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Title: A Post- Approval Study to Demonstrate the Long-term Safety and Effectiveness of the Eversense Continuous Glucose Monitoring (CGM) System

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A Post- Approval Study to Demonstrate the Long-term Safety and Effectiveness of the Eversense Continuous Glucose Monitoring (CGM) System

Approval

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Quality Approval

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Title of Protocol: A Post- Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System

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SUMMARY OF CHANGES

Protocol Version	Change Description
01	Initial release
02	Increased number of subjects, added subgroup analysis, removed plasma DEX analysis, added CGM use to exclusion criteria, added weight check, added same pocket reinsertion, removed last bullet point from SAE definition, added device malfunction returns to Senseonics, added Sensor returns to Senseonics at 12 and 24 months, added PRECISION data to Sample size justification, removed Sensor grace period, updated all visit windows to 0 to 7 days
03	Added summary of changes, increased number of subjects, number of sites and study duration/completion milestones. Updated primary safety endpoint and hypothesis, added >65 enrollment goal, added HCP experience questionnaire, made visit windows more clear, added patient call between visits for AE documentation, removed same pocket reinsertions, added DSMB and CEC to AE section, added Skin thinning to AE list, updated sample size justification, updated visit schedule table (format, visit windows, protocol
04	added patient call at 14 days after insertions for AE documentation
05	Updated physician and HCP to HCP (physicians, physician assistants, and/or nurse practitioners).
06	Updated section 8.3 to include a statement for 30% of insertions/removals performed by NPs and PAs
07	Updated abbreviations and exclusion criteria to remove MRI.

08	Update to transition study subjects to the 180-day Eversense E3 CGM System. Updated primary safety endpoint sample size justification (section 8.4) to adjust for a combination of the 90-day and 180-day sensor insertion and removal cycles to achieve at least 1400 Sensor wear cycles. Updated the clinical study background including addition of the PROMISE study and FDA approval of the Eversense E3 CGM System, and removal of OUS feasibility studies. Study visit window was updated from + 0 – 7 days to ±7 days. Expected date to complete follow-up of all study participants updated from 48 months to 60 months.
09	Changing participation from 24 to 27 months of CGM use, and adding, or until at least 1400 cycles of Sensor use are achieved.

10	Changing Other Safety Endpoints to “up to 27 months” from “through 24 months.” Clarified sections 8.4.3 and 10, that subjects will be encouraged to remain in the study up to 27 months. Updated section 6.9 (Residual DXA testing) to indicate, as applicable, that Sensors will be removed at 24 or 27 months. Clarified statement in Section 10 that follow-up for all study subjects will be complete up to 27 months (from 24 months), or after at least 1400 sensor cycles are completed study wide, after study enrollment is complete.

SYNOPSIS

Study Aspect	Description
Title:	A Post Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System
Purpose:	To evaluate the long-term safety and effectiveness of the Eversense CGM System over repeat insertion and removal cycles
Primary Safety Objective:	To demonstrate the long-term safety of the Eversense CGM System
Primary Safety Endpoint:	• Incidence of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity
Other Safety Endpoints and Analyses:	• Rate of all device-related and insertion and removal procedure-related adverse events • Rate of device breakage • Rate of device-related and insertion and removal procedure-related serious adverse events up to 27 months post-first Sensor insertion • Subgroup analysis of all safety endpoints based on: ○ Age (<65 years vs. ≥65 years, minimum 40 subjects)
Effectiveness Objective:	To demonstrate the long-term effectiveness of the Eversense CGM System
Primary Effectiveness Endpoint:	• Time in range, defined as glucose values between 70 mg/dL and 180 mg/dL, at 12 months compared to the first month post-first Sensor insertion
Effectiveness Endpoints:	• Average hours of use per day • Change in HbA1c levels at each 6-month interval
Patient Perspective Endpoint:	• Patient satisfaction with CGM system use

Other Endpoints:	• Success rate of insertion and removal procedures, overall and by HCP experience (learning curve by number of cases), to evaluate training program • Rate of serious adverse events based on HCP experience with the insertion and removal of Sensors (learning curve by number of cases) • HCP feedback questionnaire regarding insertion/removal
Study Duration:	Study Enrollment: Approximately 36 months Patient Participation: - Approximately 27months
Subject Follow-up:	Patients will return to the clinic at approximately 3-month or 6-month intervals for exchange of the Sensor and for routine follow up of their diabetes. Patients will participate for up to 27 months of CGM system use or until at least 1400 cycles of Sensor use are achieved.
Design:	Prospective, multi-center study at up to 30 sites in the U.S. enrolling up to 400 adult subjects with diabetes (to insert 273 subjects) including at least 40 subjects ≥65 years to achieve at least 1400 Sensor cycles. The subjects will have one Sensor inserted by trained health care professionals approximately every 3 to 6 months dependent upon the Sensor used (90-day Eversense Sensor or 180-day Eversense E3 Sensor).
Statistical Analysis and Study Reporting:	Statistical analysis with interim reports will be initiated per FDA PAS guidelines of every 6 months for the first 2 years and annually thereafter. Study hypotheses will be evaluated at end of study

ABBREVIATIONS

AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring System
CFR	Code of Federal Regulations
CRF	Case Report Form
DCF	Data Clarification Form
DKA	Diabetic Keto-Acidosis
DMS	Data Management System
DQMP	Data Quality Management Plan
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EN	European Standard
EU	European Union
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
HCP	Health Care Providers (physicians, physician assistants, and/or nurse practitioners)
HHD	Hand Held Device
HPA Axis	Hypothalamic-Pituitary-Adrenal axis
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITT	Intention-to-treat
MMA	Mobile Medical App
PAS	Post-Approval Study
PMA	Premarket Approval
PP	Per Protocol
RF	Radio Frequency
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SMBG	Self-Monitoring Blood Glucose
UADE	Unanticipated Adverse Device Effect

TABLE OF CONTENTS

1. INTRODUCTION, IDENTIFICATION OF THE DEVICE, AND RATIONALE

Despite 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."i 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 CGM System measures glucose levels every 5 minutes using Sensors implanted under the skin by a trained clinician. Unlike commercially available transcutaneous continuous glucose monitoring devices with short operating lives (up to 14 days), the Sensor is intended to be inserted subcutaneously with no Sensor part protruding from the skin, and the operating life is intended to be up to 90 days (for the Eversense Sensor) or 180 days (for the Eversense E3 Sensor) or until Sensor end-of-life indicator is reached.

1.1. NAMES, INTENDED USE, AND DESCRIPTION OF STUDY DEVICE

The study devices are the Eversense Continuous Glucose Monitoring System ("Eversense CGM System"), which is the 90-day system, and the "Eversense E3 CGM System", which is the 180-day system. The description below is accurate for both CGM systems.

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

- To provide real-time glucose readings directly to the user
- To provide glucose trend information

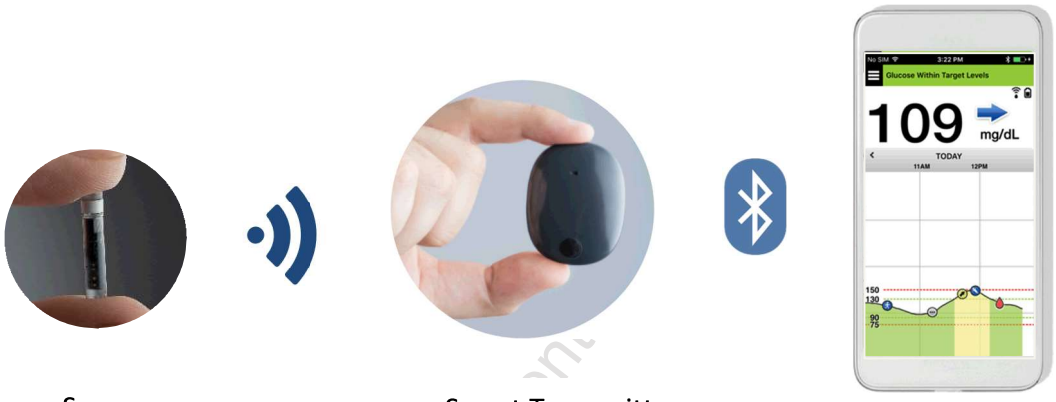
- To provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

The Eversense CGM System consists of:

1. Glucose Sensor, (approximately 3.5 mm [0.138”] diameter x 18.3 mm [0.720”] length) which has a ring that elutes the steroid dexamethasone.

2. Battery-powered external Transmitter (“Transmitter”)

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



Sensor
(Inserted subcutaneously)

Smart Transmitter
(Worn externally over Sensor)

Mobile App
(Android or iOS)

Accessories to the system include:

1. Blunt dissector for creating a pocket under the skin

2. Insertion tool used to place the Sensor into the pocket.

3. Transmitter accessories (power supply, adhesive patches)

1.1.1. DESCRIPTION

The Eversense CGM Sensor uses a selective, fully reversible binding between glucose and a unique fluorescent indicator macromolecule that is grafted on the surface of the Sensor. The fundamental recognition reaction is a reversible condensation of the cis-diol groups of glucose with the bis-boronate moiety of the indicator macromolecule. 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 Eversense 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 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. The Instructions for Use are provided with each shipment. Transmitters will be provided for single-subject use in this clinical trial.

Insertion of the Sensor is a minimally invasive procedure and clinical investigators representing the intended use population (Endocrinologists, Internists, General and Family Practitioners, including physicians, physician assistants, and/or nurse practitioners) will be appropriately trained in the procedure prior to insertion or removal of the Sensor. Training and qualifications of investigators will be documented per the formal commercial training procedure.

1.1.2. CALIBRATION

The Eversense CGM System will be calibrated by the Subjects according to the Eversense CGM User Guide, using their blood glucose meter (BG meter). The calibration process automatically moves through three phases: Warm Up, Initialization, and Daily Calibration:

- Warm Up is the first 24 hours after Sensor insertion. During this period, Glucose information is not calculated. No calibration is performed.

- Initialization can be performed a minimum of 24 hours after Sensor insertion. Following the Warm-up phase, the entering of four successful calibration BG readings within 24 hours is required for successful completion of Initialization. Glucose information will begin to be calculated after the second calibration is entered successfully.

- Daily Calibration requires 2 successful calibrations per day*, a minimum of 10 and maximum of 14 hours apart.

* The Eversense E3 CGM System transitions on day 21 to requiring a combination of 1 or 2 calibrations per day depending upon the preset rules in the firmware (the device will prompt calibration 12 or 24 hours after the prior calibration timepoint).

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

1.2. SUMMARY OF PRE-CLINICAL AND CLINICAL EXPERIENCE

Bench testing and animal testing have been conducted on the Senseonics (Eversense) CGM System to characterize performance, evaluate biocompatibility and demonstrate proof of principle in primates.

Four 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. Lastly, the U.S. pivotal study PROMISE was conducted to evaluate the safety and accuracy of the 180-day Eversense CGM System. The study was completed in May 2020 and formed the basis of FDA approval of the Eversense E3 CGM System (trade name of the 180-day system) in February 2022.

These studies demonstrated that the Senseonics (Eversense) CGM System provided reliable interstitial fluid glucose readings for periods of up to approximately 90 or 180 days (depending on the study) when compared to reference blood glucose analyzer measurements, with a favorable safety profile.

2. PURPOSE OF THIS STUDY

The purpose of this post-approval study (PAS) is to provide long-term safety and effectiveness of the Eversense CGM System (PMA Application P160048) in the post-market setting. In the premarket setting, the PRECISE II and PRECISION studies demonstrated safety and accuracy of the CGM system in estimating blood glucose levels compared to reference blood glucose analyzer levels to 90 days. The PROMISE study demonstrated safety and accuracy of the CGM system up to 180 days. This PAS study will provide safety and effectiveness data up to 27 months of repeated use.

3. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES

3.1. PRIMARY SAFETY OBJECTIVE

The primary safety objective is to demonstrate the long-term safety of the Eversense CGM System.

3.2. PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the incidence of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity.

3.3. PRIMARY SAFETY HYPOTHESIS

The primary safety composite endpoint will be evaluated in the following hypothesis test against a Performance Goal of 4%:

H_0: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is greater than or equal to 4%.

$$H_0: p \geq 4\%$$

H_1: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is less than 4%.

$$H_1: p < 4\%$$

The rate will be tested against the Performance Goal of 4%, using an exact, binomial test, with a one-sided p-value of 0.05 considered evidence of statistical significance. Data will be analyzed on a per cycle basis.

3.4. OTHER SAFETY ENDPOINTS

Other safety endpoints include:

- Rate of all device-related and insertion and removal procedure-related adverse events (serious and non-serious events) up to 27 months post-first Sensor insertion
- Rate of device breakage up to 27 months post-first Sensor insertion
- Rate of device-related and insertion and removal procedure-related serious adverse events up to 27 months post-first Sensor insertion
- Subgroup analysis of safety endpoints based on:
    - Age (<65 years vs. >65 years, minimum 40 subjects)
    - Diabetes type (I vs. II)
- Race (non-Caucasian vs. Caucasian)

3.5. EFFECTIVENESS OBJECTIVE

The primary effectiveness objective is to demonstrate the long-term effectiveness of the Eversense CGM System.

3.6. PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is Time in Range, which is defined as glucose values between 70 mg/dL and 180 mg/dL, at 12 months post-first Sensor insertion compared to the first month post-first Sensor insertion.

3.7. OTHER EFFECTIVENESS ENDPOINTS

Other effectiveness endpoints include:

- Average hours of use per day
- Change in HbA1c levels at each 6-month interval from baseline

3.8. PATIENT PERSPECTIVE ENDPOINT

Patient experiences with the CGM system will be assessed using the CGM Satisfaction Survey which is a validated patient satisfaction questionnaire specifically developed for CGM systems by the Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group. Patients will complete the CGM Satisfaction Survey (a 44-item questionnaire) at 6 months and at 12 and 24 months.

Patients will also complete the Diabetes Distress Scale, which is a 17-item scale that measures four dimensions of distress (emotional burden, regimen distress, interpersonal distress, and physician distress). Patients will complete the Diabetes Distress Scale at baseline, 6, 12 and 24 months.

3.9. HCP PERSPECTIVE ENDPOINT

3.10. OTHER ENDPOINTS

Other study endpoints include:

- Success rate of insertion and removal procedures, overall and by HCP experience to evaluate training program.
- Rate of serious adverse events based on HCP experience with the insertion and removal of Sensors (learning curve by number of cases)

4. STUDY POPULATION

The PAS will enroll up to 400 subjects (to insert 273 subjects) to ensure adequate numbers of subjects for the primary safety endpoint.

4.1. INCLUSION CRITERIA

Subjects may be included in the PAS if they fit the following inclusion criteria:

1. Subject has diabetes
2. Subject is greater than 18 years of age

4.2. EXCLUSION CRITERIA

Subjects may not be included in the PAS if they fulfill the following exclusion criteria:

1. Subject is critically ill or hospitalized
2. Subject has a known contraindication to dexamethasone or dexamethasone acetate
3. Subjects requiring intravenous mannitol or mannitol irrigation solutions
4. Female subjects who are pregnant, planning on becoming pregnant or nursing
5. Subjects on hybrid closed loop systems or closed loop systems
6. Subjects on other CGM systems

4.3. CRITERIA FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

A subject may choose to withdraw at any time for any reason without adverse effect on their care. The subject will continue with their medical follow-up, according to standard-of- care.

The treating HCP may also choose to withdraw a subject from the study, if in the best medical interest of the subject or compliance with study requirements cannot be maintained.

5. STUDY DESIGN

5.1. OVERVIEW

This is a prospective, multi-center study, whereby up to 400 subjects will be enrolled in the United States at up to 30 sites to achieve at least 1400 Sensor wear cycles at the end of the study. The subjects will have one Sensor inserted by trained HCP (physicians, physician assistants, and/or nurse practitioners) approximately every 3 months (for the 90-day Eversense Sensor) or 6 months (for the 180-day Eversense E3 Sensor). Sensors will be inserted in the upper arm of the subjects.

Follow up visits are anticipated at approximately 3- or 6- month intervals. A Sensor removal and reinsertion will be arranged once the current Sensor reaches its end of life. At each Sensor insertion and/or removal the treating HCP will be asked to report on the ease of the procedure and on any complications that occurred.

5.1.1. VISIT SCHEDULE

Visit 1 Enrollment/Sensor insertion Visit. Following the informed consent process, the screening evaluation will determine subject eligibility for Sensor insertion. Screening will include medical and diabetes history, physical examination, laboratory assessments and questionnaires. Sensors are inserted by a health care professional in the upper arm. Subject training on study and devices. Visit lasting approximately 2 to 3 hours.

5.1.1.1. SCHEDULE FOR SUBJECTS WHO ONLY RECEIVE EITHER 90-DAY OR 180-DAY SENSORS:

- 90-day Sensor - Visits 2-8 Follow-up/Sensor replacement Visit (Days 90, 180, 270, 360, 450, 540, and 630) after Visit 1 (90 days ±7 days after each insertion).

- 180-day Sensor - Visits 2-4 Follow-up/Sensor replacement Visit (Days 180, 360, 540) after Visit 1 (180 days ±7 days after each insertion)

A safety evaluation will be performed including examination of Sensor sites and collection of adverse events. Sensor replacements will occur at these visits, laboratory assessments every 6 months and questionnaires as specified.

5.1.1.2. SCHEDULE FOR SUBJECTS WHO TRANSITION FROM 90-DAY TO 180-DAY SENSORS:

- Visits for 90-day to 180-day Sensor transition subjects follow-up/Sensor replacement[1] range from Day 180 to Day 630 after Visit 1 (90- or 180-days ±7 days, dependent on prior Sensor).

Subjects will continue the 90-day visit schedule (section 5.3). A safety evaluation will be performed including examination of Sensor sites and collection of adverse events. Subjects will complete all required follow up testing and questionnaires. New Sensors will be inserted and removed at appropriate intervals.

5.2. FINAL FOLLOW-UP/SENSOR REMOVAL VISIT:

5.2.1. SCHEDULE FOR SUBJECTS WHO ONLY RECEIVE A 90-DAY OR 180-DAY SENSOR:

- 90-day Sensor – Day 720 after Visit 1 (90 days ±7 days after final insertion (Visit 9)

[1] Some subjects will have a hybrid of 90-day and 180-day Sensors due to starting the study with 90-day Sensors

- 180-day Sensor – Day 720 after Visit 1 (180 days ±7 days after final insertion for 180-day Sensor [Visit 5]

A safety evaluation will be performed including examination of Sensor sites and collection of adverse events. Sensor removal, laboratory assessment and questionnaires will occur at this visit.

5.2.2. SCHEDULE FOR SUBJECTS WHO TRANSITION FROM 90-DAY TO 180-DAY SENSORS:

Subjects who transition to the 180-day Sensor at 90-, 270-, 450- or 630-day visit will have a safety evaluation performed at the 720-day visit ±7 days including examination of Sensor sites and collection of adverse events along with laboratory assessment and questionnaire administration. The Sensor will NOT be removed at this visit.

- Follow-up Assessment calls will be made 15 and 45 days after the 720-day visit.
- Ninety (90) days ±7 days or Sensor end-of-life (whichever is earlier) following 720-day visit in the above transition subjects, the subject will return to the clinic for Sensor removal followed by a phone call for AE assessment. This call designates final participation in the study.

5.3. VISIT SCHEDULE TABLE

Visit Number (90-Day or transition from 90-day to 180-day Sensor)	1	2	3	4	5	6	7	8	9
Day[1,2]	0	90	180	270	360	450	540	630	720
Visit Number (180-Day Sensor)	1		2		3		4		5
Day[1,2]	0		180		360		540		720
Visit window	N/A	90 or 180 days ±7 days after each insertion							
Visit Type	Entry	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up /Exit
Agreement to participate	X								
Sensor Insertion	X	X	X	X	X	X	X	X	
Sensor Removal		X	X	X	X[3]	X	X	X	X[3]
Pregnancy test	X	X	X	X	X	X	X	X	
HbA1c	X		X		X		X		X
Weight	X		X		X		X		X
Subject questionnaires	X[4]		X		X		X		X

(DDS and CGM Satisfaction)									
Safety evaluation	X	X	X	X	X	X	X	X	X
Site to call patients in between visits at ~15 days after each insertion	X	X	X	X	X	X	X	X	X
Site to call patients in between visits at ~45 days after each insertion	X	X	X	X	X	X	X	X	X
HCP Survey[5]	X		X		X		X		

[1]Visit day will vary from those listed based on actual Sensor replacement dates and visit windows

[2]Subjects who transition to the 180-day Sensor at 90-, 270-, 450- or 630-day visit will have a safety evaluation performed at the 720-day visit ±7 days including examination of Sensor sites and collection of adverse events along with laboratory assessment and questionnaire administration. The Sensor will NOT be removed at this visit. Follow-up Assessment calls will be made 15 and 45 days after the 720-day visit. Ninety (90) days ±7 days or Sensor end-of-life (whichever is earlier) following 720-day visit in the above transition subjects, the subject will return to the clinic for Sensor removal followed by a phone call for AE assessment 30 days later. This call designates final participation in the study.

[3]Sensors removed at 12 and 24 months (or 27 months as applicable) (subjects 4th and 8th Sensor for 90-day Sensor and 2nd and 4th Sensor for 180-day Sensor) will be returned to Senseonics

[4]At Visit Number 1, only the DDS will be completed

[5]To be completed after the third Sensor insertion and third removal and then periodically (approximately every 6 months) thereafter.

5.4. VISIT DETAILS

5.4.1. VISIT 1 –ENROLLMENT/INSERTION

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 Enrollment/Insertion Visit includes performing/collecting the following information:

- Demographics- including age, gender at birth, race/ethnicity, 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).
- Current and Past Medical History- including concomitant prescription medications.
- Physical examination and vital signs- including height, weight, blood pressure, pulse, temperature, assessment of potential Sensor insertion sites.
- Blood samples will be drawn for the following laboratory tests:
  - Hemoglobin A1C
- Point of care testing
- Urine pregnancy test- for females of childbearing capacity (defined as not surgically sterile or not menopausal for ≥ 1 year)

5.4.1.1. SENSOR INSERTIONS

A trained study HCP (physicians, physician assistants, and/or nurse practitioners) will insert the Sensor into the subcutaneous tissue using appropriate technique described in the Eversense CGM Sensor Insertion and Removal Instructions. The location of each Sensor will be documented.

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

Subjects will be advised to keep the area dry for 24-48 hours. Subjects will be advised to change the dressing approximately 48 hours post insertion, and they will check that the healing process is going as expected (minor redness, no swellings, no increased temperature, no increased pain and no sign of infection). The subjects will be instructed to leave the steri-strips in place until they fall off on their own. If the edges of the strips

peel back, they may be trimmed. After 48 hours subjects will be advised to change the dressing as required until the incision is healed. Cleaning can be done with normal saline in the clinic, but at home they can use tap water.

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

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

5.4.1.2. DEVICE DISBURSEMENT

Subjects will be assigned the following devices:

- Eversense Continuous Glucose Monitoring (CGM) Systems consisting of:
- One Transmitter (for Eversense or Eversense E3 CGM System as appropriate) and accessories (charger, adhesive patches)
- Eversense or Eversense E3 CGM System User Guides, as appropriate

The clinical site staff will assist the subject with loading the appropriate Eversense Mobile Medical App (MMA) on their handheld device (smartphone or iPod Touch) as needed.

5.4.1.3. SUBJECT TRAINING

The subject will be provided both verbal and written instructions for proper incision care of the insertion site. 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.

The subject will be instructed on the proper use of the Transmitter and Mobile Medical Application (refer to the Eversense and Eversense E3 CGM User Guides). The transmitter should be worn over the Sensor starting approximately 24 hours post insertion. Subjects will be prompted to calibrate the Sensor using fingerstick measurements (a minimum of 2 each day, approximately 12 hours apart for the Eversense CGM System or 2 each day for the first 20 days transitioning to primarily 1 per day on day 21 for the Eversense E3 CGM System) using their BG meter.

5.4.1.4. QUESTIONNAIRES

Subjects will be asked to fill out a short questionnaire (DDS) about their diabetes.

HCPs will fill out a short questionnaire regarding their experience with the insertion/removal procedure device use and training on a periodic basis

5.4.1.5. 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.

5.4.1.6. ESTIMATED VISIT DURATION

Study visit is approximately 2-3 hours.

5.4.2. FOLLOW-UP/SENSOR REPLACEMENT VISITS

<u>90 Day Sensor</u>

- Visit 2 – Day 90 (90 days ±7 days after first insertion)
- Visit 3 – Day 180 (90 days ±7 days after second insertion)
- Visit 4 – Day 270 (90 days ±7 days after third insertion)
- Visit 5 – Day 360 (90 days ±7 days after fourth insertion)
- Visit 6 – Day 450 (90 days ±7 days after fifth insertion)
- Visit 7 – Day 540 (90 days ±7 days after sixth insertion)
- Visit 8 – Day 630 (90 days ±7 days after seventh insertion)

180 Day Sensor

- Visit 2 – Day 180 (180 days ±7 days after first insertion)
- Visit 3 –Day 360 (180 days ±7 days after second insertion)
- Visit 4 – Day 540 (180 days ±7 days after third insertion)

The above visit days and windows are approximate. Sensor life is either 90 or 180 days and will stop providing glucose values after 90 or 180 days. In the event that a Sensor is replaced prior to or after the visit day listed above, the next Sensor replacement visit should be planned for 90 or 180 days (±7 days) depending on the Sensor inserted at the last Sensor insertion. If a Sensor stops functioning prior to the scheduled replacement visit, the visit may be rescheduled earlier.

The procedures/instructions listed below will be followed for Follow-up/Sensor Replacement Visits 2-8 (90-day Sensor) and Visits 2-4 (180-day Sensor) or as described above for Sensor transition subjects (Section 5.1.1.2).

5.4.2.1. SUBJECT ADMISSION

Female subjects of childbearing capacity will perform a urine pregnancy test. If positive, the subject will discontinue study participation. Subject withdrawal will be documented.

5.4.2.2. SAFETY ASSESSMENT

Adverse events

At each visit, adverse events that occur during the visit and that occurred during home use since the previous visit will be documented. Adverse events including those associated with the insertion site will be documented on the appropriate eCRF. Study staff will contact subjects approximately 14 and 45 days post insertion to enable documentation of any adverse events. Subjects will also be reminded to notify clinic staff of any adverse events that occur during the Sensor wear period.

Subjects will be asked to provide information on the following:

- any hospitalizations that may have occurred due to hypoglycemic or hyperglycemic events, and
- any changes in systemic immune function (such as any local or systemic infections and any problems with wound healing independent of Sensor insertion sites).

Insertion Site Assessment

Assessments of the Sensor insertion and removal sites will take place by the clinician at each placement with physical exam and documentation of adverse events. Details can be found in Section 6.

5.4.2.3. LABORATORY TESTING / BIOMETRICS

Every 6 months (See section 5.3), subjects will have blood samples taken for the following laboratory tests:

- HbA1c

Every 6 months (See section 5.3), subjects will have the following biometrics collected:

- Weight

5.4.2.4. SENSOR REPLACEMENT

Insertion of New Sensor

A trained study clinician will insert the new Sensor as described in the Visit 1 section above. Each replacement Sensor will be inserted in the alternate arm.

Removal of Old Sensor

A trained study clinician will remove the old Sensor using appropriate technique described in the Eversense CGM Sensor Insertion and Removal Instructions.

Subjects will be advised that they may take over the counter pain medication if needed for any discomfort after the insertion/removal process. No medication, including medication-containing creams and patches is to be applied over the Sensor insertion/removal sites. Subjects will be advised to keep the areas dry for 24-48 hours. Subjects will be advised to change the dressing approximately 48 hours post insertion, and they will check that the healing process is going as expected (minor redness, no swellings, no increased temperature, no increased pain and no sign of infection). The subjects will be instructed to leave the steri-strips in place until they fall off on their own. If the edges of the strips peel back, they may be trimmed. After 48 hours subjects will be advised to change the dressing as required until the incision is healed. Cleaning can be done with normal saline in the clinic, but at home they can use tap water.

5.4.2.5. QUESTIONNAIRES

Subjects will be asked to fill out the DDS and CGM satisfaction questionnaires at Visit 3 (Day 180) and 5 (Day 365). HCPs will be asked to fill out a short questionnaire regarding their experience periodically.

5.4.2.6. DATA COLLECTION

The HCP performing the Sensor insertion/removal will record information about the insertion/removal procedure on the CRF as appropriate.

5.4.2.7. ESTIMATED VISIT DURATION

The total duration of the Follow-up/Sensor replacement visit is approximately 2 hours.

5.4.3. VISIT 5/9, DAY 720 FOLLOW-UP/SENSOR REMOVAL FOR SUBJECTS WHO ONLY

RECEIVE A 90-DAY OR 180-DAY SENSOR[2]

The following procedures/instructions will be followed for Follow-up/Sensor removal visit:

5.4.3.1. SENSOR REMOVAL

A trained study clinician will remove the Sensor from the subcutaneous tissue as described above in the Follow-up/Sensor Replacement Visit description.

5.4.3.2. LABORATORY TESTING / BIOMETRICS

Subjects will have blood samples taken for the following laboratory tests:

- HbA1c

Subjects will have the following biometrics collected:

- Weight

5.4.3.3. DATA COLLECTION

The HCP performing the Sensor removal will be asked to record information about the removal procedure on a CRF as appropriate.

5.4.3.4. QUESTIONNAIRES

Subjects will be asked to fill out the DDS and CGM satisfaction questionnaires at this visit.

5.4.3.5. ESTIMATED VISIT DURATION

The total duration of the Follow-up/Sensor removal visit is approximately 2 hours.

6. 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.

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[2] Subjects who transition to 180-day Sensor at 90-, 270-, 450- or 630-day visit, will have a safety evaluation performed at 720-day Visit including examination of Sensor sites and collection of adverse events along with laboratory assessment and questionnaire administration. Follow-up Assessment calls will be made 15 and 45 days after the 720-day visit Ninety (90) days or to Sensor end-of-life (whichever is earlier) following the 720-day visit the subject will return to the clinic for Sensor removal, followed by a phone call for AE assessment. This call designates final participation in the study.

Subjects will contact the Investigator with any questions or concerns. The Investigator will contact Senseonics with questions regarding recording and reporting of adverse events.

6.1. 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 medical device.

NOTE 1: This definition includes events related to the 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 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 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 study 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 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.

6.2. MONITORING OF ADVERSE EVENTS

Adverse events (AEs) may be volunteered by Subjects, elicited by Investigator or others, or observed. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device, and/or insertion or removal procedure or other study-related procedure. The Investigator will determine whether or not the event meets the serious criteria. If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the reporting process, including source documentation. Study staff will contact subjects approximately 14 and 45 days post insertion to enable documentation of any adverse events. Subjects will also be reminded to notify clinic staff of any adverse events that

occur during the Sensor wear period.

6.2.1. DATA SAFETY MONITORING BOARD

An independent data safety monitoring board will be established prior to the initiation of the study. Members will represent areas of expertise such as internal medicine and endocrinology and biostatistics. The DSMB will develop a charter and hold formal review meetings over the course of the study to assess the ongoing safety information collected as required by their charter. The DSMB will assess if the overall safety profile continues to be appropriate throughout the conduct of the study and immediately reassess if serious events such as death, serious deterioration of health or fetal distress are deemed related to the device.

6.2.2. CLINICAL EVENTS COMMITTEE

An independent Clinical Events Committee (CEC) will be established prior to the initiation of the study. The CEC will develop and follow a charter which dictates holding frequent meetings as needed whereby individual adverse events are reviewed and adjudicated. All or serious adverse events (whether judged by the site investigators to be related to the device and/or insertion or removal procedure or not) will be assessed for relatedness and severity by the CEC as requested by FDA.

6.3. ADVERSE EVENT REPORTING

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

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

All 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.

6.3.1. AE REPORTING PERIOD

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

6.3.2. 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.

6.3.3. 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.

6.4. ANTICIPATED ADVERSE EFFECTS

The following adverse effects could occur in association with insertion, removal, and/or use of the Eversense 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 incision 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 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

6.5. INSERTION SITE ASSESSMENT

Assessments of the Sensor insertion and removal sites will take place by the clinician at each placement with physical exam and documentation of adverse events. The exam will include current and all previous Sensor sites as well as the surrounding area to capture any skin reactions resulting from attachment of the transmitter to the skin. These potential events include but are not limited to:

- Adhesive Patch Location Site – Irritation including redness, excoriation or ulceration
- Sensor Location Site – Pain/Discomfort
- Sensor Location Site – Redness
- Sensor Location Site – Infection

- Skin atrophy (thinning of the skin as compared to adjacent skin) over the Sensor
- Skin depigmentation (loss of coloration as compared to adjacent skin) over the Sensor
- Prolonged healing of incision site after insertion or removal (beyond expected 5-7days)

6.6. ESCALATION PLAN FOR SUSPECTED STEROID EXPOSURE

Patients will also be checked for complications that could possibly be related to systemic steroid exposure including;

- Poor wound healing
- Increased systemic infections
- Decreased bone density and risk of osteoporosis and/or fractures
- Suppression of the normal hypothalamic/pituitary axis
- Increased insulin resistance

Any subject demonstrating one or more of the conditions that could potentially be a result of steroid exposure listed above will undergo evaluation of the hypothalamic pituitary axis with standard 24-hour urine cortisol test and blood cortisol levels to rule out any systemic suppression as a result of steroid exposure.

6.7. RESIDUAL RISKS ASSOCIATED WITH THE DEVICE/ RMR-0019 US EVERSENSE E3 CGM SYSTEM RISK MANAGEMENT REPORT

Components of the Eversense CGM System are manufactured under the Quality System provisions of ISO 13485:2016 and 21 CFR 820.

Risk analysis has been performed and adequate control put in place as prescribed in relevant provisions of applicable regulatory requirements such as 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.

6.8. DEVICE MALFUNCTIONS

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

labeling.

Sensors that fail prior to the design life of 90 or 180 days will be returned to Senseonics for evaluation of the root cause of the premature Sensor failure. Summary results of such root cause evaluations will be presented in subsequent PAS reports.

6.9. RESIDUAL DXA TESTING

All Sensors removed after 12 and 24 (or 27 months as applicable) months participation (the subject's 4th and 8th Sensor for 90-day Sensor or 2nd and 4th for 180-day Sensor) will be returned after removal to Senseonics, where they will be assessed for residual DXA content in order to assess release rates of DXA in the broader intended use population.

7. DATA MANAGEMENT

All data will be prospectively collected by the HCPs and/or study coordinators and entered onto the electronic case report form (eCRF). All device data (calibration points, hours of wear time,) will be collected using the sponsor data management system (DMS). All data will be anonymous so that it will not be possible to identify a subject at any participating clinical center.

7.1. SOURCE DOCUMENTATION, CASE REPORT FORMS AND DATA MANAGEMENT

Data in this study will be collected on electronic Case Report Forms as well as retrieved from the web-based Data Management System (DMS).

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 (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 study site, as described in the Monitoring

Plan. 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 eCRFs 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 Electronic Data Capture (EDC) User Guideline will be developed for participating study sites describing general instructions on CRF completion; this guideline also includes investigation- specific data entry, and query management instructions.

Data entered by study 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.

7.2. LABORATORY DATA

Results of laboratory tests (HbA1c) will be provided to the sponsor, with HbA1c results provided to clinical sites.

7.3. EVERSENSE CGM DATA FLOW PROCESS

Data from Subject Eversense CGM systems, including BG meter values that have been entered into the system as calibration values will be collected from the Eversense Data Management System (DMS). The Eversense Data Management System (DMS) is an accessory to compatible Eversense CGM products. It is a web-based application that may be used to view, analyze, and store glucose information from the Eversense CGM System. CGM data are wirelessly synchronized to the Eversense DMS by PAS subjects using the Share My Data feature on the Eversense mobile app.

8. STATISTICAL PLAN

The statistical plan is summarized below. Additional details concerning the analyses will be provided in the Statistical Analysis Plan (SAP) for the study.

8.1. ANALYSIS POPULATIONS

Primary Analysis population: The primary safety and effectiveness analyses will be based on data from all enrolled subjects in this post approval study (ITT, Intention-to-treat).

Per-Protocol Safety Analysis Population: A per-protocol (PP) population will be identified based on those subjects who met the original inclusion and exclusion criteria, have demonstrated substantial compliance with the protocol and no significant protocol deviations affecting the primary endpoints. Supportive analyses for the primary effectiveness endpoint and all secondary and exploratory analyses will be performed in the PP population.

8.2. PRIMARY ENDPOINTS

8.2.1. PRIMARY SAFETY ENDPOINT

The primary safety composite endpoint will be evaluated in the following hypothesis, against a Performance Goal of 4%:

H0: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is greater than or equal to 4%.

$$H0: p \geq 4\%$$

H1: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is less than 4%.

$$H1: p < 4\%$$

The rate will be tested against the Performance Goal of 4%, using an exact, binomial test, with a one-sided p-value of 0.05 considered evidence of statistical significance. For the primary analysis, data will be analyzed on a per cycle basis, with each cycle contributing an independent observation.

As an additional analysis, analysis will be performed using a logistic regression model fit via generalized estimating equations and a working compound symmetric covariance structure; this allows for the modeling of potential within-subject correlation. The model will consist of only an intercept term; estimates will be transformed to the proportion scale to facilitate comparisons to the primary analysis of the performance goal.

An additional analysis will be performed based on only the first cycle for each subject. This will be based on an exact binomial method.

For each additional analysis, the estimate of the endpoint rate and the associated one-sided

95% upper confidence bound will be calculated.

8.3. OTHER ENDPOINTS

Safety

Other safety endpoints will be summarized using descriptive statistics appropriate to the endpoint being evaluated. There are no formal hypotheses or tests for statistical significance associated with secondary endpoints.

The rates for serious and non-serious adverse events will be summarized as binomial proportions, together with the exact, one-sided upper 95% confidence bound. These will include insertion/removal procedure-related adverse events, and rate of device breakage.

Subgroup analysis of all safety endpoints based on:

- Age (<65 years vs. >65 years, minimum 40 subjects)
- Diabetes type (I vs. II)
- Race (non-Caucasian vs. Caucasian)

Effectiveness

Effectiveness will be measured as percentage change in the percent time in range (based on hours) at one month compared to 12 months using a time in range definition of glucose values between 70 mg/dL and 180 mg/dL. The Time in Range will be summarized as the mean of the subject percentages, together with the median, standard deviation, minimum, maximum, and 25th / 75th percentiles.

Summary statistics will also be provided for the change in HbA1c levels from baseline, and average hours of use per day.

Patient Perspective

Patient satisfaction as measured by validated questionnaires (CGM satisfaction survey and Diabetes Distress Scale) administered at select visits will be reported. The patient questionnaire scores will be summarized as means, median, standard deviation, minimum, maximum, and 25th / 75th percentiles.

Other Endpoints

Success rates for insertion and removal procedures will be presented to evaluate the

effectiveness of the training program. Success rate will also be presented based on the HCP experience with insertion and removing Sensors (learning curve by number of cases). It is anticipated that approximately 30% of the insertion and removal procedures will be done by nurse practitioners and physician assistants.

The rates of serious adverse events based on HCP experience with inserting and removing Sensors (learning curve by number of cases) will be examined.

8.4. SAMPLE SIZE JUSTIFICATION

8.4.1. PRIMARY SAFETY ENDPOINT:

A total of 1400 Sensor cycles contributing to the analysis is planned.

Based on data from the PRECISE (n=81 subjects), PRECISE II (n=90 subjects), PRECISION (n=35 subjects) and PMCF (n=1686 subjects) studies, a total of 31 events occurred that would meet the definition of the primary safety endpoint in this study. With a total of 1892 subjects, this equates to an observed rate of approximately 1.6% with an associated 95% confidence interval of 1.1% to 2.3%. As there is variability associated with this sample, as evidenced by the confidence interval, a conservative expected rate of events for this study is 2.3%. The planned sample size of 1400 total cycles) with this expected rate should provide greater than 95% power for the test of the performance goal of 4%.

Meeting the performance goal of 4% for the planned sample size would require a worst-case observation of a rate of approximately 3% or less (i.e., 41 or fewer events among 1400 cycles). This result will be clinically acceptable and similar to results observed in past studies.

8.4.2. EFFECTIVENESS ENDPOINT

Descriptive statistics will be used to describe the effectiveness measures.

8.4.3. TOTAL ENROLLMENT AND FOLLOW-UP

At least 273 enrolled subjects will be inserted with Sensors to achieve at least 1400 Sensor cycles. Subjects will be encouraged to remain in the study up to 27 months of follow-up or after at least 1400 Sensor cycles are completed study wide.

9. OTHER ETHICAL AND REGULATORY CONSIDERATIONS

9.1. 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, 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 as well as respective internal review boards. No deviation from the protocol will be implemented without the prior review and approval of sponsor and/ or IRB except where it may be necessary to eliminate an immediate hazard to a subject.

9.2. INFORMED CONSENT AND INTERNAL 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. 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 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.

9.3. SUSPENSION OR PREMATURE TERMINATION OF CLINICAL INVESTIGATION

The study may only be terminated prematurely for safety reasons.

9.4. AMENDMENTS TO THE PAS PLAN

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

9.5. DEVICE ACCOUNTABILITY

The Eversense CGM System will be used in accordance with its approved product labeling. The treating HCP will follow applicable hospital (institutional) guidelines. The HCP shall maintain complete records of the date of implantation, subject identification and follow applicable hospital guidelines in relation to traceability of implantable devices.

9.6. INTERIM REPORTING REQUIREMENTS TO FDA

In order to allow HCPs and patients to make informed health care decisions while this post-approval study is being implemented, information about this ongoing study will be provided to the US FDA on an ongoing basis including:

- Number of study sites enrolled (to be updated after submission of each interim report)
- Number of patients enrolled (to be updated after submission of each interim report)
- Interim summary data on study endpoints.

Information will be provided every 6 months during the first two years of the study and then annually thereafter.

10. STUDY ENROLLMENT, FOLLOW-UP AND COMPLETION MILESTONES

The PAS is expected to meet the following enrollment, follow-up and completion milestones:

- expected monthly number of study sites with IRB approvals
  - 4 sites per month up to 30 sites
- expected date of initiation of subject enrollment
  - first quarter 2019
- expected number of subjects enrolled per month
  - 15 subjects total per month
- expected date for subject enrollment completion
  - within 36 months of first subject enrollment
- expected date to complete follow-up of all study participants

- 60 months from first enrollment

Enrollment of subjects will not be competitive, as the goal will be to spread the subject total across the clinical sites. It is not expected that each site will enroll the same number of subjects, as the ability to recruit appropriate subjects will vary from site to site.

Subjects will be encouraged to remain in the study for up to 27 months of follow-up or after at least 1400 sensor cycles are completed study wide through the recruitment of subjects with a genuine interest in using new technology to improve the control of their diabetes, and by providing financial assistance to subjects whose insurance may not cover the Eversense CGM System.

The data collected will be analyzed and interim reports will be submitted every 6 months post PAS approval for the first two years and annually thereafter.

It is expected that follow-up for all study subjects will be complete up to 27 months or after at least 1400 sensor cycles are completed study wide after study enrollment is complete (60 months after PAS approval). The final study report will be available approximately 6 months after final subject follow-up.

[i] Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P, Klingensmith GJ. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes. 2009 Sep;10 Suppl 12:71-81.