis will be performed.

Other safety endpoints include:

- Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use.
- Incidence of all adverse events in the clinic and during home use.
- Incidence of hospitalizations due to hypoglycemia, hyperglycemia or ketoacidosis occurring during home use.
- Incidence of reported hypoglycemic and hyperglycemic events occurring during home use.

For each of the adverse event (AE or SAE) categories above, the numbers of AEs and the percentage of patients with AEs will be reported for each AE type that is observed and be stratified by the target age enrollment categories (Tables 4A-4E in APPENDIX 1). A listing (Table 5 in APPENDIX 1) will be prepared that identifies each patient with a reported AE or SAE, and relevant information including date of onset, severity level, seriousness, relatedness to the device or procedure, classification as anticipated or unanticipated, corrective action(s) taken, and resolution status (resolved or ongoing).

11.3 Effectiveness Endpoints

11.3.1 Summary

The effectiveness endpoint will be the mean absolute relative difference (MARD), calculated for all paired Sensor and reference measurements through 90 days post-insertion. For the planned interim analysis, MARD will be based on the first 30 days post-insertion data.

11.3.2 Effectiveness Endpoint

11.3.2.1 Effectiveness Endpoint: Criteria

The effectiveness objective is to descriptively document the distribution of absolute relative difference across all evaluable subjects and to estimate the MARD. The MARD will be estimated initially when all the subjects complete 30 days of Sensor use for the interim analysis, followed by the MARD based on all the follow-up data through 90 days of Sensor use. Descriptive statistics will be provided for the MARD. There is no hypothesis to be tested. No inferential statistical analysis will be performed.

The effectiveness endpoint is the mean absolute relative difference (MARD), defined as the average of absolute difference of paired Senseonics CGM System and reference glucose readings divided by the reference glucose reading (reference) for all reference glucose values, that is:

$$\mathbf{MARD} = \left(\left(\sum \frac{|\ (\mathbf{Glucose})_{\mathbf{SENSOR}} - (\mathbf{Glucose})_{\mathbf{REFERENCE}}\ |}{(\mathbf{Glucose})_{\mathbf{REFERENCE}}}\right) \ /\ \mathbf{n}\right) \times \mathbf{100\%},$$

Where, n is the total number of CGM and reference glucose pairs during the evaluation period, that is, after 30 days of Sensor use for the interim analysis, and after 90 days of use for the final analysis.

11.3.2.2 Sample Size and Power Calculation

This study does not feature any inferential statistics. The sample size for the study was not determined based on a power calculation. Instead, the sample size of 36 subjects with sensors inserted was selected based on the objectives of the study and was mutually agreed upon between the Sponsor and the FDA.

11.3.2.3 Other Exploratory Effectiveness Measures

Other exploratory effectiveness measures are discussed in this section. Only descriptive statistics will be provided for these exploratory outcomes.

11.3.2.3.1 Mean Absolute Difference (MAD) between sensor and reference measurements

$$\mathrm{MAD} = \left(\sum |\ (\mathrm{Glucose})_{\mathrm{SENSOR}} - (\mathrm{Glucose})_{\mathrm{REFERENCE}}\ |\right) \ /\ \mathrm{n}$$

11.3.2.3.2 Mean Relative Difference (RD) between sensor and reference measurements

$$\text{Mean RD} = \left(\left(\sum \frac{(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}}{(\text{Glucose})_{\text{REFERENCE}}}\right) / \text{n}\right) \times 100\%$$

11.3.2.3.3 Median Absolute Relative Difference (ARD) between sensor and reference measurements

Median ARD = Median $\left(\left(\frac{|\,(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}\,|}{(\text{Glucose})_{\text{REFERENCE}}}\right)_i\right)$ x 100%, i = 1, 2, …, n

11.3.2.3.4 Median Absolute Difference between sensor and reference measurements

$$\text{Median AD} = \text{Median}\,(\,|\,(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}\,|_i), \text{i} = 1,2,\ldots,\text{n}$$

11.3.2.3.5 Median Relative Difference between sensor and reference measurements

$$\text{Median RD} = \text{Median}\left(\left(\frac{(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}}{(\text{Glucose})_{\text{REFERENCE}}}\right)_i\right) \times 100\%, \text{i} = 1, 2, \ldots, \text{n}$$

11.3.2.3.6 System agreement with reference

The Agreement of the CGM System to reference measurements will be assessed by looking at proportions of all differences { (Glucose)SENSOR – (Glucose)REFERENCE } in intervals of [0 – 15%], [0 – 20%], [0-30%], and [0-40%). For readings less than or equal to 80 mg/dL, the absolute difference in mg/dL between the two glucose results will be calculated. For values greater than 80 mg/dL, the absolute percent difference (%) from the reference values will be calculated.

11.3.2.4 Effectiveness measures in full glucose range and different glycemic regions

Mean/median absolute relative difference, mean/median relative difference, mean/median absolute different when reference YSI≤80 mg/dl, and Agreement between CGM and YSI glucose will be stratified based on YSI glucose ranges. Similar stratification based on CGM glucose will also be performed. (Tables 6A-6D in APPENDIX 1).

11.3.2.5 Concurrence of System Readings and YSI values

Tables for concurrence of system and YSI values will be tabulated (Tables 7A and 7B in APPENDIX 1).

11.3.2.6 Stability of the system throughout sensor life

For the full 90 day duration of the study, performance of the system overtime will be assessed by visit number (Table 8 in APPENDIX 1).

11.3.2.7 Sensor precision analysis

Sensor precision will be evaluated by paired absolute relative difference (PARD) and percent coefficient of variation (PCV). PARD is the absolute value of the Primary Sensor reading minus the paired Secondary Sensor reading divided by the average of the two

Sensor readings. PCV is the standard deviation of the two paired Sensor readings divided by the average of the two paired Sensor readings. The mean values of PARD and PCV will be tabulated (Table 9 in APPENDIX 1).

$$\text{PARD} = \left(\left(\sum \frac{|\text{Glucose})_{\text{SENSOR 1}} - (\text{Glucose})_{\text{SENSOR 2}}|}{(\text{ Mean Glucose})_{\text{SENSOR 1 and 2}}}\right) / \text{ n}\right) \times 100\%$$

$$\text{PCV} = \left(\left(\sum \frac{\text{SD of (Glucose)}_{\text{SENSOR 1}} \text{ and (Glucose)}_{\text{SENSOR 2}}}{(\text{ Mean Glucose})_{\text{SENSOR 1 and 2}}}\right) / \text{ n}\right) \times 100\%$$

11.3.2.8 Effect of compression on sensor performance during sleep challenges

For the sleep assessment periods during visits 4 & 5, compression may occur to the sensor site when the subject is sleeping at night. The system's difference and agreement with reference and between system precision will be compared between the night time and the day time (Tables 10A and 10B in APPENDIX 1).

12 DEVICE ACCOUNTABILITY

Only an approved Investigator and investigational site may receive and use the Senseonics CGM System. The product will be packaged and labeled to clearly indicate that it is for clinical investigational use only, and the investigational device must only be used in subjects enrolled in this investigation. The Investigator is responsible for investigational product accountability, reconciliation, and record maintenance. The accountability includes storage of the investigational supplies in a secured location according to the conditions set forth for the device on the label. The investigator must maintain investigational product accountability records throughout the course of the investigation including receipt, use, and final disposition of investigational inventory. The accountability includes documenting the part number, lot number, serial number (and expiration date for sterile components) of investigational device (as applicable) assigned to each subject.

All investigational product (used or not used) must be returned to Senseonics unless otherwise instructed by Senseonics. Explanted Sensors will also be returned to Senseonics using Biohazard Return instructions and supplies.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Statement of Compliance and Good Clinical Practice

This clinical investigation will be conducted in compliance with the principles that have their

origin in the Declaration of Helsinki (Revision 6, 2008), this clinical investigation plan, requirements of the approving IRB or EC, US Code of Federal Regulations applicable to clinical studies, ICH GCP E6, ISO 14155 and other applicable regulatory requirements.

This clinical investigation will not be initiated until approval has been obtained from the FDA or local regulating authority as well as IRB/ EC. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and /or IRB except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the IRB and Sponsor per their reporting requirements.

13.2 Informed Consent and Investigational Review Board

The Investigator is responsible for assuring that informed consent is obtained from each subject or (legally authorized representative) prior to participation in the clinical investigation, according to the local clinical site's IRB and applicable regulatory requirements.

The Investigator will prepare an informed consent form (ICF) in accordance with this protocol and applicable regulatory requirements. Prior to the start of the study or revision to study, the informed consent form will be reviewed by the Sponsor for consistency with protocol, and then must be submitted to and approved by the IRB. A copy of the final IRB approved consent form and notification of approval of the clinical protocol must be received and approved by the Sponsor prior to start of study or revision to study. Timely approvals for the continuation of the trial as well as the informed consent form at each clinical site must also be forwarded to the Sponsor.

While an Investigator may discuss general availability of the investigation with a prospective subject without first obtaining consent, informed consent must be obtained from a subject prior to initiation of any clinical procedures dictated by the protocol (e.g., pregnancy testing) that are performed solely for the purpose of determining eligibility to participate in the clinical investigation.

The informed consent process includes both verbal and written explanation. Subjects must be fully counseled and informed of their options, risks and benefits, and have every opportunity to ask questions about participation in the investigation. Insurance coverage will be explained to the subject. This process includes a thorough explanation of the informed consent document that the subject will be asked to sign acknowledging that they understand and desire to participate in the investigation. The subject will be provided a copy of the signed informed consent form. The original ICF remains at the investigational site.

If new information regarding the investigational device becomes available and/or the protocol changes and this information can significantly affect a subject's future health and medical care, subjects will be informed of the information and may be asked to sign a revised informed consent form.

The Investigator will notify the Sponsor within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

13.3 Payment for Participants

Subjects will be compensated for their time and travel expenses as detailed in the Informed Consent document.

13.4 Amendments to the Protocol

Investigators may not modify this protocol without obtaining written concurrence of the sponsor and approval by the IRB and required regulatory authorities.

13.5 Sponsor Responsibilities

As the Sponsor of this clinical trial, Senseonics Incorporated has the overall responsibility for the conduct of the clinical trial, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies. In this study, the Sponsor will have certain direct responsibilities and may delegate other responsibilities to another organization such as a Contract Research Organization (CRO).

The Sponsor will submit all reports required by the appropriate regulatory authorities, including unanticipated adverse device effects, withdrawal of IRB approval, current investigators list, annual progress reports, final report, and protocol violations.

The Sponsor will select the qualified Investigators who will conduct clinical investigations of medical devices under 21 CFR Part 812 and applicable local and regulations.

The Sponsor will maintain copies of correspondence, all data, device shipment records, adverse events, device accountability, and required study documentation as required by the appropriate regulatory authorities.

13.6 Investigator Responsibilities and Delegation of Study-Specific Tasks

The Investigators commit themselves to conducting the investigation in accordance with the Clinical Trial Agreement, Protocol, and applicable FDA and local regulations for patient safety and control of investigational devices. Investigators are responsible for submitting and obtaining initial and continuing review of the clinical trial at least annually unless otherwise directed by the IRB, and completing all required reports.

Study-specific tasks may be delegated by an Investigator to individuals who are qualified by education, training, and experience. However, the Principal Investigator remains responsible for the conduct of the clinical trial.

A Delegation of Authority Log will be maintained to document the study personnel and their roles and delegated tasks. No study-specific tasks may be performed prior to the appropriate training and completion of the Delegation of Authority Log.

Records to be maintained by the Investigator include, but are not limited to: clinical trial investigational plan and all amendments, signed clinical study agreement, signed financial disclosure forms, IRB communication including approvals and informed consent forms, IRB membership list, correspondence related to the trial, curriculum vitae, delegation of authority documentation, sponsor sign-in documentation, laboratory certification and normal ranges, reports (including annual reports, final reports). For each subject enrolled: signed informed consent form(s), all completed case report forms with source documentation supporting the data, and supporting documentation related to any complication or adverse event.

13.7 Training

The Sponsor or designee will provide training to the investigator(s) and site personnel. Training will occur before the first device use and/or protocol-specific task. To ensure protocol and regulatory compliance as well as accurate data collection, site training will include a detailed review of the protocol, device accountability, CRF completion, investigation-specific procedures, monitoring logistics, and regulatory requirements. The appropriate investigator(s) and site personnel will be trained on procedures for insertion and removal of the Sensor by qualified personnel (e.g. trained investigators and investigative staff, Sponsor personnel) using appropriate training materials (e.g. investigator meetings, , demonstrations, labs, webinars, etc.). Only the personnel responsible for the insertion and removal of the sensor will be required training on the insertion/removal procedures.

Documentation of site personnel qualification and training will be maintained in the site's clinical files and Sponsor files. Training will be updated as appropriate, for example for protocol amendments, revisions, and any device changes.

13.8 Protocol Compliance

Senseonics will evaluate protocol deviations and Subject compliance during the investigation. Individual event corrective and preventive actions may be recommended.

Deviations occurring across investigational sites will be reviewed by Senseonics on an ongoing basis to determine if more global preventive actions may be required.

13.9 Protocol Deviation

Ongoing monitoring of protocol compliance will be performed for each site. The sponsor has the right to suspend enrollment at sites deemed to have excessive protocol compliance issues.

The investigator agrees to conduct the investigation in accordance with this protocol. An investigator must not intentionally deviate from the protocol without prior approval from the Sponsor, except when necessary to eliminate apparent immediate hazards to a subject, or when the changes(s) involves logistical or administrative aspects of the study and do not affect the subject's rights, safety and well-being, or the scientific integrity of the study. .

Protocol deviations are documented on CRFs. Investigators will also adhere to procedures for reporting investigation deviations to the IRB in accordance with the specific IRB reporting policies and procedures.

Under emergency circumstances, deviations from this protocol to protect the rights, safety and well-being of a subject may proceed without prior approval of the Sponsor and the IRB. Such deviations must be reported to the Sponsor within 48 hours of occurrence and respective regulatory bodies as soon as possible per applicable reporting requirements.

13.10 Document Storage and Retention

All study records will be maintained according to local regulatory requirements or for two years after marketing approval is obtained or two years after the site is notified that this research protocol has been terminated by the Sponsor. Record retention dates will be provided to all parties concerned by the Sponsor. Following the end of the retention period, all records may be destroyed (papers shredded or deleted from electronic media).

It is the investigator's responsibility to meet applicable local retention requirements for all investigation-related records and the investigator must notify Senseonics prior to discarding any of these records.

13.11 Confidentiality of Data

All information and data pertaining to the clinical trial will be considered confidential. Only authorized personnel may have access to the confidential data. Authorized personnel from the regulatory authorities have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the Subject.

13.12 Clinical Study Monitoring

The Sponsor or its designee will conduct investigational site monitoring visits to ensure compliance with the protocol and the Investigator Agreement.

Monitoring will be carried out in compliance with 21 CFR Part 812, ISO 14155, Good Clinical Practice (GCP) Guidelines, regulatory requirements, written standard operating procedures, and an investigation-specific Monitoring Plan. The Monitoring Plan will specify the relative frequency, scope, and general conduct of monitoring visits as well as identify any relevant study-specific monitoring responsibilities.

The monitoring responsibilities may be delegated by the Sponsor to a Clinical Research Organization (CRO). Monitors for this study must be qualified by education, experience, and training. The qualifications of monitors will be kept on file.

The investigator or their designee will permit access to subject source documents and study documentation in order to verify that information on case report forms (CRFs) is accurate and complete and study documentation is up to date and complete.

13.13 Medical Monitor

A Medical Monitor will be appointed to provide safety oversight for the investigation. The appointed Medical Monitor will be an independent physician with relevant therapeutic and medical expertise that is not participating as a clinical investigator in the clinical trial and does not have a financial, scientific, or other conflict of interest with the clinical trial.

Specific responsibilities of the Medical Monitor will include the following:

- Provide medical and scientific input to review applicable clinical data, subject medical safety data and laboratory values
- Maintain ongoing assessment of the safety profile of the investigational device during the investigation
- Provide medical surveillance and evaluation of all device or procedure related adverse events, including serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) on a periodic basis
- Ensure implementation of the study stopping rule(s)
- Adverse event adjudication including:
    - Assess and assign device and procedure relatedness used in the safety endpoint analysis
    - Provide adverse event categorization and physiologic system assignment
    - Provide adverse event characterization for Severity and if anticipated or unanticipated

- Other safety management/oversight as called upon by Senseonics during the study

In addition to engagement in individual adverse event adjudication, the Medical Monitor will complete a safety data review of summary data across all sites to include:

- Adverse event summaries
- Adverse event endpoint review
- Unanticipated adverse device effects review
- Summary of protocol deviations, device deficiencies, subject terminations, and subject withdrawals related to device or procedure safety
- Study stopping rule assessment

Safety data review procedures will comply with the Safety Management Plan, which will include processes for individual event review and adjudication, periodic safety data review and safety surveillance, and adverse event reporting requirements. Safety data review minutes will be documented in the study file.

13.14 Auditing

The Sponsor or designee may perform periodic site and study file audits to evaluate compliance with standards and Good Clinical Practice. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

13.15 Insurance and Indemnity

Clinical trial insurance will be secured prior to investigation initiation.

14 FINAL REPORT

Upon completion or termination of the study, the PI must submit a final written report to the Sponsor and IRB as required by the regulations. The report should be submitted within approximately 3 months (90 days) of completion or termination of the trial.

The Sponsor will submit a final report as required by the appropriate regulatory authorities.

15 PUBLICATION POLICY

Publication by Senseonics

Senseonics may at any time publish the results of and information pertaining to the investigation Subject only to ensure compliance with regulatory requirements pertaining to subject protected health information.

Publication by the Investigational Sites

Investigators will be invited to publish the results of this clinical investigation. The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

16 REFERENCES

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17 APPENDIX 1 EXAMPLE FIGURES AND TABLES OF STATISTICAL ANALYSIS RESULTS

Figure 1. Subject Accountability (Sample Data)

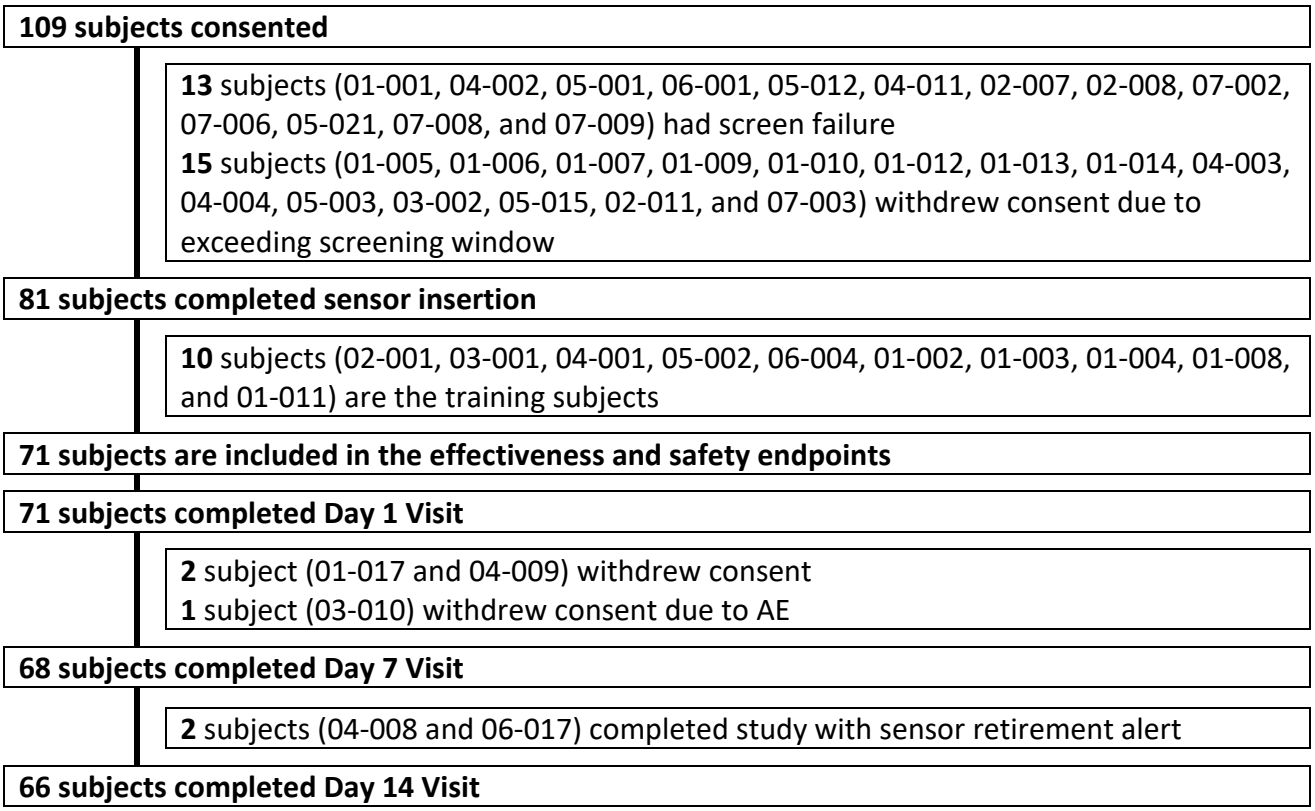

Table 1. Investigational Transmitter Deficiencies (Sample Data)

Type of Transmitter Deficiency	Number Reported	% of Total
Package Label	0	0%
Product Defect	21	87.5%
Damaged Package	0	0%
Product Safety	0	0%
Product Performance	1	4.2%
Other	2	8.3%

Table 2. Investigational Sensor Deficiencies (Sample Data)

Type of Sensor Deficiency	Number Reported	% of Total
Package Label	0	0%
Product Defect	21	87.5%
Broken Sterile Seal	0	0%
Damaged Package	0	0%
Product Safety	0	0%

Product Performance	1	4.2%
Other	2	8.3%

Table 3. Summary of Serious Adverse Events (Sample Data)

SAEs by Relationship to Study	Number of SAEs	Number of Patients with SAEs (%; 95% Confidence Interval)
All SAEs	1	1 (1.4%; 0.0%-7.6%)
Device Related SAEs	0	0 (0.0%; 0.0%-5.1%)
Sensor Insertion/Removal Procedure Related SAEs	0	0 (0.0%; 0.0%-5.1%)
Unrelated to Study SAEs	1	1 (1.4%; 0.0%-7.6%)

Table 4A. Other Safety Endpoint (Sample Data)

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use	12	11 (15.5%)
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)
Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

Table 4B. Other Safety Endpoint for Subjects between 18 and 20 Years Old (Sample Data)

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use	12	11 (15.5%)
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)
Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

Table 4C. Safety Endpoint for Subjects between 21 and 44 Years Old (Sample Data)

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use	12	11 (15.5%)
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)

Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

Table 4D. Safety Endpoint for Subjects between 45 and 65 Years Old (Sample Data)

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or device-related adverse events in the clinic and during home use	12	11 (15.5%)
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)
Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

Table 4E. Safety Endpoint for Subjects over 65 Years Old (Sample Data)

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or	12	11 (15.5%)

device-related adverse events in the clinic and during home use		
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)
Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

Table 5. Full List of Adverse Events (Sample Data)

Descriptions

	ID	AE Description
1	1-16	Depressive period
2	1-22	Hypoglycaemic episode during the night, patient had to be assisted to drink glucose to regain full conciousness.
3	1-22	Reduced vision due to ocular ischaemia
4	1-23	Contact dermatitis at the precise location of the transmittersticker. left arm - Dermatitis has healed
5	2-02	Cold and runny nose - allergies? ?hayfever

Characteristics

	ID	AE Category	AE Physiologic System	Implant Date	Date AE Onset	Resolution Date	Status	Seriousness	Severity	Device Related	Procedure Implant/Removal Related
1	1-16	Psychological disorder	Other	04-DEC-2014	22-DEC-2014	31-DEC-2014	Resolved	Not SAE	Moderate	Possibly Related	Not Related
2	1-22	Hypoglycemic Event	Endocrine	20-JAN-2015	29-JAN-2015	29-JAN-2015	Resolved	Not SAE	Moderate	Not Related	Not Related
3	1-22	Ocular ischemia	HEENT	20-JAN-2015	24-DEC-2014	.	Ongoing	Not SAE	Moderate	Not Related	Not Related
4	1-23	Dermatitis	Dermatological	20-JAN-2015	28-FEB-2015	18-MAR-2015	Resolved	Not SAE	Moderate	Definitely Related	Not Related

5	2-02	Allergy - Seasonal	HEENT	19-JAN-2015	01-FEB-2015	16-FEB-2015	Resolved	Not SAE	Mild	Not Related	Not Related

Table 6A. CGM System Difference to YSI within YSI Glucose Range (Sample Table)

YSI Glucose Ranges (mg/dL)	Number of Paired CGM-YSI	Mean Relative Difference (%)	Median Relative Difference (%)	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall					
<40*					
40-60*					
61-80*					
81-180					
181-300					
301-350					
351-400					
>400					

*For YSI ≤80 mg/dl, the differences in mg/dl are included instead of percent difference (%).

Table 6B. CGM System Difference to YSI within CGM System Glucose Range (Sample Table)

CGM System Glucose Ranges (mg/dL)	Number of Paired CGM-YSI	Mean Relative Difference (%)	Median Relative Difference (%)	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall					
40-60*					
61-80*					
81-180					
181-300					
301-350					
351-400					

*For CGM ≤ 80 mg/dL, the differences in mg/dL are included instead of percent difference (%).

Table 6C. CGM System Agreement to Reference within YSI Glucose Ranges (Sample Table)

YSI Glucose Range (mg/dL)	Number of Paired Eversense™ CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall						
< 40						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						
351 - 400						
> 400						

Table 6D. CGM System Agreement to Reference within CGM System Glucose Ranges (Sample Table)

CGM System Glucose Range (mg/dL)	Number of Paired Eversense™ CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						
351 - 400						

Table 7A. Concurrence of CGM System Readings and YSI Values within YSI Glucose Ranges (Sample Table)

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40										
40-60										
61-80										
81-120										
121-160										
161-200										
201-250										
251-300										
301-350										
351-400										
>400										

Table 7B. Concurrence of CGM System Readings and YSI Values within CGM System Ranges (Sample Table)

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each YSI Glucose Range for Each CGM Glucose Range YSI (mg/dL)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
40-60												
61-80												
81-120												
121-160												
161-200												
201-250												

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each YSI Glucose Range for Each CGM Glucose Range YSI (mg/dL)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
251-300												
301-350												
351-400												

Table 8. CGM System Accuracy by Visit Number (Sample Table)

Day Number	Number of Paired CGM-YSI	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Day 1								
Day 7								
Day 14								
Day 30								
Day 60								
Day 90								

Table 9. CGM System between System Precision (Sample Table)

Level of Mean Glucose (mg/dL)	Mean Difference (Sensor 1 - Sensor 2) (mg/dL)	SD of Difference (mg/dL)	N Pairs
<= 70			
71-180			
> 180			
All			
PARD			
PCV			

Table 10A. CGM System Performance during Sleep Challenges (Sample Table)

Night Time (Y/N)	Number of Paired CGM-YSI	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Y								
N								

Table 10B. CGM System between System Precision during Sleep Challenges (Sample Table)

Night Time (Y/N)	N Pairs	PARD
Y		
N		