Cover Page

Title: PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days

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PROMISE Study

Approval

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Quick Approval

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Title of Protocol: PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days

Protocol Number: CTP-0036

Protocol Version: 9

Senseonics, Incorporated

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Confidential Information

SUMMARY OF CHANGES

Protocol Version	Change Description
01	Initial release
02	Additional visits on days 7, 14 and 22. Added cohorts A and B to determine which subjects attend those visits. Changed sampling duration from 6.5 to 8 hours. Increased number of subjects with 2 sensors. Decreased total number of subjects inserted from 125 to 124. Added safety criteria for withdrawing subjects and stopping the study.
03	Update to subject withdrawal criteria (7.6.4) and disqualification for glucose challenge (4.3.4) for subjects who develop DKA or severe hypoglycemia
04	Increased number of subjects inserted from 124 to 160. Increased possible sites from 8 to 15. Modified visit schedule. Added randomization for (1) day 1 visits to occur at 1-12 or 12-24 hours after first CGM glucose value, (2) subjects to complete either day 7 or day 14 visits. Added enrollment targets. Accuracy visit lengths increased. Visit windows increased. Screening may occur up to 45 days prior to insertion.
05	Day 1 subjects to be randomized to one of three, 8 hour sampling (10 hour accuracy visits), Sampling decreased to 8 hours for all visits for all subjects except for Day 180 visit which has 10 hour sampling. Glucocorticoids use allowed expect for topical over sensor. Allowed for repeat of screening if insertion cannot be scheduled within window. During the study the primary system may go into a “blinded mode” (called Clinical Mode by the device).
06	Updated sections 3.2.2, 7.6.4 and 8.6 to removed MRI scan from the study exclusion criteria, subject withdrawal criteria, and as possible interaction with concomitant medical treatment; updated sections 4.2.8, 4.2.9, 4.3 and 4.3.7 to clarify CGM system calibration per system requirements during accuracy visits; updated section 4.3.7.2 to clarify that CGM System calibration should be performed using SMBG values from the study-supplied meter (Contour Next One meter).

07	Increased sample size from 180 enrolled to 210 enrolled. Increased number of subjects inserted from 160 to 180. Updated study duration to reflect timelines for additional enrollment.
08	Increased wear period for subjects with a secondary sensor to one year and added an additional primary sensor cycle for observational purposes. Added 3 accuracy visits in follow up phase at 240, 300 and 365 days.
09	Removed Accuracy visits at D240, D300, and D360. Adjusted for site visits to be for device download and safety review.

PROTOCOL SIGNATURE PAGE (Sponsor)

PROMISE Clinical Study Protocol (CTP-0036)

Signed and Dated Electronically

Katherine Tweden, PhD, Vice President, Clinical Sciences	Date
Chris Mullin, MS, NAMSA Statistical Consultant	Date

*Updates to Rev 09 do not impact statistical methods; review by statistician not required

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	PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days
Sponsor	Senseonics, Inc.
Investigational Device	Eversense® 180 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 accuracy of the Eversense® Continuous Glucose Monitoring System (Eversense® 180 CGM System) measurements when compared with reference standard measurements up to 180 days of sensor use. The investigation will also evaluate safety of the Eversense® 180 CGM System usage.
Target Indication for Use	The Eversense® 180 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 Eversense® 180 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 prospective, multi-center study, enrolling adult subjects with diabetes mellitus in the United States at up to 15 sites. The investigation will include both clinic visits and home use of the Eversense® 180 CGM System. Subjects will have one Sensor inserted in the upper arm by trained Investigators. A minimum of 80 subjects will have two sensors inserted. The accuracy of the system will be evaluated during clinic visits, comparing CGM glucose with laboratory reference values. For qualifying subjects, during the clinic visits, there are planned hyperglycemia and hypoglycemia challenges. All diabetes care decisions will be based on blood glucose values, rather than CGM results.

	Random assignment will be used to obtain sufficient numbers of subjects for each shift of the day 1 accuracy visit (hours 1-8 vs. hours 9-16 vs. hours 17-24 after first CGM glucose value) and for the timing of the Visit 4 accuracy assessment (day 7 or 14). Each randomization (2 total, with 3 conditions for day 1 and 2 conditions for days 7/14) will be independent. Randomization is only intended to ensure adequate numbers of subjects within conditions and is not intended to form the basis for formal statistical comparisons. Visit Schedule: • **Screening Visit** (Visit 1). Following informed consent process, screening evaluation will determine subject eligibility for enrollment. Visit lasts approximately 2 hours. Visit includes screening medical and diabetes history, examination and laboratory assessments. Baseline blood draw for HbA1c and Quality of Life Questionnaire will be done. At this visit subjects will be randomized to determine the subsequent follow-up visit schedule. • **Day 0** (+0-45 days from screening) **Sensor Insertion Visit** (Visit 2). Sensors will be inserted by Investigator in the upper arms. Subjects will receive one sensor or two sensors (one in each arm). In two sensor subjects, one sensor will be designated the secondary system and will not require calibration. This system will have the ability to collect and log data only and will not display glucose. Subject receives training on study and devices. **Sensor Accuracy Visits.** The following visits include Sensor accuracy assessment with reference laboratory glucose comparison, Sensor calibration with blood glucose (BG) meter, and safety assessments. Blood draws to measure HbA1c will be done at the 90 and 180-day visits. • **Day 1 – hours 1-8** (± 0 Day) Visit 3A. Visit lasts approximately 11 hours (Day 1 Early Shift Group). • **Day 1 – hours 9-16** (± 0 Day) Visit 3B. Visit lasts approximately 10 hours (Day 1 Middle Shift Group).

	• **Day 1 – hours 17-24** (± 0 Day) Visit 3C. Visit lasts approximately 10 hours (Day 1 Late Shift Group). • **Day 7** (± 1 Day) Visit 4A. Visit lasts approximately 10 hours (Day 7 Accuracy Group). • **Day 14** (± 1 Day) Visit 4B. Visit lasts approximately 10 hours (Day 14 Accuracy Group). • **Day 22** (± 1 Day) Visit 5. Visit lasts approximately 10 hours (all subjects). • **Day 30** (-3/+7 Days) Visit 6. Visit lasts approximately 10 hours (all subjects). • **Day 60** (-7/+7 Days) Visit 7. Visit lasting approximately 10 hours (all subjects). • **Day 90** (-7/+7 Days) Visit 8. Visit lasting approximately 10 hours (all subjects). • **Day 120** (-7/+7 Days) Visit 9. Visit lasting approximately 10 hours. • **Day 150** (-7/+7 Days) Visit 10. Visit lasting approximately 10 hours. • **Day 180** (-3/+2 Days) Visit 11. Visit lasting approximately 12 hours. A subset of subjects inserted with 2 sensors may be requested to continue participation in the study after Day 180. Those subjects will not participate in any additional accuracy visits. Subjects will return to the clinic for device downloads and safety assessments for Adverse Events approximately every 2 months A blood draw will be done at the 365-day visit to measure HbA1c. • **Day 240** (±7 Days) Visit 13. Visit lasting approximately 1 hours. • **Day 300** (±7Days) Visit 14. Visit lasting approximately 1 hours.

- **Day 365** (+7 Days) Visit 15. Visit lasting approximately 1 hours.

Following the day 180 accuracy visit, Sensors are removed at end of visit or within 7 days of the day 180 visit. For subjects with two sensors, only the primary sensor will be removed following the day 180 visit. At the removal visit, a new primary sensor will be inserted for an additional 180 days of wear. Both sensors will be removed following the 365 clinic visit (+7 days). Blood draws for HbA1c and quality of life questionnaires will be conducted at the removal visits. In the case that a sensor enters clinical mode prior to removal, subjects will be asked to complete the quality of life questionnaires at the visit following confirmation of Clinical Mode.

- **Follow-up Visit:** Visit 12**.** Sensor Site Assessment is performed approximately 10 days (-3/+7 days) after Sensor removal and insertion, as applicable, 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.

  Visit 16. Sensor Site Assessment is performed approximately 10 days (-3/+7 days) after final sensor removals 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 Eversense® 180 CGM glucose values. Subjects will be advised to wear the Transmitter over the Sensor for data collection, except during transmitter charging.

Subjects will calibrate the CGM using the study-provided Subject SMBG Meter as prompted by the CGM and according to Instructions for Use. Subjects 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 approximately 7 times per day. Subjects will be monitored for compliance to a minimum of 4 SMBG readings per day including at least 1 pre-prandial and one bedtime reading. All SMBG readings will be requested to be entered into the Eversense mobile app as events. The cohort of subjects that are participating in the PROMISE extension to 365 days will have the accuracy of their new 180 day sensor monitored approximately every 2 weeks to ensure that the distribution of performance for that cohort is consistent with what was seen in previous clinical studies. If the performance is not consistent with what has been seen in previous clinical studies, the study subject's SMBG entry compliance will be monitored on a daily basis until performance comes back within the distribution. If performance is not restored to the expected distribution within 2 weeks, the 180-day sensor will be placed in blinded Clinical Mode for the remainder of the study. The subject will be blinded to glucose values, alerts and alarms. **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 Eversense® 180 CGM System results. During sampling periods, blood samples will be collected for 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> 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, PA or nurse practitioner will be available at all times during hypoglycemia and hyperglycemia challenges.

	The sensor insertion site(s) 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 performed 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 HbA1c measurements will be made at Screening, Day 90, Day 180, and Day 365 (Visits 1, 8, 11 & 15).
Estimated Study Duration of Study and Subject Participation	Enrollment Period: Approximately 8 months Individual Subject Participation: Approximately 8 months and up to 14 months for subjects with two sensors Duration of Study: Approximately 18 months for the primary analysis and up to 26 months for the 365-day analysis group
Study Sites	Up to 15 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 210 adult subjects will be enrolled and approximately 180 will be inserted with the CGM Sensor in the investigation. Subgroups based on diabetes type (approximately 70% type 1), baseline HbA1c and age ranges will be targeted for enrollment.
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
	Subjects meeting any of the following exclusion criteria at the time of screening will be excluded from this study: 1. History of unexplained 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. Subjects with gastroparesis. 4. 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.

Exclusion Criteria	5. A condition preventing or complicating the placement, operation, or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition. 6. 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. 7. Hematocrit <30% or >60% 8. History of hepatitis B, hepatitis C, or HIV 9. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study 10. History of adrenal insufficiency 11. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); topical glucocorticoids over sensor site only; antibiotic for chronic infection (e.g. osteomyelitis, endocarditis) 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)
	<u>Effectiveness Objective</u>: To determine accuracy of the Eversense® 180 CGM System measurements through approximately 180 days post-insertion.

Investigation Objectives	Safety Objective: To demonstrate safety of the Eversense® 180 CGM System through 180 days post-Sensor insertion or removal and follow-up by measuring the incidence of device-related and insertion/removal procedure-related serious adverse events during the investigation. After completion of Visit 8 (day 90 accuracy visit), analysis may be performed for the corresponding endpoints and may serve as the basis of a regulatory submission. After completion of Visit 12, analysis will be performed for subsequent visits. There are no formal hypothesis tests so there are no type I error concerns.
Measures/Endpoints	Effectiveness Measures: The effectiveness measure will be mean absolute relative difference (MARD) for paired Sensor and reference measurements through 180 days post-insertion for reference glucose values from 40-400 mg/dL. Effectiveness measures will be evaluated descriptively. Neither inferential analysis nor hypothesis testing will be performed. Safety Endpoint: Incidence of device-related or sensor insertion/removal procedure-related serious adverse events through 180 days post-Sensor insertion or 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
EDC	Electronic Data Capture
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 Eversense® 180 CGM System measures glucose levels every 5 minutes and is implanted under the skin by a trained health care professional (HCP). Unlike commercially available transcutaneous continuous glucose monitoring devices with short operating lives (up to 14 days), the Eversense® 180 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 180 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 Eversense® 180 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 Eversense® 180 CGM System ("System"). The Eversense® 180 Continuous Glucose Monitoring System is a glucose monitoring device intended to measure interstitial fluid glucose levels every 5 minutes in individuals with diabetes for the operating life of the sensor. The Eversense® 180 Continuous Glucose Monitoring System is intended to be used:

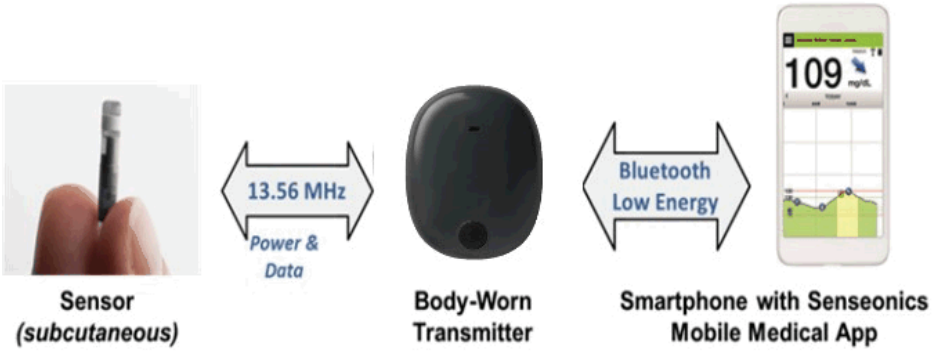
- To provide real-time glucose readings directly to the user
- To provide glucose trend information
- To provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

The Eversense® 180 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, primary and secondary (in subjects with 2 sensors)

2. Battery-powered external Transmitters ("Transmitter", primary and secondary (in subjects with 2 sensors)

3. Mobile Medical Application (MMA) for display of glucose information that runs on a Handheld Device (HHD).



Insertion Tools
(Blunt Dissector and Sensor Inserter)

Accessories to the system include:

1. Adhesive Patch: To secure the Transmitter over the Sensor

2. Insertion tool (Blunt dissector, Sensor Inserter): To place the Sensor into the subcutaneous space.

3. Charger and Charging Cradle: To charge the Transmitter.

The use of the Eversense® 180 system in this clinical study is outside the current commercial indications for use.

1.1.1 DESCRIPTION

The 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 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 Eversense® 180 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 and their medical staff) 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 Eversense® 180 CGM System will be calibrated by the Subjects according to the Eversense® 180 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 WarmUp 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 a minimum of 2 calibration per day.

The secondary Eversense® 180 CGM System will not require calibration and will have the ability to collect and log raw data only, and it will not calculate or store glucose information.

1.2 SUMMARY OF CLINICAL EXPERIENCE

Three major pivotal safety and efficacy studies have been completed and submitted for regulatory approval. The European pivotal study, PRECISE was completed in August 2015 and Senseonics received CE Mark in May 2016; two U.S. pivotal studies (PRECISE II, completed in July 2016 and PRECISION, completed in February 2018) were also completed and FDA approval was received in June 2018. These studies demonstrated that the Eversense® 180 CGM System provided reliable glucose readings for periods of up to approximately 180 days when compared to laboratory blood glucose analyzer measurements, with no notable safety issues.

2 STUDY OBJECTIVES

2.1 EFFECTIVENESS

The effectiveness objective is to determine accuracy of the Eversense® 180 CGM System measurements through approximately 180 days post-insertion. The exploratory objectives are to determine other relevant Eversense® 180 CGM System performance measures during the period of Sensor use and are detailed further in Section 11.3.

2.2 SAFETY

The safety objective is to demonstrate safety of the Eversense® 180 CGM System through 180 days post-insertion by measuring the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAEs) during the investigation.

After completion of Visit 8 (day 90 accuracy visit), analysis may be performed for the corresponding endpoints and may serve as the basis of a regulatory submission. After completion of Visit 12, analysis will be performed for subsequent visits. There are no formal hypothesis tests so there are no type I error concerns.

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 unexplained 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. Subjects with gastroparesis
4. 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
5. A condition preventing or complicating the placement, operation or removal of the Sensor or wearing of transmitter, including upper extremity deformities or skin condition
6. 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.
7. Hematocrit <30% or >60%

8. History of hepatitis B, hepatitis C, or HIV
9. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study
10. History of adrenal insufficiency
11. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); topical glucocorticoids over sensor site only; antibiotics for chronic infection (e.g. osteomyelitis, endocarditis)
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*

* 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 prospective, multi-center study, whereby approximately 210 subjects will be enrolled, and 180 subjects will be inserted in the United States at up to 15 sites. The investigation will include both clinic visits and home use of the Eversense® 180 CGM System. A minimum of 80 subjects, will have two Sensors inserted by trained Investigators. The Sensor(s) will be inserted in the upper arms of the subjects. The accuracy of the Eversense® 180 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 4.3.

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 Eversense® 180 CGM System results.

To ensure adequate numbers of subjects for specific scenarios of interest, there will be two randomizations:

- Shift of the Day 1 sensor accuracy assessment: early (hours 1-8) vs. middle (hours 9-16) vs. late (hours 17-24)
- Day of the Visit 4 accuracy assessment: Day 7 vs. Day 14

Shift of the Day 1 assessment will be for the Day 1 of sensor life (the day after insertion). Both randomizations are independent of one another.

The Subject visit schedule includes 12 visits over a period of approximately 8 months (inclusive of visit windows from screening visit through follow-up visit). For the subset of subjects inserted with 2 sensors, the subject visit schedule includes 16 visits over a period of proximately 14 months.

The study is anticipated to take approximately 26 months, including the enrollment period.

3.3.2 JUSTIFICATION FOR CLINICAL INVESTIGATIONAL 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. Guidance. 2012.[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

- **Screening Visit (Visit 1)**: 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, quality of life questionnaire and laboratory assessments including EKG. Randomization as described above will occur at this visit.
- **Day 0 (+0-45 days) Sensor Insertion (Visit 2):** Sensors are inserted by Investigator in the upper arm(s). A minimum of 80 subjects, will have two Sensors inserted. Subject training on study and devices. Visit lasting approximately 2 to 3 hours.
- **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.
    - **Day 1 – Hours 1-8** (±0 Days) Visit 3A. Visit lasting approximately 11 hours. (Day 1 Early Shift)
    - **Day 1 – Hours 9-16** (±0 Days) Visit 3B. Visit lasting approximately 10 hours. (Day 1 Middle Shift)
    - **Day 1 – Hours 17-24** (±0 Days) Visit 3C. Visit lasting approximately 10 hours. (Day 1 Late Shift)
    - **Day 7** (± 1 Day) Visit 4A. Visit lasts approximately 10 hours. (Day 7 Group)
    - **Day 14** (± 1 Day) Visit 4B. Visit lasts approximately 10 hours. (Day 14 Group)
    - **Day 22** (± 1 Day) Visit 5. Visit lasts approximately 10 hours. (all subjects)

- **Day 30** (-3/+7 Days) Visit 6. Visit lasting approximately 10 hours (all subjects).
- **Day 60** (-7/+7 Days) Visit 7. Visit lasting approximately 10 hours (all subjects).
- **Day 90** (-7/+7 Days) Visit 8. Visit lasting approximately 10 hours (all subjects).
- **Day 120** (-7/+7 Days) Visit 9. Visit lasting approximately 10 hours (all subjects).
- **Day 150** (-7/+7 Days) Visit 10. Visit lasting approximately 10 hours (all subjects).
- **Day 180** (-3/+2 Days) Visit 11. Visit lasting approximately 12 hours (all subjects).

    - Following the Day 180 accuracy visit, Sensors are removed at end of visit or within 7 days of the day 180 accuracy visit. For subjects with 2 sensors, only the primary sensor will be removed and a new sensor will be inserted. The Secondary sensor will remain in situ. Subjects will complete the following additional visits.

- **Clinic Visits**: Subjects with 2 sensors will return to the clinic approximately every 60 days (±7 days) after completion of the first 180 day phase of the study. The subject's transmitters and study meter will be downloaded. Study staff will review fingerstick and study compliance with the subject. Study staff will assess for any new or ongoing Adverse Events.
    - **Day 240** (±7 Days) Visit 13. Visit lasting approximately 1 hours (2 sensor subjects).
    - **Day 300** (-±7 Days) Visit 14. Visit lasting approximately 1 hours (2 sensor subjects).)
    - **Day 365** (+7 Days) Visit 15. Visit lasting approximately 1 hours (2 sensor subjects).
- **Follow-up Visits** (Visit 12 & 16): Sensor Site Assessment is performed approximately 10 days (- 3/ +7 days) after Sensor removals and insertion, as applicable, 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.

4 STUDY METHODS, PROCEDURES AND CLINIC VISITS

Each visit is described in detail in this section.

Day Post-Insertion	-45 -0	0	1	7	14	22	30	60	90	120	150	180	10 Day Follow-up	240	300	365	10 Day Follow-up
Visit Type	Screening	Sensor Insertion & Training	Accuracy Visit.	Accuracy Visit (Day 7)	Accuracy Visit (Day 14)	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit & Sensor Removal	Follow-up	Clinic Visit	Clinic Visit	Clinic Visit & Sensor Removal	Follow-up
Study Visit and Window	Visit 1	Visit 2 (+0 to 45 days after Visit 1)	Visit 3A, 3B, 3C (± 0 Days)	Visit 4A (± 1 Day)	Visit 4B (± 1 Day)	Visit 5 (± 1 Day)	Visit 6 (-3/+7 Days)	Visit 7 (±7 Days)	Visit 8 (±7 Days)	Visit 9 (±7 Days)	Visit 10 (±7 Days)	Visit 11 (-3/+2 Days)	Visit 12 (-3/+7 days)	Visit 13 (±7 Days)	Visit 14 (±7 Days)	Visit 15 (+7 Days)	Visit 16 (-3/+7 days)
Anticipated Length of Visit	2 Hours	2-3 Hours	10-11 hours	10 hours	10 hours	10 hours	10 hours	10 hours	10 hours	10 hours	10 hours	12 hours	1 Hour	1 Hour	1 hour	1 hour	1 Hour
ICF Process	X																
Screening history, exam, labs to assess I&E	X																
Sensor Insertion		X										X					
Device Training		X															
Urine pregnancy	X	X	X	X	X	X	X	X	X	X	X	X					
IV Catheter			X	X	X	X	X	X	X	X	X	X					
Approximate length of time to collect blood Samples			8 Hours	8 Hours	8 Hours	8 Hours	8 Hours	8 Hours	8 Hours	8 Hours	8 Hours	10 Hours					
HCT	X		X	X	X	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	X	X	X	X	X					
Download Transmitter and BG Meters			X	X	X	X	X	X	X	X	X	X		X	X	X	
Assess changes in medications and Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Sensor site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemia Hyperglycemia Challenge[1]			X	X	X	X	X	X	X	X	X	X					
Questionnaires[2]	X								X			X				X	

Sensor Removal												X				X	
Approximate Samples for glucose analysis			43	43	43	43	43	43	43	43	43	51					
Estimated Blood Draw Volume	2		86	86	86	86	86	86	88	86	86	104					

1 Only hypoglycemia challenge or hyperglycemia challenge, depending on glucose level Investigator discretion and patient safety will also be considered in determining appropriate challenge.
2 Diabetes Distress Scale at screening, day 90 and day 180/removal and day 365(visits 1, 8, 11, and 15); CGM satisfaction scale at day 180/removal and day 365/removal (visit 11 and Visit 15). Questionnaires may also be given at the time the subject's primary sensor is confirmed to enter clinical mode.

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 45 days before the Sensor Insertion Visit (V2). In the event that an insertion visit cannot be scheduled within the 45 day window, a qualified subject may repeat the screening visit.

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).
- 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 2 ml total) will be drawn for hemoglobin A1c (HbA1c)
- Quality of Life questionnaire - The diabetes distress scale will be administered

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)

4.1.2 RANDOMIZATION

To ensure adequate numbers of subjects for specific scenarios of interest, there will be two randomizations:

- Shift of the Day 1 sensor accuracy assessment: early (hours 1-8) vs. middle (hours 9-16) vs. late (hours 17-24)
- Day of the Visit 4 accuracy assessment: Day 7 vs. Day 14

Both randomizations are independent of one another.

4.2 DAY 0-VISIT 2- SENSOR INSERTION/TRAINING

4.2.1 SUBJECT ADMISSION

The subject will arrive at the clinic, at an appropriate time to allow for sensor insertion to occur a minimum of 24 hours before any planned 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.
- Fingerstick glucose and ketones will be measured.
- 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 4.3.1.3.

4.2.3 SENSOR INSERTIONS

Each subject will have the Sensor(s) 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(s) into the subcutaneous tissue using appropriate technique described in the Eversense® 180 CGM Sensor Insertion and Removal Instructions. The location of the sensor(s) 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 sites.

Subjects will be advised on the proper incision care:

- Do not swim or soak in a tub for five days
- Avoid strenuous activities that may pull at the incision or cause a lot of sweating around the insertion area while the incision heals
- Replace Tegaderm™ if it becomes saturated; otherwise, leave it on over the Steri-Strips™ for at least 2 days
- Leave Steri-Strips™ on until they fall off
- Trim the edges of the Steri-Strips™ if they start to curl; do not remove them when doing so
- Place the smart transmitter over the Tegaderm™ after the first day

Subjects will be advised to notify the study doctor if:

- Steri-Strips™ come off before incision is fully closed
- They develop a fever, or experience pain, redness, swelling, warmth or drainage at the incision site
- They experience a significant change in health or well-being that they believe is related to the incision site

A minimum of 80 subjects will have two sensors inserted, one in each upper arm.

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

After Sensor insertion, the transmitter(s) will be worn briefly (approximately 20 minutes) while the sensor is linked to the transmitter, and to ensure proper operation of the system (confirmation of system operation).

4.2.4 DEVICE DISBURSEMENT

Subjects will be assigned the following devices:

- Eversense® 180 Continuous Glucose Monitoring (CGM) Systems consisting of the following:
  - One Transmitter and accessories (charger, adhesive patches)

- Handheld Device (1 per Subject) running the Mobile Medical Application (MMA)
- Eversense® 180 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

For those subjects with two sensors inserted, a second transmitter will be provided. See Section 4.2.10 for a description of the operation requirements of two separate CGM systems.

4.2.5 SUBJECT TRAINING

Subjects will be issued transmitters as appropriate and trained in their use along with a hand-held device which will be used for entering calibration 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)). Subjects will be requested to enter all SMBG readings into the Eversense® app as glucose events. Subjects will be monitored for compliance to a minimum of 4 SMBG readings per day including at least 1 pre-prandial and 1 before bedtime, and will be contacted by the study site if they are found to be out of compliance. Subjects will be requested to enter all insulin injections/boluses into the Eversense app to aid in evaluation of subject compliance with adjunctive use of the CGM system.

The subject will be instructed on the proper use of the Transmitter and Mobile Medical Application (refer to the Eversense® 180 CGM User Guides). The transmitter(s) will be worn over the sensor at all times (except while charging) starting approximately 24 hours post insertion. Subjects will be prompted to calibrate the sensor using fingerstick measurements using the Subject SMBG meter.

4.2.6 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.

4.2.7 ESTIMATED VISIT DURATION

The total duration of the inpatient visit is approximately 2-3 hours

4.2.8 SUBJECTS ASSIGNED TO Day 1 Early Shift Group

Subjects in Day 1 Early Shift Group will leave their transmitters at the clinical site and will return the following day for visit 3A sensor accuracy visit. They will place the transmitters and perform their first calibrations at the clinical site as prompted by the Eversense® 180 CGM System.

4.2.9 SUBJECTS ASSIGNED TO Day 1 Middle and Late Shift Groups

Subjects in Day 1 Middle and Late Shift Groups will be instructed to start wearing the transmitters approximately 24 hours after the sensor was inserted. Subjects will then be prompted by the Eversense® 180 CGM System to enter their first calibration, and the Eversense® 180 system will enter the initialization phase. The clinical site should communicate with the subject during this time to make sure the subject was successful with entering initialization.

4.2.10 SUBJECTS WITH TWO SENSORS INSERTED

Subjects with two sensors inserted will be issued two transmitters to be worn over the sensors. Transmitters will be designated as primary (left arm) and secondary (right arm) and will have distinguishing visual marks to ensure matching to the correct limb. Each transmitter is linked to a specific sensor as described in the Eversense® 180 CGM system User Guide. Subjects will be issued a hand-held display which will be used for entering calibration information into the primary transmitter only. The secondary transmitter worn on the opposite arm will have the ability to collect and log data only and will not calculate and store glucose. The handheld device, when paired to the secondary transmitter, will only display battery level and the placement guide used for wearing the transmitter as described in the Eversense® 180 CGM system User Guide.

The secondary transmitter will use the SMBG calibration points collected and entered into the primary system (using the same time stamp information) for calculation of glucose results in the analysis data set.

This subset of subjects will be used to explore the following endpoints: PARD, and dominant vs non-dominant arm effects. Analysis of data from subjects with two sensors inserted is further described in Section 11. Additionally, this subset of subjects will continue participation for 365 days of sensor wear. At Day 180, the primary sensor will be removed and a new sensor will be inserted. The secondary sensor will remain in situ for observation of sensor life for up to 365 days.

4.3 SENSOR ACCURACY VISITS

Day 1 (Day 1 Early Shift Group only) **– Visits 3A**

Approximate visit duration - 11 hours
Approximate sampling duration – 8 hours

Approximate visit timeline:

Approximate time*	Activity**	Time relative to first IV sample
~06:00	Admission	T=0 -2:00
~07:15-07:45	Free range glucose control	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 <70 mg/dL for 1 hour • Sampling every 5 min when glucose ≤70 mg/dL • Challenge may be stopped once 13 YSI values ≤70 mg/dL are collected • Subjects fed at end of challenge • Note: Subjects should not be held <55 mg/dL for more than 20 minutes	T=0 0:00 – +5:00

Approximate time*	Activity**	Time relative to first IV sample
~08:00 – 13:00	Alternatively, for qualifying subjects, hyperglycemia challenge to achieve hyperglycemia target >300 mg/dL for 75 minutes • Sampling every 5 min when glucose ≥300 mg/dL • Challenge may be stopped once 16 YSI values ≥300 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
~14:00	Fingerstick blood glucose	T=0 +6:00
~15:00	Fingerstick blood glucose	T=0 +7:00
~16:00	Fingerstick blood glucose	T=0 +8:00
~ 15:00 – 16:00	Discharge preparation period	
~16:00	Last IV blood sample draw	T=0 +8:00
~16:30	Discharge	T=0 +8:30

*Times may change based on time sensors are inserted.

** CGM calibration will be performed as prompted by the Eversense® 180 CGM System throughout the visit.

Other 8-Hour Sampling Sensor Accuracy Visits – Visits 3B (Day 1 Middle Shift Group), **3C** (Day 1 Late shift Group) **and Visits 4-10** (all subjects)

Approximate visit duration - 10 hours

Approximate sampling duration – 8 hours

Approximate time*	Activity**	Time relative to first IV sample
~07:30	Admission	T=0 -:30
~07:30-07:45	Free range glucose control	T=0 -0:45 - -0:15
~08:00	First IV blood sample drawn.	T=0 0:00

Approximate time*	Activity**	Time relative to first IV sample
~08:00 – 13:00	For qualifying subjects, hypoglycemia challenge to achieve hypoglycemia target <70 mg/dL for 1 hour • Sampling every 5 min when glucose ≤70 mg/dL • Challenge may be stopped once 13 YSI values ≤70 mg/dL are collected • Subjects fed at end of challenge • Note: Subjects should not be held <55 mg/dL for more than 20 minutes	T=0 0:00 – +5:00
~08:00 – 13:00	Alternatively, for qualifying subjects, hyperglycemia challenge to achieve hyperglycemia target >300 mg/dL for 75 minutes • Sampling every 5 min when glucose ≥300 mg/dL • Challenge may be stopped once 16 YSI values ≥300 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
~14:00	Fingerstick blood glucose	T=0 +6:00
~15:00	Fingerstick blood glucose	T=0 +7:00
~16:00	Fingerstick blood glucose	T=0 +8:00
~ 15:00 – 16:00	Discharge preparation period	
~16:00	Last IV blood sample draw	T=0 +8:00
~16:30	Discharge	T=0 +8:30

*Times may change based on time sensors are inserted.

** CGM calibration will be performed as prompted by the Eversense® 180 CGM System throughout the visit.

10-Hour Sampling Sensor Accuracy Visit –Visit 11 (all subjects)

Approximate visit duration - 12 hours
Approximate sampling duration – 10 hours

Approximate time	Activity**	Time relative to first IV sample
~07:30	Admission	T=0 -:30
~07:30-07:45	Free range glucose control	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 <70 mg/dL for 1 hour • Sampling every 5 min when glucose ≤70 mg/dL • Challenge may be stopped once 13 YSI values ≤70 mg/dL are collected • Subjects fed at end of challenge • Note: Subjects should not be held <55 mg/dL for more than 20 minutes	T=0 0:00 – +5:00
~08:00 – 13:00	Alternatively, for qualifying subjects, hyperglycemia challenge to achieve hyperglycemia target >300 mg/dL for 75 minutes • Sampling every 5 min when glucose ≥300 mg/dL • Challenge may be stopped once 16 YSI values ≥300 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
~13:00-18:00	Recovery Period with meal/bolus and glucose stabilization	T=0 +5:00 - +8:00
~14:00	Fingerstick blood glucose	T=0 +6:00
~15:00	Fingerstick blood glucose	T=0 +7:00
~16:00	Fingerstick blood glucose	T=0 +8:00
~17:00	Fingerstick blood glucose	T=0 +9:00

Approximate time	Activity**	Time relative to first IV sample
~18:00	Fingerstick blood glucose	T=0 +10:00
~ 17:00 – 18:00	Discharge preparation period	
~18:00	Last IV blood sample draw	T=0 +10:00
~18:30	Discharge	T=0 +10:30

** CGM calibration will be performed as prompted by the Eversense® 180 CGM System throughout the visit.

4.3.1 THE FOLLOWING PROCEDURES/INSTRUCTIONS WILL BE FOLLOWED FOR ALL ACCURACY VISITS

4.3.1.1 PRE-VISIT PHONE CALL (DAY 7-180 VISITS)

Approximately 12 hours prior to the Accuracy Visit, site personnel will contact the subject to ensure the subject is in compliance with study device wear prior to the scheduled start of glucose sampling. Subjects may be instructed to calibrate at a specific number of hours before the scheduled visit start in order to assess accuracy over the entire calibration window. Subjects may also be given appropriate instructions regarding pre-visit medications and meals.

4.3.1.2 SUBJECT INSTRUCTIONS PRIOR TO ADMISSION

Prior to admission, subjects should take morning medications 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 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.

4.3.1.3 DEVICE SET UP

4.3.1.3.1 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 as appropriate.

4.3.1.3.2 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 Eversense® 180 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 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.

4.3.2 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.

4.3.3 SUBJECT ADMISSION

The subject will arrive at the clinic and the following tests will be performed to confirm eligibility for participation in the visits:

- Hematocrit will be assessed using local lab or Point of Care testing device. Subject must be within reference range to participate in accuracy 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.
- Study subjects using tetracyclines within 4 days of visit start will be asked to reschedule the visit.
- Study subjects using sorbitol/mannitol within 12 hours of visit start will be asked to reschedule the visit.
- 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 transmitter and that the transmitter and hand-held device are in communication and functioning.
- The subject will be rescheduled if he/she did not bring his/her Transmitter 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.

4.3.4 ADVERSE EVENTS

Upon admission subject will be asked about any adverse events or changes in medication since the last study visit. If subjects experienced DKA or Severe hypoglycemia during the past 30 days, they will be excluded from participating in the glucose challenge, but may continue with the accuracy visit under observation only. The sensor insertion site will be examined. Adverse events including those associated with the insertion site will be documented on the appropriate eCRF.

4.3.5 KETONE TESTING

Ketone (β-hydroxybutyrate (β-HOB)) measurements will be made using a study supplied FDA-approved self-monitoring ketone meter and strips as described in 5.2.3. Subject blood ketones should be evaluated from capillary or venous blood using the ketone meter while in the clinic for sensor insertion and accuracy visits at the following times:

- On arrival 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 7.5.3.

4.3.6 SMBG TESTING

During in-clinic days, subjects should continue testing blood glucose using the study-supplied Subject SMBG Meter following the schedule for each visit (hourly). 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 will be requested to enter all SMBG readings into the Eversense® app as glucose events. Subjects will be monitored for compliance to a minimum of 4 SMBG readings per day including at least one pre-prandial and one bedtime reading, and will be contacted by the study site if they are found to be out of

compliance. Subjects will be requested to enter all insulin injections/boluses into the Eversense app to aid in evaluation of subject compliance with adjunctive use of the CGM system.

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.

4.3.7 SYSTEM CALIBRATION

The Eversense® 180 Continuous Glucose Monitoring (CGM) System (primary sensor) will be calibrated and maintained per Eversense® 180 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:

4.3.7.1 IN CLINIC

During the in-clinic sessions, subjects will calibrate as prompted by the Eversense® 180 CGM System.

4.3.7.2 AT HOME

During periods of home use, it is required to calibrate the Eversense® 180 CGM System using SMBG values from the study-supplied meter, the Contour Next One blood glucose meter. Calibration is best done when glucose is neither rapidly rising nor falling. The Eversense® 180 CGM System will prompt the user when it is time to calibrate.

4.3.8 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 Eversense® 180 CGM System results.

4.3.9 IV/BLOOD DRAW GUIDELINES

4.3.9.1 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.

4.3.9.2 TIMING OF BLOOD SAMPLING

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

- BG ≥ 300 mg/dL: every 5 minutes (+/- 2 minutes) *
- BG >70 mg/dL and < 300 mg/dL: every 15 minutes (+/- 2 minutes)
- BG ≤70 mg/dL: every 5 minutes (+/- 2 minutes)

*When > 400 mg/dL, sampling may be reduced to every 15 minutes

Blood sampling can also be reduced to every 15 minutes after the challenge is met. 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.

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

4.3.9.3 SAMPLE VOLUME

Approximately 0.5 ml IV blood samples will be collected (after 1.5 ml waste 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.

4.3.9.4 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). Samples should be discarded if not run within this time frame.

4.3.10 GLUCOSE CHALLENGES

4.3.10.1 SUBJECT ELIGIBILITY

Subjects not on insulin therapy will not be expected to undergo hypoglycemic challenges. Eligible subjects will be required to participate in glucose challenges. Subjects unable to participate in glucose challenges will participate in the accuracy sessions using free range glucose control.

4.3.10.2 GUIDELINES FOR DETERMINING WHICH CHALLENGE TO CHOOSE (ALL VISITS)

Subject BG levels and direction of those levels determined using the first three SMBG/YSI readings will inform whether the subject will participate in the hypoglycemia or hyperglycemia challenge on that study day, according to the following table as a guideline:

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

*Investigator discretion and patient safety will also be considered in determining appropriate challenge. Additional SMBG can be done to determine the appropriate challenge.

4.3.10.3 INITIATING THE GLUCOSE CHALLENGE

Hyperglycemia challenges may be initiated by administering a mixed meal of (30 to 40%) carbohydrate content gradually targeting maintaining a glucose level of >300 mg/dL for 75 minutes, based on subject's insulin/carbohydrate ratio. Liquid carbohydrates (such as Boost, soda, juice) can be given in small volumes only if the mixed meal is not successful in reaching the target. Hypoglycemia challenges may be initiated by administrating SQ fast-acting insulin targeting maintaining <70 mg/dL for 1 hour, based on subject's insulin sensitivity ratio. Details about all carbohydrates (time, type and amount) will be recorded for entry into the study database, as well as all bolus insulin given.

4.3.11 DOWNLOADING DEVICES

The study issued Subject SMBG meter and the Transmitter(s) will be downloaded at the end of each sensor accuracy visit (Days 1-180 visits), during each clinic visit for subjects in the cohort continuing to 365 days, or at any unscheduled visit as appropriate. Transmitter data will also be uploaded to a data management system to monitor calibration compliance. Additionally, for the subjects continuing to 365 days of sensor wear with the secondary sensor and a new primary sensor, accuracy of the new 180 day primary sensor will be monitored for performance approximately every 2 weeks. Since the compliance monitoring of the daily SMBG entry will continue on for the second primary sensor, the performance monitoring with use entered SMBG points to assess that the accuracy is within the distribution of the 20/20% agreement per day from the PRECISE II study throughout that two week monitoring interval. If performance is not restored to within the PRECISE II distribution within 2 weeks, the 180-day sensor will be placed in blinded

Clinical Mode for the remainder of the study. The subject will be blinded to glucose values, alerts and alarms.

4.3.12 HbA1c BLOOD DRAW

Blood samples will be drawn for HbA1c measurement at the 90-day, 180-day, and 365-day visits, as applicable. All samples will be collected and processed as described in the instructions provided by the central lab.

4.3.13 QUESTIONNAIRES

At visits 8 (Day 90 visit), 11 (Day 180 visit), and 15 (Day 365 visit) subjects will complete the Diabetes Distress Scale questionnaire. At the removal visit, subjects will complete the CGM Satisfaction questionnaire. Subjects who have a sensor enter Clinical Mode prior to the designated visits, the Diabetes Distress Scale questionnaire and CGM Satisfaction questionnaire may be completed at the visit following confirmation of Clinical mode.

4.3.14 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. Subjects may be discharged when they have had 2 glucose readings taken at least 15 minutes apart that are >75 and < 300 mg/dL. Ketones should be ≤1.5mmol/L. Site will document any adverse events that may have occurred during the visit.

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 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.

4.3.15 ESTIMATED TOTAL BLOOD VOLUME

Approximately 43-51 blood samples will be obtained throughout the course of each of the respective visits in addition to the blood samples (2 ml) required for HbA1c analysis (as required) and fingersticks. The estimated amount of blood for each accuracy visit is approximately 2 ml per sample, exclusive of lab draws.

4.3.16 ESTIMATED VISIT DURATION

The total duration of the inpatient visit is approximately 10-12 hours depending on the visit. The study time may be extended for glucose stabilization prior to discharge.

4.4 SENSOR REMOVAL

All sensors will be removed approximately 180 days post insertion. Removal of the Sensor may also be scheduled after the Day 180 accuracy visit if more convenient for subject and clinicians. Sensor removal before or after the specified visit will not be considered a protocol deviation provided that removal is performed no longer than 189 days post-insertion and Visit removal procedures/activities are followed.

Subjects will be asked to complete *Diabetes Distress Scale* and *CGM Satisfaction* questionnaires related to their experiences at the end of sensor wear period.

Prior to Sensor removal, the Investigator will assess the Sensor location visually as well as by palpation. The Sensor will be removed following the procedure in the Eversense® CGM Sensor Insertion and Removal Instructions.

The removed Sensor(s) will be handled in compliance with institution/regulatory requirements for biomedical waste, and will be returned following Eversense® instructions, using the provided Biohazard Return Kit.

4.4.1 Day 180 Sensor Removal and Insertion (2 Sensor Subjects)

For subjects with 2 sensors, only the primary sensor will be removed approximately 180 days post insertion. A new Eversense 180 sensor will be inserted in the same arm. The secondary sensor will remain in situ. The Investigator will determine if the initial incision created for the removal of the primary sensor is adequate for the insertion of the new sensor per recommendations of Deiss D, et all[13]. Based on Investigator discretion, a new incision and insertion location may be used for placement of the new sensor. Based on recommended practices, durable performance of multiple sensor cycles is expected with consecutive insertions[14,15]. Both sensors will be removed 365 days post insertion of the secondary sensor. Sensor removal before or after the specified visit will not be considered a protocol deviation provided that removal is performed no longer than 374 days post-insertion for the secondary sensor and Visit removal procedures/activities are followed.

4.5 POST-SENSOR REMOVAL FOLLOW UP, VISIT 12 AND VISIT 16

Subjects will return to the clinic approximately 10 days following Sensor removal (sensor removal date +7 to +17 Days). The healing of the Sensor site will be evaluated at this planned final visit. If there is a concern by the investigator about healing of the Sensor site, the subject will be asked to return to the clinic in approximately 10 days, and followed until resolution. Any adverse event would be reported. Clinicians may request photographic images as part of the follow-up process if subjects are unable to return to the clinic.

Subjects will exit the study after the Follow-up Visit 12 is completed as above. The subset of subjects with 2 sensors completing additional visits 13-15 will exit the study after Follow-up Visit 16. 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 MEASUREMENT DEVICES– MAINTENANCE/CONTROL TESTING

Study equipment (bedside YSI glucose analyzer, ketone meter and study-supplied (SMBG) meter) are described in detail below.

5.2.1 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.

5.2.2 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.

5.2.3 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.

5.3 SENSOR REPLACEMENT

Primary sensors that fail within 30 days of sensor insertion will be replaced at an unscheduled visit. Subjects will continue to follow their originally scheduled visits.

5.4 PRIMARY SENSOR BLINDING

During the study the primary system may go into a “blinded mode” (called Clinical Mode by the device). Under these circumstances subjects will continue to wear the system, and enter calibrations (as prompted) and SMBG values, but the system will not provide sensor glucose information or glucose related alerts. Subjects should continue with all remaining sensor accuracy visits with the blinded system.

If a primary sensor displays a “sensor replacement” alert, it (and the secondary sensor if applicable) will be removed at an unscheduled visit, and the subject will be withdrawn.

5.5 SPONSOR PRESENCE AT VISITS

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

5.6 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.

At the discretion of the study Sponsor and primary investigator, at any visit, the locations of the devices may be documented for safety reasons through a variety of means including, but not limited to, photography, x-ray, and ultrasound examination.

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 for glycemic challenges and for laboratory measurement of HbA1c. Blood loss will not exceed the American Red Cross Guidelines of more than 475 ml over any 8-week period. Hematocrit will be assessed using local lab or Point of Care testing device.

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.

7.2 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, PA 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/PA will be at the bedside or on the unit throughout the entire visit.

7.3 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, the sensor will be removed. In the event of an insertion site infection and sensor removal in a subject with one sensor only, the subject will be withdrawn from the study and not replaced. In Subjects with two sensors, if the primary sensor is removed due to infection, the other sensor will become the primary sensor.

7.4 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 as scheduled with study exit as described in section 7.6.5 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 febrile in the 24 hours prior to Clinic Visits 2-15.
- IV access is required during most clinic visits. 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 of the hyperglycemia challenge, unlimited sugar free oral fluids should be provided to subjects to prevent dehydration secondary to hyperglycemia.

7.5 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 IV.

7.5.1 GUIDELINES FOR TREATMENT FOR HYPOGLYCEMIA WHEN NOT IN A CHALLENGE PERIOD

Subject safety prevails, and Investigator may treat for hypoglycemia when clinically indicated at any time. However, when the subject is not in a challenge and becomes hypoglycemic and safety is a concern, the guidelines below should be followed to treat the hypoglycemia.

Glucose level	Glucose administration	Safety
<60 mg/dL	Treat hypoglycemia as appropriate using oral carbohydrates such as glucose tablets (~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 (~10 g. and check glucose in 15 minutes minimum, repeat) until BG >75 mg/dL	

- 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 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/PA 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).

7.5.2 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.

Fingerstick blood ketones, using a commercially available ketone meter, will be monitored if blood glucose ≥300 mg/dl hourly until resolved. 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.

If blood ketones > 1.5 mmol/L; subject participation in glucose challenges will be stopped for the day (see below). 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. 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).

7.5.3 GUIDELINES FOR TREATMENT OF HYPERGLYCEMIA AND KETONES WHEN NOT IN A CHALLENGE

Subject safety prevails, and Investigator may treat for hyperglycemia when clinically indicated at any time. However, when the subject is not in a challenge and becomes hyperglycemic and safety is a concern, the guidelines below should be followed to treat the hyperglycemia.

		Ketone		
		<0.6	**0.6-1.5**	**>1.5**
BG	**<300**		• Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ or IV insulin targeting 120mg/dL using subject's insulin sensitivity factor	• Glucose challenges will be stopped, and subject will enter free range glucose control • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ or IV insulin targeting 120mg/dL using subject's insulin sensitivity factor
	>300	• Ketone testing will be repeated hourly until BG <300	• Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ or IV insulin targeting 120mg/dL using subject's insulin sensitivity factor • Continue monitoring until BG <300	• Glucose challenges will be stopped, and subject will enter free range glucose control • Ketone testing will be repeated hourly until <0.6 • Subject will be treated with SQ or IV insulin targeting 120mg/dL using subject's insulin sensitivity factor • Continue monitoring until BG <300

- 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.

7.6 SUBJECT STOPPING RULES

7.6.1 STOPPING CHALLENGES – REATTEMPT IN FUTURE GLUCOSE CHALLENGES

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

- Subject requests to end the challenge due to discomfort (desires food and/or insulin)
- Subject ketone measurement >1.5 mmol/L

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

7.6.2 STOPPING CHALLENGES – NO RE-ATTEMPT IN FUTURE GLUCOSE CHALLENGES

- 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, and the administration of glucagon is required
- The subject experiences symptoms of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior)

7.6.3 STOPPING ACCURACY VISIT

During accuracy 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 visit

- Subject develops DKA

7.6.4 SUBJECT WITHDRAWAL

Subjects will be withdrawn from the study if:

- Subject is noted to be pregnant
- The subject may withdraw if he/she had a serious adverse event that is deemed either related to study device or procedures
- Subject voluntarily withdraws from study
- There is an infection at the sensor insertion site that has not responded to treatment within 3 days and subject has only one functional sensor
- Subject develops more than one instance of DKA or more than one instance of severe hypoglycemia which require stopping an accuracy visit.
- Investigator determines it is in Subject's best interest to withdraw.
- Subject is lost to follow-up
- Subject dies

7.6.5 STUDY EXIT

A Subject's participation is considered complete after the follow-up Visit post-Sensor removal. 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 or 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.

7.6.6 REPLACEMENT OF SUBJECTS

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

replaced.

7.7 STUDY STOPPING RULES

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

- Subject safety issue
- More than 3 subjects require withdrawal from the study due to Severe hypoglycemia or DKA
- 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.

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.

7.8 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 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

Studies have shown that real-time CGM use improves patients overall glycemic control.[10] Improved glycemic control may not be achieved by all subjects. However, subjects 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 Eversense® CGM System has been approved for measuring interstitial fluid glucose for up to 90 days by FDA in June 2018. However, the Eversense® 180 CGM System for measuring interstitial fluid glucose for up to 180 days is considered investigational in the United States. To evaluate the Eversense® 180 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.

8.3 ANTICIPATED ADVERSE EFFECTS

The following adverse effects could occur in association with insertion, removal, and/or use of the Eversense® 180 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
- Skin thinning
- 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 Eversense® 180 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

8.4 RESIDUAL RISKS ASSOCIATED WITH THE INVESTIGATIONAL DEVICE

Components of the Eversense® 180 CGM System are manufactured under the Quality System provisions of ISO 13485:2016.

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 13485:2016. 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.

8.5 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 per 8 weeks; 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

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.

8.6 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

The transmitter is incompatible with magnetic resonance imaging (MRI) procedures. The transmitter is MR Unsafe and must be removed before undergoing an MRI procedure. Before undergoing an MRI procedure, the subjects should contact the study staff. Subjects should also let the MRI staff know that they have a sensor and transmitter.

The sensor is MR conditional and subjects can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5T or 3.0T
- Maximum spatial field gradient of 2000 gauss/cm (20 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode)

8.7 DEXAMETHASONE

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.

8.8 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.

8.9 EFFORTS TO MINIMIZE RISK

This investigation will be conducted by investigators who are qualified by training and experienced 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/PA will be present at the bedside or unit at all times. A study physician/PA 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[11], regulations by local regulatory authorities and requirements of the approving Investigational Review Boards.

8.10 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 Eversense® 180 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;

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 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 3 days 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 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 3 days after the Investigator first learns of the event. The AE form of the CRF must be completed as soon as possible but no later than 3 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 related to the device or procedure 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, then 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.

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 TRANSMITTER 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 TRANSMITTER 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.

10.2.5 DATA RETENTION

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 Eversense® 180 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 DATA POOLING

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 measure (MARD) will be analyzed with data pooling across sites. Site effects will be examined, but only descriptively.

Analyses will be performed based on aggregating all patients in the study, and again separately for each randomized groups. The analysis by randomized groups will be only performed descriptively and there will be no formal statistical comparisons. Transmitters will be designated as primary (left arm) and secondary (right arm).

Analyses will be performed for subgroup of interest (based on type of diabetes (type I vs. type 2), age (≥ 65 years of age vs. < 65), and baseline HbA1c (≥8% vs. < 8%).

11.1.3 SENSOR EVALUATION PERIOD

The Eversense® 180 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 targeted as follows:

	Day 1	Day 7	Day 14	Day 22	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Total through 180 days
YSI Range / Min # of subjects	160	80	80	160	160	160	155	140	130	112-120	
40-70 mg/dL	1040	520	520	1040	1040	1040	1008	910	845	728-780	8691-8743
71-299 mg/dL	4400	2200	2200	4400	4400	4400	4263	3850	3575	3976-4260	37664-37948
300-400 mg/dL	1280	640	640	1280	1280	1280	1240	1120	1040	896-960	10696-10760
Total	6720	3360	3360	6720	6720	6720	6510	5880	5460	5600-6000	57050-57450
									Total paired points		**57050-57450**

*Estimates based on 160 subjects inserted, with challenge type distributed equally

11.1.5 EVALUABLE DATA FOR ANALYSIS

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

11.1.6 ANALYSIS POPULATION

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 Eversense® 180 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.

11.1.7 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).

11.1.8 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.

11.1.9 TABULATION OF INVESTIGATIONAL DEVICE DEFICIENCIES

11.1.9.1 TRANSMITTER DEFICIENCIES

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

11.1.9.2 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 180 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 measure will be the mean absolute relative difference (MARD), calculated for all paired Sensor and reference measurements through 180 days post-insertion.

11.3.2 EFFECTIVENESS MEASURE

11.3.2.1 EFFECTIVENESS MEASURE: CRITERIA

The effectiveness objective is to descriptively document the distribution of absolute relative difference across all evaluable subjects and to estimate the MARD. MARD will be calculated based on all the data through 180 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 measure is the mean absolute relative difference (MARD), defined as the average of absolute difference of paired Eversense® 180 CGM System and reference glucose readings divided by the reference glucose reading (reference) for all reference glucose values, that is:

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

Where, n is the total number of CGM and reference glucose pairs during the evaluation period, that is, through 180 days of Sensor use.

11.3.2.2 SAMPLE SIZE AND POWER CACULATION

This study does not feature any inferential statistics. The sample size for the study was not determined based on a power calculation but was based on the desire to obtain a minimum number subjects at the 180 day visit (i.e. 120)

Additionally, the enrollment target of 20 patients per subgroup of interest (based on type of diabetes (type I vs. type 2), age (≥ 65 years of age vs. < 65), and baseline HbA1c (≥8% vs. < 8%) will provide a clinically reasonable amount of data to characterize these subgroups. A subgroup of size 20 will provide an 80% probability of observing one or more rare events in that subgroup for a subgroup population rate as low as 8%.

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

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

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

11.3.2.3.4 MEDIAN ABSLOUTE DIFFERENCE BETWEEN SENSOR AND REFERENCE MEASUREMENTS

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

11.3.2.3.5 MEDIAN RELATIVE DIFFERENCE BETWEEN SENSOR AND REFERENCE MEASUREMENTS

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

11.3.2.3.6 SYSTEM AGREEMENT WITH REFERENCE

The Agreement of the CGM System to reference measurements will be assessed by looking at the differences ($\frac{|(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}|}{(\text{Glucose})_{\text{REFERENCE}}}$) x 100% 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 MEASURE IN FULL GLUCOSE RANGE AND DIFFERENT GLYCEMIC REGIONS

Mean/median absolute relative difference, mean/median relative difference, mean/median absolute different when reference YSI≤70 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 180 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 10 in APPENDIX 2).

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

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

11.3.2.8 CALIBRATION FREQUENCY ANALYSIS

After the conduct of the study, additional effectiveness analyses will be performed with a modified calibration scheme to support 1 calibration per day after Day 21 following Sensor insertion (i.e., calibration will be performed twice (2) per day for Days 1-21, followed by once (1) per day for Days 22 until the end of Sensor life). It is important to note that the raw clinical data that is collected by the Sensor is independent of the calibration values that are entered into the MMA. Performing the effectiveness analyses after the collection of Sensor data is analogous to how the effectiveness analyses were performed to demonstrate the accuracy of the algorithm change that was included in Software 602 (SW602), which was approved in the Eversense CGM System PMA (P160048). A separate statistical analysis plan will be developed for this analysis to evaluate the new calibration frequency.

12 DEVICE ACCOUNTABILITY

Only an approved Investigator and investigational site may receive and use the Eversense® 180 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 REPONSIBILITIES 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 minimum 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)

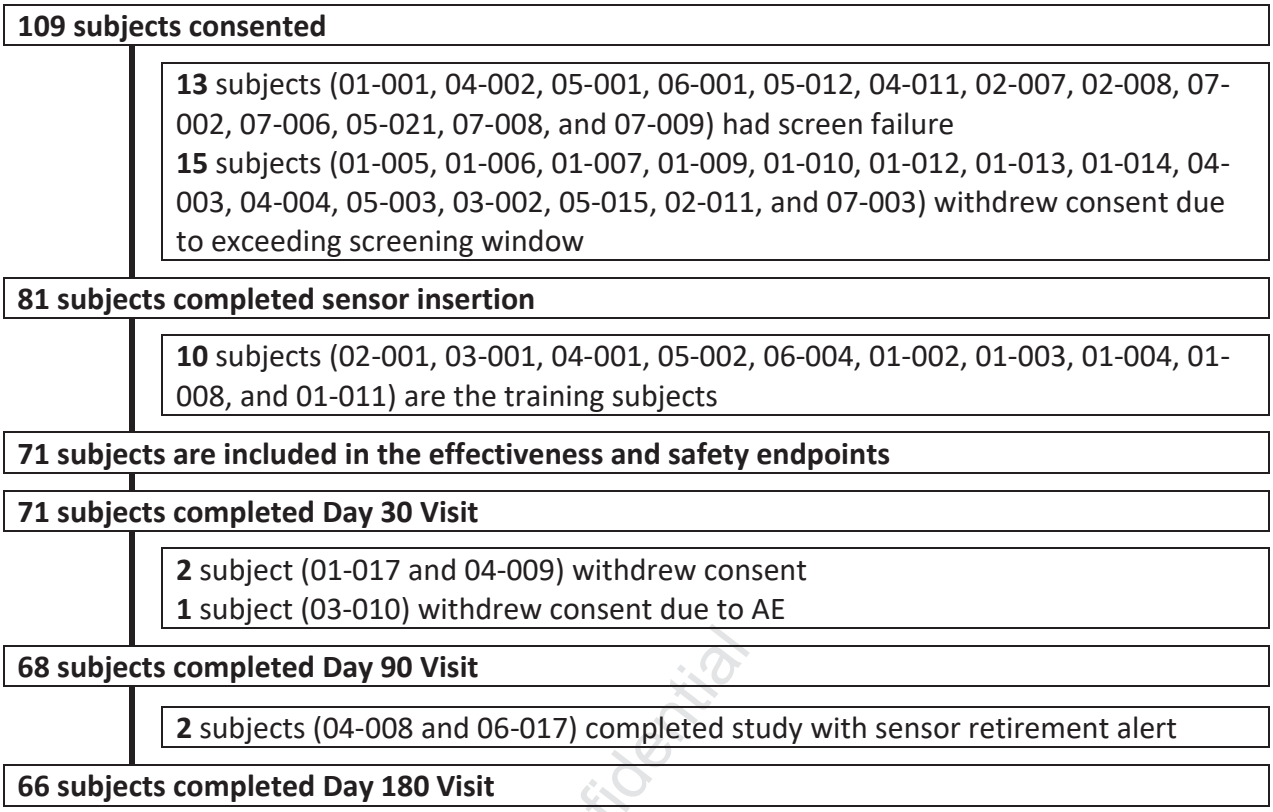

Table 1. Investigational Transmitter Deficiencies (Sample Data)

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										

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
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												
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 22								
Day 30								
Day 60								
Day 90								
Day 120								
Day 150								
Day 180								

Table 10: CGM System between System Precision

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

PARD	
PCV	