SENSEONICS PROPOSED SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. SCOPE

This document is Sponsor's proposed version of the Summary of Safety and Effectiveness Data to be basis for the final approved SSED. The material included in this document is part of Sponsor's Executive Summary and was previously provided as part of the PMA submission P160048. There is no new information included in this document.

II. INDICATIONS FOR USE

The Eversense Continuous Glucose Monitoring System is indicated for continually measuring interstitial fluid glucose levels in adults (age 18 and older) with diabetes for the operating life of the sensor.

The system is intended to:

- Provide real-time glucose readings.
- Provide glucose trend information.
- Provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

The system is a prescription device. Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns seen over time.

The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.

III. CONTRAINDICATIONS

- The Sensor and Smart Transmitter are incompatible with magnetic resonance imaging (MRI) procedures. DO NOT undergo an MRI procedure while the sensor is inserted or when wearing the smart transmitter. Should an MRI be required, please contact your physician to arrange for sensor removal before the procedure.
- The system is contraindicated in people for whom dexamethasone or dexamethasone acetate may be contraindicated.
- Mannitol or sorbitol, when administered intravenously, or as a component of an irrigation solution or peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of your sensor glucose results. Sorbitol is used in some artificial sweeteners, and concentration levels from typical dietary intake do not impact sensor glucose results.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Eversense Continuous Glucose Monitoring System labeling.

V. DEVICE DESCRIPTION

The Eversense Continuous Glucose Monitoring (CGM) System provides continuous glucose measurements over a 40-400 mg/dL range. The small, portable system calculates glucose, trends and provides alerts for high and low glucose available for display on a Mobile platform. It consists of a miniature glucose sensor (Eversense Sensor) that is inserted under the skin with Insertion Tools; an externally worn Eversense Smart Transmitter (Transmitter); and the Eversense Mobile Medical Application (MMA), which runs on a handheld device, such as a Smartphone or iPad (see Figure 1). The inserted Sensor is a radiofrequency (RF)-powered device that collects readings and sends them to the Transmitter. The Transmitter calculates, stores, and transmits the glucose data via Bluetooth Low Energy (BLE) to a MMA on a handheld device (HHD).

Figure 1: Eversense Continuous Glucose Monitoring System

The CGM System consists of three principal components.

1. **Sensor:** The Sensor, inserted subcutaneously, receives RF-power from the Transmitter to measure interstitial fluid glucose every 5 minutes. The Sensor sends fluorescence measurements to the Transmitter for calculation and storage of glucose values. The Sensor has a silicone collar component that contains a small amount of an anti-inflammatory steroid drug (dexamethasone acetate) that elutes locally to reduce

tissue inflammation around the Sensor. The Sensor operating life is up to 90 days or until the device's end-of-life is reached. The Sensor is provided sterile, for single use in a Sensor Holder. The Sensor is inserted using the provided Insertion Tools.

2. **Transmitter:** The Transmitter, worn externally over the inserted Sensor, is a device with rechargeable battery that powers the Sensor, calculates the glucose values from the Sensor-measured fluorescence readings, and using secure BLE wirelessly sends the glucose information to the MMA for display on the HHD. An adhesive patch holds the Transmitter in place. The Transmitter is charged with USB connection via a charging cradle. The Transmitter also provides vibration signals for alerts and notifications, such as low glucose levels, irrespective of whether the MMA is in the vicinity or not.

3. **MMA:** The MMA is a software application that runs on a HHD (e.g., compatible mobile device) for display of glucose information provided by the Transmitter. The MMA receives and displays the calculated glucose information from the Transmitter, including glucose trend information and glucose alerts. The MMA also allows the user to calibrate the CGM System. It also communicates with the Senseonics server for a one-time download of calibration parameters specific for each Sensor. The MMA also provides the user an option to upload the data to Senseonics Data Management System (DMS) for historic viewing and storing of glucose data.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternative practices used for managing diabetes, and often more than one practice is recommended by health care providers. This includes oral and/or injectable medications, as well as self-monitoring of blood glucose using home blood glucose monitoring devices. Self-monitoring blood glucose meters and test strips provide a blood glucose measurement at a single point in time, whereas CGM provides continual glucose measurements. Additionally, behavior changes related to physical activity and healthy eating can aid in successful diabetes management.

Each alternative has its own advantages and disadvantages. Patients should thoroughly discuss the alternatives with their physician to choose the method that best suits individual expectations and lifestyles.

VII. MARKETING HISTORY

The Eversense Continuous Glucose Monitoring (CGM) System has been approved since May 2016 for commercial distribution in the European Union and European Economic Area countries requiring CE Mark.

The system has not been withdrawn from commercial distribution for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with use of the device. The adverse effects fall into two general categories: 1) those related to the insertion/removal procedures as well as use of the system over the operating life, and 2) those related to potential inappropriate use of the glucose related alerts provided by the system.

Anticipated potential adverse effects related to insertion, removal and wear of the sensor include:

- Allergic reaction to adhesives
- Bleeding
- Bruising
- Infection
- Pain or discomfort
- Scarring or skin discoloration
- Second procedure to remove Sensor
- Sensor fracture during removal
- Skin inflammation, thinning, discoloration or redness

The majority of these adverse events are of short duration and resolve without treatment. All devices that have a subcutaneous or transcutaneous component have a potential risk of breakage that could result in a fragment retained under the skin. Based upon the results from the clinical study, the materials and size of the Sensor components and post-market experience with this device and similar devices, these events and their severity do not raise major concerns.

The second group of device risks are related to the potential inappropriate use of the glucose related alerts provided by the system. Potential adverse events related to the inaccurate glucose values include missed alerts and false negative hypoglycemic and hyperglycemic readings, resulting in patients not being alerted to the need to perform a fingerstick. Additionally, there is a risk associated with false alerts and false positive readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. However, since patients who only use blood glucose meters to manage their diabetes without the aid of a CGM would also be unaware of the need to perform additional testing to detect an abnormal blood glucose level (unless they were exhibiting symptoms of an abnormal blood glucose), the risk of inaccurate results related to the use of this device is no greater than the risk of managing diabetes with a blood glucose meter alone. The mitigation for both inaccurate Sensor readings and patient use of CGM for treatment decisions is proper labeling, training programs and customer support that emphasizes appropriate use of the device.

For the specific adverse events that occurred in the clinical study, see Section X – Summary of Primary Clinical Study.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Pre-clinical testing has been conducted to demonstrate the Eversense CGM System performs as intended and meets its product requirements (see Table 1). The verification and validation tests included compliance with international standards and/or guidance documents where available. The CGM System and its components have various levels of specifications and technological characteristics. Therefore, a combination of full system testing, subsystem and component level testing was performed to demonstrate that the device meets its requirements and is safe for use.

Device and Electrical Safety: The Transmitter has undergone testing to demonstrate that the device meets the requirements for medical device safety, including electrical safety, according to the following international standards: IEC 60601-1, 3rd Edition, Medical electrical equipment – General requirements for basic safety and essential performance.

Electromagnetic Compatibility: The Transmitter has undergone testing to demonstrate the device meets the following international standard: IEC 60601-1-2, 4th Edition, Medical electrical equipment – Part 1-2, General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests.

Home Health Care Products: The Transmitter has undergone testing to demonstrate that the device meets the requirements for medical device safety for home health care products, according to the following international standards: IEC 60601-1-11,2nd Edition. Medical electrical equipment – General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.

Battery Standards: The Transmitter batteries have undergone testing to demonstrate that the batteries meet the requirements for safety for batteries containing alkaline or other non-acid electrolytes, according to the following international standards: IEC 62133, 2nd Edition. Secondary cells and batteries containing alkaline or non-acid electrolytes – Safety requirements for portable sealed secondary cells, and for batteries made from them for use in portable applications.

Electrical Testing for Batteries and Bluetooth Function: Transmitters were subjected to the electrical verification testing summarized in Table 1. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria for battery recharge, and communication longevity.

Table 1: Summary of Preclinical Testing of the Eversense Smart Transmitter

Test Name/ Description	Test Purpose	Acceptance Criteria
Device Safety and Electrical Testing	To verify compliance with IEC 60601-1, 3rd Edition	Complies with standard
EMC Testing	To verify compliance with IEC 60601-1-2, 4th Edition	Complies with standard
Home Health Care Products	To verify compliance with IEC 60601-1-11, 2nd Edition	Complies with standard
Battery Standards	To verify compliance with IEC 62133, 2nd Edition	Complies with standard
Power 1 – Initial Charge	To verify length of time to fully charge dormant Transmitter	Battery should be fully charged in less than 120 minutes
Power 2 - Transmitter Battery Recharge Time	To verify whether the charger can recharge the battery within the specified time	Battery in the fully empty condition should be fully recharged in less than 20 minutes
Power 3 – Low Battery Indication	To verify the Transmitter lasts for at least 4 hours after low battery indication	Battery shall last at least 4 hours after 10% battery remaining indication before entering dormant mode
Cycled Battery Charge Time	To verify the battery life after 100 charge/discharge cycles	Battery when fully charged should last a minimum of 36 hours after 100 charge/discharge cycles
	To verify the battery life after 400 charge/discharge cycles	Battery when fully charged should last a minimum of 8 hours after 400 charge/discharge cycles
Bluetooth Range	To verify whether the Transmitter provides reliable communication via Bluetooth within the specified range, and re-establishes communication after moving to and from maximum specified range	Transmitter should communicate with hand-held device within a maximum of 10 meters (32.8 feet)
Antenna 1	To verify peak frequency	13.56 Mhz ± 7 Khz
Antenna 2 - NFC Read performance at 12mm	To verify the Transmitter can communicate with the Sensor from the specified distance	Transmitter shall be able to communicate with the Sensor from the 12 mm maximum distance
Charging Cradle Reliability	To verify charging cradle function following 1200 cycles of inserting and detaching the Transmitter to/from the charging cradle	After 1200 cycles, the charging cradle charges the Transmitter, and the Transmitter remains connected to the charging cradle
Button Reliability	To verify Transmitter button function after actuation (Phoenix Transmitter System High Level Functional Test Procedure)	Verify that after 3000 button presses that the Transmitter's button does not have significant physical damage or wear, and is able to pass all steps of the High Level Functional Test Procedure that involve system responses to button presses
Adhesive Patch Operational Test	To verify adhesive patch function following submersion in water for 30 minutes (Phoenix Transmitter System High Level Functional Test Procedure)	Verify that the adhesive patch passes the functionality test

Transmitter Environmental Exposure and Mechanical Testing: Transmitters were subjected to the following functional and environmental tests described in Table 2.

Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria.

Table 2: Mechanical Testing of the Eversense Smart Transmitter

Test Name/ Description	Test Purpose	Acceptance Criteria
Shipping	To verify devices as packaged can meet functional requirements after simulated shipping conditions, including conditioning based upon ISTA 3A and Shipping Simulation testing according to ASTM D4169-16 Cycle 13, Assurance Level I	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Thermal Shock	To verify devices function following thermal shock	Devices must pass Phoenix Transmitter System High Level Function Test Procedure
Storage Conditions	To verify devices function following storage at low and high temperatures (0 and 35ºC)	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Operating Conditions Test – Temperature and Humidity	To verify devices function following exposure to extreme temperatures and humidity (5 to 40ºC and relative humidity 15 to 90%)	Devices must pass Phoenix Transmitter System High Level Function Test Procedure
Mechanical Shock	To verify devices function following mechanical shock conditions as specified in IEC 60601-1-11	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Vibration	To verify devices function following vibration conditions	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Drop	To verify devices function as intended following repeated drops from a height of 1 meter unto a hardwood board	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Push	To verify devices function following application of a steady force of 250 N ± 10 N (56.2 lb ± 2.2 lb) for a period of 5 seconds, using a test tool which provides contact over a circular plane surface 30mm	Devices must pass visual inspection and Phoenix Transmitter System High Level Function Test Procedure
Operational Life Test	To verify devices ability to function over a 1 year life	Devices must pass functional requirements
Water Ingress Test	To evaluate transmitter compliance with IP67 rating and charging cradle compliance with IP22 rating of IEC 60529	Transmitter must demonstrate no water ingress. Transmitter and charging cradle must pass a comprehensive functional test procedure following exposure to the water ingress stress conditions

Insertion Tools: The Insertion Tool and Blunt Dissector were subjected to the following functional and environmental tests described in Table 3. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria.

Table 3: Mechanical and Environmental Testing of the Eversense Insertion Tools

Test Name/ Description	Test Purpose	Acceptance Criteria
Actuation Mechanism Test	To evaluate the mechanism of actuation of the insertion tool by locking and unlocking	Verification of lock and unlocked positions
Push and Pull Test	To evaluate the mechanical strength of the cannula of the insertion tool and metal portion of the blunt dissector following compression and tension	Withstand minimum push or pull force of 44.5 N
Actuation Force Test	To evaluate the force needed for the actuation mechanism of the insertion tool	Actuate with less than 2.2 lbf
Marking Durability	To evaluate the markings on the tool remains visible	Marks remain visible and do not degrade
Shipping and Handling Extremes	To evaluate whether the devices within their packaging can withstand exposure to extreme temperatures and humidity	Verification of package integrity and device function

Sensor Environmental Exposure and Electrical Testing: Sensor verification testing was performed to evaluate the Sensor electronics and glucose indicator to verify the design meets the essential performance described in Table 4. Sensors were subjected to testing to evaluate label marking durability through shipping tests, dimensional, and maintaining electrical essential performance. Protocols, test reports and acceptance criteria were reviewed and found to be acceptable. The device met the pre-determined acceptance criteria.

Table 4: Environmental and Electrical Testing of the Eversense Sensor

Test Name/ Description	Test Purpose	Acceptance Criteria
Sensor Electro-optical Interface Circuit Testing	To evaluate functionality of the near field communication and electro-optical circuitry	Sensor electronic can communicate via the ISO 15693 protocol, and are able to excite the fluorescent glucose indicator and detect its emitted fluorescent light according to Specification limits
Sensor Glucose Indicator Test	To evaluate the glucose responsivity of the fluorescent glucose indicator	Sensor must meet specification limit for fluorescent signal strength and sensitivity to glucose levels
Marking Durability	To evaluate that the Sensor package marking is protected against the effects of temperature and humidity.	The marking on the sensor packaging shall not visibly deteriorate upon humidity exposure.
Shipping and Handling Extremes	To evaluate whether the devices within their packaging can withstand exposure to extreme temperatures and humidity	Following the shipping exposure, the samples shall meet the essential performance requirement

Biocompatibility Testing: Biocompatibility studies were selected and performed in consultation with international recognized safety standards (ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing) and in accordance with the FDA guidance document entitled "Use of International standard ISO 10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process" dated June 16, 2016. All studies cited in this section were conducted in compliance with 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies (GLPs). All studies had passing results. Results of the biocompatibility studies are summarized in Tables 5, 6, and 7.

Table 5: Summary of the Biocompatibility Tests and Results for the Eversense Sensor

Biocompatibility Test	**ISO Standard**	**Test Method**	**Results**
Cytotoxicity	ISO 10993-5	MEM Elution	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Intracutaneous Reactivity	Pass – Nonirritant
Systemic Toxicity	ISO 10993-11	Acute Systemic Toxicity	Pass - Not toxic
Systemic Toxicity	ISO 10993-11	Material Mediated Pyrogen	Pass – Not pyrogenic
Subchronic Toxicity and Implantation	ISO 10993-6	4 and 13 Week Systemic Toxicity in Rats-Subcutaneous Implant	Pass - Not systemically toxic
Chronic Toxicity and Implantation	ISO 10993-6	26 Week Systemic Toxicity in Rats-Subcutaneous Implant	Pass - Not systemically toxic
Genotoxicity/Carcinogenicity	ISO 10993-3	Bacterial Reverse Mutation	Pass - Non-mutagenic
Genotoxicity/Carcinogenicity	ISO 10993-3	Mouse Lymphoma	Pass - Non-mutagenic
Genotoxicity/Carcinogenicity	ISO 10993-3	Peripheral Blood Micronucleus Test	Pass - No damage to chromosomes
Chemical Characterization	ISO 10993-17 ISO 10993-18	Exhaustive Extraction Infrared Analysis Semi-volatile Organics by GC-MS Non-volatile Organics by UPLC-MS Volatile Organic Compounds by GC-MS Headspace ICP-MS for inorganic metals and elements	Pass - no leachables/extractables from the Sensor are likely to cause adverse effects in patients
Particulate Tests	ISO 14708-1	Light Obscuration Method	Pass - Particulate count did not exceed requirement

Table 6: Summary of the Biocompatibility Tests and Results for the Eversense Transmitter and Adhesive Patch

Biocompatibility Test	ISO Standard	Test Method	Results
Cytotoxicity	ISO 10993-5	Transmitter: MEM Elution Adhesive Patch: Agarose Overlay Method	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Transmitter: Maximization Sensitization Adhesive Patch: Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Transmitter: Primary Skin Irritation Adhesive Patch: Primary Skin Irritation	Pass – Nonirritant

Table 7: Summary of the Biocompatibility Tests and Results for the Eversense Insertion Tools

Biocompatibility Test	ISO Standard	Test Method	Results
Cytotoxicity	ISO 10993-5	MEM Elution	Pass – Not cytotoxic
Sensitization	ISO 10993-10	Maximization Sensitization	Pass - Not Sensitizing
Irritation	ISO 10993-10	Intracutaneous Reactivity	Pass – Nonirritant
Systemic Toxicity	ISO 10993-11	Acute Systemic Toxicity	Pass - Not toxic
Systemic Toxicity	ISO 10993-11	Material Mediated Pyrogen	Pass - Non-pyrogenic

Software: The applicant performed software verification and validation testing in accordance with the FDA guidance document entitled "Guidance for the Contents of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005. Verification and validation testing included units test, system level verification tests (which included functional testing to demonstrate the device meet its requirements), code review, traceability linking and validation testing to ensure the software conforms to user needs and intended uses.

Human Factors/Usability: Human factors Validation testing was conducted per the FDA guidance entitled, "Applying Human Factors and Usability Engineering to Medical Devices" dated February 3, 2016. The Human Factors Validation testing considered the intended users, uses and use environments in the design of the simulated use testing. The testing was also designed to assess the instructions for use and training provided. The final test included both the physicians who insert the Sensor, and the end users of the device with a range of backgrounds and experiences with diabetes therapy. Both groups completed simulated scenarios and were asked for their response following completion of the scenarios. Based upon the data gathered in the human factors validation testing, it has been concluded that the Eversense CGM System has been found to be safe and effective for the intended users, uses and use environments.

Sterility: The Sensor with its holder is a provided sterile for single-use and is sterilized using ethylene oxide (EO). The sterilization process was validated in accordance with ISO 11135-1, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices and in consideration of ISO 11135-2, Sterilization of Health Care Products – Ethylene oxide – Part 2: Guidance on the application of ISO 11135-1. The device is sterilized to a sterility assurance level (SAL) of 10^{-6}. EO and ethylene chlorohydrin (ECH) residuals are monitored and meet the limits specified in ISO 10993-7, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals. The Sensor is provided pyrogen free.

The Insertion Tools are provided sterile for single-use, and are sterilized using EO. The sterilization process was validated in accordance with ISO 11135-1, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices, and in consideration of ISO 11135-2, Sterilization of Health Care Products – Ethylene oxide – Part 2: Guidance on the application of ISO 11135-1. The device is sterilized to a SAL of 10^{-6}. EO and EC residuals are monitored and meet the limits specified in ISO 10993-7, Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.

Shelf Life and Packaging: The Sensor with the sensor holder is provided sterile for single use with recommended storage between 2°C and 8°C (36°F and 46°F) and a labeled expiration date set at 1 month. Shelf life studies of the Sensor are ongoing under an approved protocol and the shelf life will be updated upon successful completion of each subsequent test time point. The Insertion Tools are provided in a single package, sterile for single use with recommended storage at room temperature and a labeled shelf life of 6 months.

B. Animal Studies

A separate animal study was conducted to compare the biocompatibility of the Sensor with steroid eluting collar to a steroid eluting pacing lead, (an approved medical device) that elutes the same drug (dexamethasone acetate) from a silicone carrier. The Sensor and the pacing lead were implanted subcutaneously in Sprague Dawley rats (one device per animal) in a 90-day implantation study and local tissue histology analyzed after 30 and 90 days of implantation. No adverse tissue reactions were observed after 30 or 90 days with either the Sensor or the pacing lead.

C. Additional Studies

The Eversense Sensor was exposed to X-ray and ultrasonic energy test conditions stated in EN 45502-1. The mentioned tests were completed at VPTRad and Acertara Test Labs, respectively. Essential performance was verified on the samples after the completion of exposure.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study (PRECISE II) to establish a reasonable assurance of safety and effectiveness of the Eversense CGM System for its intended use. This clinical study was performed in the United States under an approved IDE application G150165. A supportive clinical study (PRECISION) was performed to collect data during the early Sensor life under an approved IDE supplement. Data from these clinical studies form the primary basis for the PMA approval decision.

A. Study Designs

This Pivotal Study (PRECISE II) was a non-randomized, blinded, prospective, single-arm, multi-center study, evaluating 90 adult subjects with diabetes mellitus in the United States at 8 sites. The investigation included both, clinic visits and home use of the Eversense CGM System. The majority of subjects had one Sensor inserted in the upper arm by trained Investigators. A subset of 15 subjects, at one clinical site, had two Sensors inserted. The accuracy of the CGM System was evaluated during clinic visits on days 1, 30, 60 and 90 by comparing Sensor glucose values and plasma glucose values drawn every 5 to 15 minutes for a period of approximately 4 ½ to 12 ½ hours and measured on a bedside glucose analyzer. During Sensor accuracy clinic visits, qualifying subjects participated in hyperglycemia and hypoglycemia challenges, as well as upper arm exercise sessions and separate compression sessions for a duration of 30 minutes each.

The CGM glucose values and all glucose-related alerts were blinded to both the subjects and the investigators for the duration of the study. All diabetes care decisions were based on SMBG blood glucose values and clinical standard of care, rather than CGM System results. The subjects did use the device for non-glucose related notifications such as calibration reminders and battery levels.

The subject visit schedule which included 7 visits over a period of approximately 5 months is summarized in Figure 2 below:

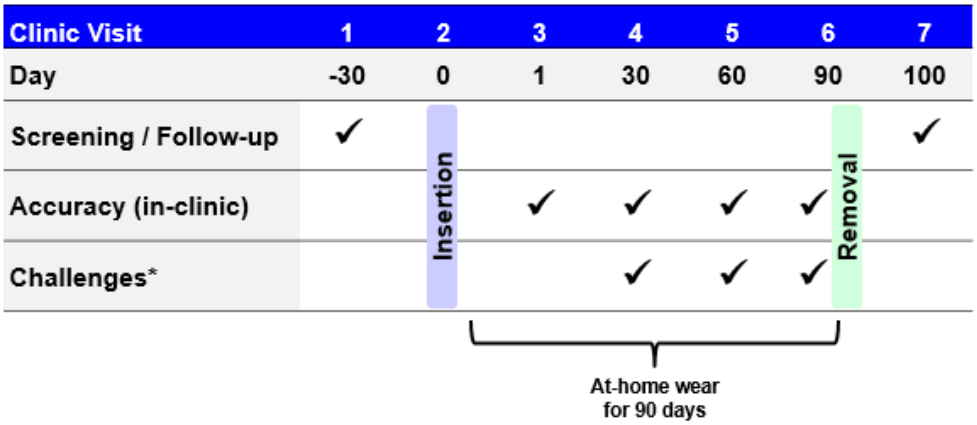

Figure 2: Primary Clinical Study Visit Schedule for PRECISE II

The Supportive Study (PRECISION) shared the same design as the PRECISE II with the following exceptions (see Figure 3). Additional accuracy assessments were added on Day 7 and Day 14 to characterize Sensor accuracy early after insertion, and patients underwent sleep assessments to evaluate accuracy and system performance during sleep. In addition, patients were not blinded to the glucose values and alerts during PRECISION as the overall accuracy of the CGM System had been sufficiently established in the PRECISE II study.

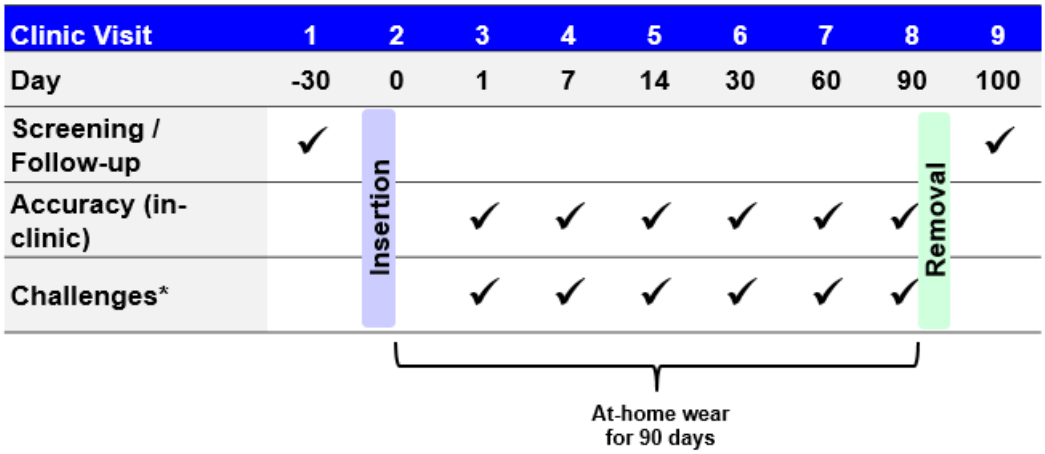

Figure 3: Primary Clinical Study Visit Schedule for PRECISION

B. Inclusion/Exclusion Criteria for the Studies

Inclusion Criteria

Male and Female Subjects meeting the following inclusion criteria were included in this study:

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

Exclusion Criteria

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

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

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

C. Follow-up Schedule

At the end of the Day 90 Clinic Visit, the Sensor was removed per the Eversense Physician Insertion & Removal Instructions; all the Sensor insertion sites were examined and evaluated by the study staff. A follow-up visit was scheduled 10 days later for evaluation of the Sensor site and close out. All used and unused Systems and sub-components, except for used insertion tools, were returned by study staff to Senseonics for examination. Study investigators documented any Adverse Device Effects and evaluated safety issues related to system use during the study.

D. Accountability of Study Subjects and Time of Exposure

In the PRECISE II study, 90 subjects were inserted with the Sensor and 87 (97%) completed the study. The mean duration of Sensor use was 92.2 days and the median duration was 93.0 days, resulting in 9,773 in vivo days of Sensor use in 90 subjects to assess safety. A total of 106 sensors were inserted, including 75 subjects with 1 Sensor and 15 with 2 Sensors, and 1 Sensor replacement during the study. Two subjects withdrew consent and had Sensors removed on Days 62 and 92. One subject was lost to follow up, but subsequently returned to the site and had the sensor removed 196 days after insertion.

In the PRECISION study, 36 subjects were enrolled and 35 were inserted with Sensors with 8 receiving one (1) Sensor and 27 receiving two (2) Sensors. All 35 subjects completed all visits at Day 1, 7, 14, 30, 60 and 90 resulting in 6,064 in vivo days of Sensor use.

E. Study Population Demographics and Baseline Parameters

A summary of demographic characteristics is presented in Table 8.

Table 8: Study Demographics

Demographic	**PRECISE II (n=90)**	**PRECISION (n=35)**
Gender [n (%)]		
Male	54 (60)	18 (51)
Female	36 (40)	17 (49)
Age (years) [mean (SD)]	45(16)	52 (16)
Min, Max	18, 77	18, 75
Race n (%)		
Caucasian	77 (86)	32 (91)
Black or African American	7 (8)	1 (3)
Asian	3 (3)	2 (6)
American Indian or Alaska Native	2 (2)	0 (0)
Native Hawaiian or Other Pacific Islander	1 (1)	0 (0)
Dominant Hand [n (%)]		
Right	78 (87)	33 (94)

Demographic	PRECISE II (n=90)	PRECISION (n=35)
Left	12 (13)	2 (6)
Body Mass Index Class [n (%)] [mean (SD)] Min, Max	29 (6) 19, 50	28 (5) 19, 44
Normal (<25 kg/m^2)	22 (24)	9 (26)
Overweight (≥25 and <30)	27 (30)	11 (31)
Obese (≥30)	41 (46)	15 (43)

Within the study populations, 68% (N=61) and 71% (N=25) had Type I diabetes for the PRECISE II and PRECISION studies, respectively. The study populations also included 48% and 54% continuous insulin infusion pump users in PRECISE II and PRECISION, respectively.

F. Safety Analysis

The same safety endpoints and evaluations performed in the PRECISE II study and the PRECISION study were the same. At each study visit a safety evaluation was performed. Sensor sites were evaluated and assessed for any signs of irritation or infection, including increased temperature, pain, redness, warmth, swelling or purulence. In addition, subjects were queried at each visit for Sensor site assessment between visits, as well as other adverse events. Subjects were asked at the beginning of each visit if anything had changed medically since their last visit. All adverse events identified, regardless of relatedness to the device or insertion/removal procedure, were documented.

G. Primary Safety Analysis

The primary safety analysis was based upon all subjects in the investigation who were not screen failures or withdrawals prior to a first insertion attempt. Ninety (90) subjects were successfully inserted with a Sensor in the PRECISE II Study and 35 in the PRECISION Study, forming the basis of the safety populations. In the PRECISE II study, 15 subjects had two (2) Sensors inserted (one in each arm) and 75 subjects had one (1) Sensor inserted. One subject had a replacement Sensor inserted after the primary Sensor had a suspected electrical or mechanical failure. In the PRECISION study, 8 subjects had one (1) Sensor inserted and 27 had two (2) Sensors inserted (one in each arm).

The primary safety endpoint was the incidence of device-related or Sensor insertion/removal procedure-related serious adverse events (SAE) through 90 days post insertion or Sensor removal and follow-up. An adverse event relationship was considered non-related, possibly related, related or unknown based upon review and categorization by the independent medical monitor. An analysis was provided through Sensor removal as shown in Table 9. The proportion of subjects experiencing a serious adverse event is presented together with the associated 95% confidence interval. The rate of serious adverse events related to the device or the insertion procedure was low in both studies.

Table 9: Safety Endpoints in the PRECISE II and PRECISION Studies

SAEs by Relationship to Study	PRECISE II (N=90)		PRECISION (N=35)	
	Number of Subjects with SAEs (%)	95% Confidence Interval	Number of Subjects with SAEs (%)	95% Confidence Interval
All SAEs	1 (1.1%)	0.0% - 6.0%	3 (8.6%)	1.8%-23.1%
Device-Related SAEs*	0 (0.0%)	0.0% - 4.0%	0 (0.0%)	0.0%-10.0%
Sensor Insertion/Removal Procedure-Related SAEs*	1 (1.1%)	0.0% - 6.0%	0 (0.0%)	0.0%-10.0%
Study Procedure-Related SAEs	0 (0.0%)	0.0% - 4.0%	0 (0.0%)	0.0%-10.0%
Unrelated to Study SAEs	0 (0.0%)	0.0% - 4.0%	3 (8.5%)	1.8%-23.1%

* Primary safety endpoint is the rate of device- and insertion/removal procedure-related serious adverse events

H. Secondary Safety Analysis

The secondary safety endpoints included:

- Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor.
- 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.

Table 10 shows the safety data from each study. Fourteen (14) adverse events that were determined to be device- and/or insertion/removal procedure- related or possibly related, including the one (1) SAE mentioned above, occurred in the PRECISE II study among 7 (7.7%) subjects. All events adjudicated as related or possibly related to the device and/or insertion/removal procedures had complete resolution by study completion with exception of one subject. One subject had a delayed report of intermittent pain adjudicated as possibly related. Eight (8) adverse events occurred in 5 subjects (14.3%) in the PRECISION study, and all device-related adverse events were mild or moderate in severity and resolved within 2 weeks of Sensor removal. Importantly, most subjects received two Sensors in the PRECISION study, which resulted in higher device-related adverse events rate when compared to PRECISE II study. There were no unanticipated adverse events and no UADEs. There were no infections observed in either study, resulting in an infection rate of 0.0%.

Table 10: Adverse Events Related or Possibly Related to the Study Device or Insertion/removal Procedure

	PRECISE II (n=90)		PRECISION (n=35)	
	Number of Events	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Event Physiologic System	**14**	**7 (7.7%)**	**8**	**5 (14.3%)***
Dermatological	**8**	**4 (4.4%)**	**6**	**4 (11.4%)**
Bruising	2		0	
Erythema	2		0	
Pain/Discomfort	4		2	
Dermatitis	0		2	
Hyperpigmentation of skin	0		2	
Musculoskeletal/Rheumatologic	**1**	**1 (1.1%)**	**0**	**0 (0.0%)**
Pain/Discomfort	1		0	
Neurological	**2**	**2 (2.2%)**	**0**	**0 (0.0%)**
Paresthesia	1		0	
Syncope-vasovagal	1		0	
Other	**3**	**3 (3.3%)**	**2**	**1 (2.9%)**
Device fragment not recovered	2		0	
Additional procedure to remove Sensor	1		2	

* Most subjects received two Sensors in the PRECISION study

XI. ACCURACY ANALYSIS FROM PIVOTAL STUDY

A. Primary Effectiveness Analysis

For the Primary Study (PRECISE II), the statistical analysis of the effectiveness data focused on assessing system performance by comparing CGM glucose values to the YSI Reference Glucose values by using metrics based on matched pairs. When compared to YSI Reference, these metrics included absolute difference (AD), defined as |GlucoseSensor – GlucoseYSI|, or absolute relative difference (ARD), defined as 100×|GlucoseSensor – GlucoseYSI|/ GlucoseYSI. The primary effectiveness endpoint was the mean absolute relative difference (MARD) from the matched CGM and YSI pairs. In order to be deemed a success, the study needed to demonstrate a MARD less than 20% based on all paired CGM and YSI reference measurements collected during clinic visits through 90 days post-insertion from all 90 patients (91 implanted sensors). The test statistic was adjusted for the within-patient and between-patient components of variances estimated from a one-way random effects analysis of variance with patient as the random effect. The statistically significant (p-value <0.0001) primary accuracy assessment for PRECISE II from 15,753 paired Eversense CGM and YSI Reference points had a Mean Absolute Relative Difference (MARD) of 8.5%. The full results from the Primary Accuracy Assessment are in Table 11.

Table 11: Primary Accuracy Assessment

Measurements	Level	Results
Mean ARD (%)	All Results	8.5 (7.9) / 15753
Mean AD (mg/dL)	All Results	13.8 (13.2) / 15753
Median ARD (%)	All Results	6.5 (7.9) / 15753
Mean ARD (%)	Reference > 80 mg/dL	7.9 (7.0) / 14099
Mean AD (mg/dL)	Reference ≤ 80 mg/dL	8.4 (7.6) / 1654

*ARD is **Absolute Relative Difference,** AD is **Absolute Difference**

B. CGM System and Reference Agreement in Different YSI Glucose Ranges

In this analysis, CGM system performance as measured by agreement with YSI within 15 mg/dL or 15%, 20 mg/dL or 20%, 30 mg/dL or 30% or 40 mg/dL or 40% (referred to as 15/15%, 20/20%, 30/30% and 40/40%) of YSI levels was stratified by the YSI glucose range in different categories: <40, 40-60, 61-80, 81-180, 181-300, 301-350, 351-400, and > 400 mg/dL (see Table 12).

Table 12: CGM System and Reference Agreement in Different YSI Glucose Ranges

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 (40-400)	15753	86.8%	94.3%	98.6%	99.6%	0.4%
< 40	7	71.4%	71.4%	100.0%	100.0%	0.0%
40 - 60	488	89.5%	95.1%	98.8%	99.8%	0.2%
61 - 80	1159	84.5%	92.0%	97.7%	99.1%	0.9%
81 - 180	7540	85.6%	93.0%	98.0%	99.4%	0.6%
181 - 300	5378	88.4%	95.9%	99.4%	99.9%	0.1%
301 - 350	820	88.4%	97.4%	99.8%	100.0%	0.0%
351 - 400	326	86.5%	96.6%	98.5%	100.0%	0.0%
> 400	35	91.4%	100.0%	100.0%	100.0%	0.0%

C. CGM System and Reference Agreement in Different CGM Glucose Ranges

In this analysis, CGM system performance as measured by agreement with YSI within 15/15%, 20/20%, 30/30% and 40/40% of YSI levels was stratified by the CGM glucose range in 40-60, 61-80, 81-180, 181-300, 301-350, and 351-400 mg/dL (see Table 13).

Table 13: CGM System and Reference Agreement in Different CGM Glucose Ranges

CGM 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 (40-400)	15753	86.8%	94.3%	98.6%	99.6%	0.4%
40 – 60	480	85.4%	92.1%	97.7%	99.6%	0.4%
61 – 80	1111	83.3%	90.7%	97.4%	99.1%	0.9%
81 – 180	7844	85.6%	93.5%	98.3%	99.6%	0.4%
181 – 300	5377	88.3%	95.6%	99.1%	99.7%	0.3%
301 – 350	692	90.8%	98.0%	99.7%	99.9%	0.1%
351 – 400	249	96.8%	99.2%	100.0%	100.0%	0.0%

D. Concurrence of CGM System Readings and YSI Values and Reference Agreement in Different YSI Glucose Ranges

Concordance analysis between CGM and YSI values was analyzed with categories of < 40 (YSI only), 40-60, 61-80, 81-120, 121-160, 161-200, 201-250, 251-300, 301-350, 351-400, and > 400 mg/dL (YSI only) (see Table 14).

Table 14: Concurrence of System Readings and YSI Values

CGM (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each YSI Glucose Range for Each CGM Range (mg/dL)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
40-60	480	1%	63%	34%	3%	0%	0%	0%	0%	0%	0%	0%
61-80	1111	0%	16%	63%	20%	1%	0%	0%	0%	0%	0%	0%
81-120	3066	0%	0%	9%	76%	14%	0%	0%	0%	0%	0%	0%
121-160	3245	0%	0%	0%	11%	73%	15%	0%	0%	0%	0%	0%
161-200	2812	0%	0%	0%	0%	15%	64%	21%	0%	0%	0%	0%
201-250	2614	0%	0%	0%	0%	0%	13%	68%	18%	0%	0%	0%
251-300	1484	0%	0%	0%	0%	0%	1%	17%	58%	23%	1%	0%
301-350	692	0%	0%	0%	0%	0%	0%	1%	19%	59%	20%	0%
351-400	249	0%	0%	0%	0%	0%	0%	0%	0%	20%	66%	13%

E. Low and High Glucose Alerts

Detection refers to the ability of CGM in confirming a hypoglycemic or hyperglycemic reference event with various alert cutoff settings. When a reference event had occurred, a Confirmed Threshold Alert was a CGM measurement or predicted CGM measurement beyond the alert threshold and occurred within ±15 minutes from the aforementioned reference event. In contrast, a True Threshold Alert was a CGM measurement or predicted CGM measurement beyond the hypoglycemic or hyperglycemic alert threshold

when at least one reference measurement within ±15 minutes was also beyond the same alert threshold. Results using YSI readings as reference for low glucose alerts are summarized in Table 15.

Table 15: In-Clinic Hypoglycemic Event Detection: CGM vs. YSI

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	89%	11%	72%	28%
70	96%	4%	84%	16%
80	96%	4%	85%	15%
90	98%	2%	85%	15%

Results using YSI readings as reference for high glucose alerts are summarized in Table 16.

Table 16: In-Clinic Hyperglycemic Event Detection: CGM vs. YSI

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	97%	3%
140	99%	1%	96%	4%
180	98%	2%	93%	7%
200	96%	4%	93%	7%
220	95%	5%	90%	10%
240	94%	6%	89%	11%
300	87%	13%	85%	15%

F. CGM System Stability by Study Visit Number

The results per clinic visit day for the Pivotal Study are presented in Table 17.

Table 17: CGM System Stability by Visit Number

Day	Number of Readings	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
1	1708	10.7	8.2	76.8%	87.1%	96.3%	98.5%	1.5%
30	5081	7.4	5.5	90.7%	96.0%	99.3%	99.8%	0.2%
60	4725	8.2	6.3	87.3%	94.7%	98.8%	99.8%	0.2%
90	4239	9.1	7.3	85.4%	94.7%	98.6%	99.6%	0.4%

G. Calibration Stability

This analysis was to demonstrate the performance of the CGM system spanning the duration between calibration points is stable. For the Primary study, agreement between

CGM and YSI measurements were assessed over the entire calibration period by stratifying matched pairs data in 2-hour increments over the period of 0 to 12 hours post calibration (see Table 18).

Table 18: Calibration Stability

Time from Calibration	Number of Paired CGM-YSI	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
0 – 2 Hours	4347	85.0	92.2	97.8	99.3	0.7
2 – 4 Hours	2800	87.5	94.8	98.9	99.7	0.3
4 – 6 Hours	2396	85.5	93.8	98.5	99.7	0.3
6 – 8 Hours	2115	87.6	95.6	99.1	99.6	0.4
8 – 10 Hours	2019	87.8	95.9	99.3	100.0	0.0
10 – 12 Hours	1815	88.9	95.8	98.8	99.6	0.4

H. System Longevity and Reliability

A Kaplan Meier analysis was performed to estimate the in vivo Sensor life. An important advantage of the Kaplan Meier curve is that the method can take into account some types of censored data, particularly right-censoring, which occurs, for example, if a subject withdraws from a study or is lost to follow-up. By taking into account the number of subjects followed over time and the date of occurrence of the event, the Kaplan Meier curve provides an estimate of the true event rate at any given point in time, and allows for a better understanding of the temporal pattern of the event over time. As shown in Figure 3, 91% of the sensors remained functional through 90 days.

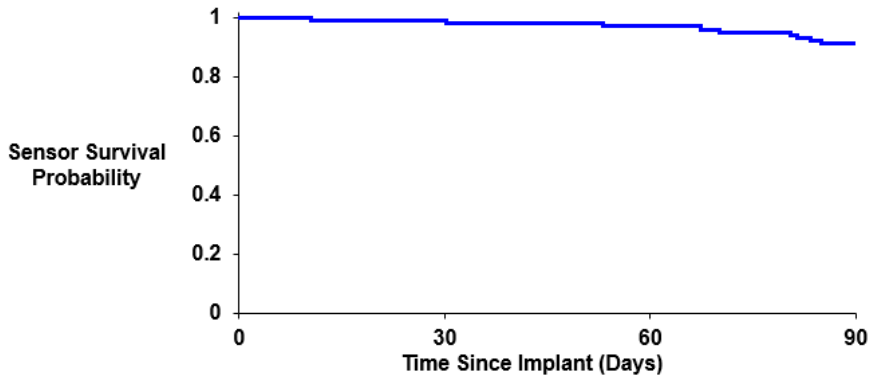

Figure 3: Kaplan Meier Estimate of Sensor Survival

With the Eversense CGM System, continuous glucose values (or readings) are available when the Transmitter is worn by the user over the Sensor. The system reliability assesses the percent of glucose readings that the user receives when using the Transmitter. As a user may elect to remove the Transmitter, such as re-charging, system reliability includes actual Transmitter usage rather than total number of hours the Sensor remains inserted. Transmitter usage is retained in the system's local memory.

Table 19 shows the percent of total possible glucose readings provided to the user. Similar analysis showing the system readings throughout the study duration is shown in Table 20, which shows an average of 96% for all days.

Table 19: System Reliability

% of Total Possible Readings Provided	Total Readings Provided Min, Max	% of Systems Providing that Number of Readings
0 - 25%	--	0%
26 - 50%	--	0%
51 - 75%	58 out of 98*, 18189 out of 24485	3%
76 - 100%	2667 out of 2701, 26718 out of 26798	97%

* Subject was lost to follow-up after Day 1

Table 20: System Reliability over Time

	Days 1-7	Days 8-14	Days 15-30	Days 31-60	Days 61-90	All Days
Mean	96%	97%	96%	96%	96%	96%
Median	98%	100%	100%	99%	99%	99%
STD	8%	9%	10%	7%	10%	7%

I. Integrated Safety Analysis

Subjects from PRECISE II and PRECISION studies were pooled for an integrated safety analysis (N=125) as both studies enrolled similar patient populations and followed similar safety evaluation procedures through 90 days post-insertion. The integrated analysis summarizes all safety data collected to date from both studies with over 11,700 patient-days of Sensor exposure. The integrated incidence of device or insertion/removal procedure-related SAEs across the 2 studies was 0.8% (1 out of 125 patients). In the integrated analysis, there were 22 device or insertion/removal-related AEs occurring in 12 patients for an overall incidence rate of 9.6%, as shown in Table 19.

Table 21: Adverse Events Related to the Device or Insertion/Removal Procedure from Integrated Studies

Event Physiologic System and Category	Number of Events	Patients (N=125)
Dermatological, n (%)	**14**	**8 (6.4%)**
Pain/Discomfort	6	5 (4.0%)
Redness/Erythema	2	1 (0.8%)
Dermatitis at Patch Location	2	1 (0.8%)
Bruising	2	1 (0.8%)
Skin Hyperpigmentation	2	1 (0.8%)
Neurological, n (%)	**2**	**2 (1.6%)**
Paresthesia	1	1 (0.8%)
Syncope-vasovagal	1	1 (0.8%)
Musculoskeletal Rheumatologic, n (%)	**1**	**1 (0.8%)**
Pain	1	1 (0.8%)
Other, n (%)	**5**	**4 (3.2%)**
Device Fragment Not Recovered	2	2 (1.6%)
Additional Procedure to Remove Sensor Following First Attempt	3	2 (1.6%)
TOTAL	**22**	**12 (9.6%)**

XII. SUPPORTING CLINICAL DATA

A. Additional Effectiveness Data

Additional accuracy assessments were tabulated for the Supportive Clinical Study (PRECISION), which characterized Sensor accuracy early (Day 7 and 14) after insertion and during sleep. The stratified results by visit day for the supportive study are shown in Table 22.

Table 22: CGM System Stability by Visit Number for the Supportive Study

Visit Day	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	15170	85.4%	92.8%	98.1%	99.3%	0.7%
Day 1	2665	79.1%	88.9%	95.8%	98.5%	1.5%
Day 7	2926	86.1%	93.3%	98.1%	99.0%	1.0%
Day 14	2997	88.1%	94.6%	98.8%	99.6%	0.4%
Day 30	2284	88.0%	94.3%	98.9%	100.0%	0.0%
Day 60	2133	86.9%	93.7%	98.5%	99.6%	0.4%
Day 90	2165	83.9%	92.2%	98.5%	99.3%	0.7%

The results from the Supportive Clinical Study are also stratified by CGM glycemic range in Table 23.

Table 23: CGM System and Reference Agreement in Different CGM Glucose Ranges for the Supportive Study

CGM (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	15170	85.4%	92.8%	98.1%	99.3%	0.7%
40 - 60	1236	91.9%	96.0%	98.4%	99.3%	0.7%
61 - 80	2003	87.3%	94.1%	99.1%	99.6%	0.4%
81 - 180	5786	80.5%	89.9%	97.2%	99.0%	1.0%
181 - 300	3566	84.8%	92.8%	98.1%	99.2%	0.8%
301 - 350	1628	92.8%	97.5%	99.1%	99.9%	0.1%
351 - 400	951	91.5%	95.8%	98.6%	99.8%	0.2%

B. European Patient Registry

An ongoing, prospective, European patient registry providing real-world data and evidence regarding the performance of the Eversense CGM System in a heterogeneous patient population provide supporting clinical data for this PMA application. As of February 2018, over 1600 patients have received the Eversense CGM System in over 350 trained sites. Over 400 patients have gone through multiple sensors, with some patients currently on their seventh sensor.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the pivotal clinical study establish a reasonable assurance of the effectiveness of the Eversense Continuous Glucose Monitoring (CGM) System to be used as intended in the intended use population. The primary effectiveness measurements for the Pivotal study were based on the performance evaluation of the Eversense CGM System compared to the blood glucose values measured by the reference analyzer during the in-clinic sessions that spanned the wear period of the device (up to 90 days) during which 15,753 matched pairs were collected.

The performance data presented in the Accuracy Analysis sections are comparable to current CGM system performance and therefore support effectiveness conclusions. The data establish the accuracy across the claimed measuring range (40 to 400 mg/dL), precision, 90-day wear period for the Sensor, the alerts for detection and prediction episodes of hypoglycemia and hyperglycemia and the ability to track trends.

The clinical study demonstrates that the Eversense CGM System is effective in the study population designed to be representative of the intended use population.

B. Safety Conclusions

The risks of the device are based on the preclinical laboratory data, as well as data collected in the clinical study conducted under an approved IDE application (G150165) and described in Table 21 above and summarized below.

The following related adverse events were observed from using the Eversense CGM system: pain/discomfort, bruising, erythema, retained Sensor fragment, failure to remove Sensor on first attempt, skin hyperpigmentation, dermatitis at patch location, paresthesia, and syncope-vasovagal.

There are potential risks related to either an inaccurate sensor value outside of the patient's normal range or a false alert that results in performing an unnecessary additional blood glucose test to confirm the erroneous reading. The risk of medical harm is mitigated through labeling and training, which emphasizes that patients should confirm all CGM readings prior to making treatment decisions.

There are potential risks due to missed alerts and false negative hypoglycemic and hyperglycemic readings related to patients not being alerted to the need to perform a fingerstick. Additionally, there is a risk associated with false alerts and false positive readings related to the need to perform unnecessary fingersticks to confirm an erroneous low or high reading. However, since patients who only use blood glucose meters to manage their diabetes without the aid of a CGM would also be unaware of the need to perform additional testing to detect an abnormal blood glucose level (unless they were exhibiting symptoms of an abnormal blood glucose), the risk of inaccurate results related to the use of this device is no greater than the risk of managing diabetes with a meter alone unless patients omit a blood glucose test that they would have otherwise performed if they were not using the sensor or the sensor was not reading within their target glucose range.

Inaccurate calculation of the rate of change of glucose by the CGM could present a patient from performing additional blood glucose tests or taking measures to stop a trend of increasing or decreasing glucose levels, which could lead to serious hypoglycemia or hyperglycemia if not action is taken to stop these glucose trends. However, as patients often do test frequently enough with a meter to calculate the rate of change, this risk is not greater than with traditional glucose monitoring with a meter. Inaccurate estimation of the rate of change of glucose could also lead to unnecessary additional blood glucose tests or inappropriate measures to stop an incorrect trend of increasing or decreasing glucose level. However, the risk of medical harm is limited to instances where the user relies on the rate of change calculated by the sensor without confirmation by a blood glucose meter. This risk is partially mitigated by the requirement for users to base treatment decisions on blood glucose levels.

C. Benefit-Risk Conclusions

Summary of Benefits:

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

The device is intended to supplement self-monitoring of blood glucose to track and trend glucose levels related to estimates of blood glucose excursions. Patients are notified of potential hyper- and hypoglycemia events via customizable settings that alert them to the need to use their blood glucose meter to confirm their blood glucose value and take appropriate action as needed to treat or prevent a hyper- or hypoglycemic event.

The use of a continuous glucose monitor gives patients and physicians glucose tracking and trending information not available from traditional self-monitoring blood glucose devices as blood glucose meters only provide discrete, episodic blood glucose values. CGM measurements are performed every 5 minutes for up to 90 days via the inserted sensor and unlike SMBG, CGM measurements do not require use of a lancing device to capture each measurement. Additionally, unlike other CGM systems, the long-term sensor eliminates the need for patients to insert a new sensor every 7 days, and the transmitter can be removed without ending the sensor life.

Patients and physicians can also review the tracking and trending data by day and time of day, such as nighttime when fewer fingersticks are performed. The historical CGM data trends and patterns may reveal the need to adjust therapy for improved diabetes management, such as changes to basal rates, bolus dose calculations, carbohydrate intake, and oral medication adjustments.

Furthermore, the continuous glucose monitor provides real time knowledge of glucose levels that can be displayed on a handheld device. The system can be set to provide notifications and alerts based upon Sensor trends and threshold settings adding information unavailable by traditional discrete monitoring. Trending information can be used to provide rate of change alerts that notify the user that glucose level is increasing or decreasing at a rate that raises concern for hyperglycemia or hypoglycemia. Predictive high and low thresholds can be set to notify the user that the Sensor glucose is approaching a threshold of concern. These alerts may be especially helpful for users with hypoglycemia unawareness (that is, individuals who may develop severe hypoglycemia without the normal warning symptoms), those with nocturnal hypoglycemia, or during times when users may be less aware of the warning symptoms. These alerts may also be very helpful at identifying hyperglycemia, which is associated with long term complications. Traditional blood glucose monitoring is not able to capture the data that can show patterns of potentially dangerous episodes of asymptomatic hypoglycemia and episodes of hyperglycemia. Therefore, if used as intended, the device provides significant benefits to users not available using traditional glucose monitoring.

This system is able to provide these benefits to users for an expected life of up to 90 days, far longer than any of the continuous glucose monitors currently commercially available.

Summary of Risks:

Adverse events observed during the clinical trial were similar to those for other approved CGM systems, and the most adverse events were dermatological in nature.

A minor risk of this device is that users may need to perform unnecessary fingersticks to evaluate blood glucose when the CGM gives a false positive or negative reading also mitigates these risks.

Patient Perspective:

Patient perspectives considered during the review included patients' preference for longer CGM sensor wear times, elimination of frequent self-insertion, and a totally subcutaneous sensor. The comparatively short sensor life of 6-10 days for other CGM systems, the need to self-insert the sensor, and the inconveniences of wearing a percutaneous sensor that can be easily dislodged during normal activities have been main sources of patient dissatisfaction. The benefits of the Eversense CGM System may result in increased utilization of CGM technology.

D. Overall Conclusions

In conclusion, the Eversense CGM has demonstrated accuracy and safety in bench, pre-clinical, pilot and finally pivotal controlled multi-center trials. The data in this application support the reasonable assurance of the safety and effectiveness of this device when used in accordance with the indication for use. The benefits of using the Eversense CGM System outweigh the risks.