SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sensor, glucose, implanted, non-adjunctive use
Device Trade Name:	Eversense® E3 Continuous Glucose Monitoring System
Device Procode:	QHJ
Applicant's Name and Address:	Senseonics, Incorporated 20451 Seneca Meadows Pkwy Germantown, MD 20876
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160048/S016
Date of FDA Notice of Approval:	February 11, 2022

A PMA Supplement (P160048/S006) for the Eversense Continuous Glucose Monitoring (CGM) system was approved on June 6, 2019 with the following indications:

The Eversense® CGM System is indicated for continually measuring glucose levels in adults (age 18 and older) with diabetes for up to 90 days. The system is indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions.

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 intended for single patient use.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to change the sensor design, glucose calculation algorithm, and system calibration frequency, and to revise the indications for the Eversense® CGM System as described below. The

indicator hydrogel on the sensor has been modified to improve sensor survival for up to 180 days; the glucose calculation algorithm has been modified to improve sensor performance up to 180 days; the system calibration frequency has been modified to allow for either one or two calibrations per day after day 21 of sensor wear. The details of these design changes are discussed below in this document.

II. INDICATIONS FOR USE

The Eversense® E3 CGM System is intended for continually measuring glucose levels in adults (18 years and older) with diabetes for up to 180 days. The system is indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions.

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 and trends seen over time.

The system is intended for single patient use.

III. CONTRAINDICATIONS

The following contraindications are included in the labeling:

- The Smart Transmitter is incompatible with magnetic resonance imaging (MRI) procedures. The Smart Transmitter is MR unsafe and MUST BE REMOVED before undergoing an MRI (magnetic resonance imaging) procedure. For information on the sensor, please see MRI Safety Information.
- 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® E3 Continuous Glucose Monitoring System labeling.

V. DEVICE DESCRIPTION

The Eversense® E3 Continuous Glucose Monitoring System (Eversense® System, or System) provides continuous glucose measurements over a 40-400 mg/dL range. The system provides real-time glucose values, glucose trends, and alerts for high and low glucose through a mobile application installed on a compatible mobile device platform (e.g., Android or iOS device). The Eversense® E3 System consists of a fluorescence-based glucose sensor (Eversense® E3 sensor) that is inserted under the skin by a Health Care Provider with Insertion Tools; an externally worn Eversense® Smart Transmitter (transmitter); and the Eversense® Mobile Medical Application (MMA), which runs on a compatible mobile device. 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 the MMA on the mobile device.

The System consists of four principal components:

1. **Sensor:** The sensor uses a fluorescence sensing mechanism to detect glucose in the interstitial fluid (ISF). The sensor is inserted subcutaneously by a Health Care Provider and 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 1.75 mg of an anti-inflammatory steroid drug (dexamethasone acetate) that elutes locally to reduce tissue inflammation around the sensor. The sensor operating life is the lesser of 180 days or until the device's end-of-life is reached. The sensor is provided sterile to the Health Care Provider, for single use in a sensor holder. The sensor is inserted by a qualified Health Care Provider using the provided Insertion Tools.

   As described in Section X, "Summary of Primary Clinical Studies" in this document, the primary clinical study (the PROMISE study) included two versions of the Eversense® sensor: the primary (or original) sensor as approved in P160048 and P160048/S006, and the E3 sensor. The indicator hydrogel formulation in the E3 sensor was modified to extend in vivo functional life of the sensor. In this Panel Track Supplement, the approved version of the Eversense® E3 System only includes the E3 sensor.

2. **Transmitter:** The transmitter, worn externally over the inserted sensor, is a device 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 handheld device (HHD). An adhesive patch holds the transmitter in place. The transmitter contains a rechargeable battery which is charged with a charging cradle powered by a USB connection. 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 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 by input of blood glucose measurements. 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.

4. **Insertion Tools:** Insertion Tools (a Blunt Dissector and Insertion Tool) are provided to the Health Care Provider for sensor insertion. The Blunt Dissector is used to create the subcutaneous space in which the sensor is placed. The sensor holder in which the sensor is stored during transport and sterilization is used to transfer the sensor to the Insertion Tool. The Insertion Tool is used to place the sensor into the subcutaneous space.

This medical device product has functions subject to FDA premarket review as well as functions that are not subject to FDA premarket review. For this application, if the product has functions that are not subject to FDA premarket review, FDA assessed those functions only to the extent that they either could adversely impact the safety and effectiveness of the functions subject to FDA premarket review or they are included as a labeled positive impact that was considered in the assessment of the functions subject to FDA premarket review.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are a number of 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 continuous 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 Health Care Provider to choose the method that best suits individual expectations and lifestyles.

VII. MARKETING HISTORY

The Eversense E3 Continues Glucose Monitoring System has not been marketed in the United Stated or any foreign country.

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.

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
- sensor fracture during removal
- Skin inflammation, thinning, discoloration or redness

There are risks relating to difficulty with sensor removal, and potential risks associated with subsequent procedures required for sensor removal. Six instances of inability to remove the sensor on first attempt were observed in an on-going post approval study for the Eversense® Continuous Glucose Monitoring System approved under P160048. In the PROMISE study (the pivotal study conducted to support the current application), all sensors were removed on their first attempt. Based on post-market data and the results observed in this clinical study, the occurrence of these events is low.

There is a risk of sensor breakage leaving a sensor fragment under the skin. Three instances of sensor breakage were documented in the post approval study. No instance of sensor breakage occurred in the PROMISE study. Based on post-market data and the results observed in this clinical study, the occurrence and severity of these events is low.

There may be potential risks relating to repeated insertion and removal procedures, including buildup of scar tissue over time at the sensor insertion site, in a small range of locations on the outside surface of the upper arms. Based on post-market data available, this happened at a low rate in 3 study participants in the post approval study.

The Eversense® E3 CGM System has a drug component, consisting of 1.75 mg of dexamethasone acetate (DXA), contained in a dexamethasone eluting silicone collar placed on the outside of the Eversense® sensor. Based on information and clinical evaluations performed, the sponsor has demonstrated that risks relating to both local and potential systemic exposures to the dexamethasone component of the device, as well as repeated exposure to the dexamethasone component of the device, are not expected to occur.

These risks appear to be remote based on the results observed in these clinical studies, although these clinical studies did not include subjects taking dexamethasone (or other glucocorticoid medications).

There is a minor risk of skin irritation, inflammation, or infection due to either the sensor or the adhesive.

There are potential adverse effects associated with making diabetes treatment decision when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

The risks of making treatment decisions based on inaccurate calculation of the rate of change of glucose could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

The device also provides glucose alerts; these alerts may cause a user to take action to prevent potential future glycemic events. Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia.

There are potential risks associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The body-worn transmitter component of the system provides an alternate means of delivering alerts to users through vibratory feedback. The level of information necessary to understand the safety aspects of the user interface, and how it supports the user and reduces the potential for use error was provided by the sponsor and found to be adequate. There may be an additional risk that the display, or alerts related to the CGM device may

not be able to override other applications or functions (phone, camera, SMS) within the mobile device. This risk could potentially result in missed alerts, or temporary loss of access to the display. Missed alerts, or inability to access the display could result in missed opportunities to detect or prevent hypoglycemia or hyperglycemia and are discussed above. Human factors studies conducted assessed the safety of the user interface of the mobile app (sole display) for this device, and the ability for users to receive and understand alerts and notifications via the transmitter vibration feature. The human factors studies sufficiently assessed the potential for user error associated with comprehension of the impact of mobile device and app settings on notifications and Bluetooth communications, as well as use of the audio override feature.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Non-clinical performance characteristics and preclinical validation of the Eversense® CGM System were established in preclinical studies summarized in the SSED for P160048. The changes from the approved Eversense® CGM System to the Eversense® E3 CGM system that required additional preclinical testing include a change to the formulation of the sensor indicator hydrogel, as well as transmitter and Mobile App software changes. Therefore, selected preclinical studies previously described in the SSED for P160048, including selected sensor tests, and software verification and validation studies were repeated.

A. Laboratory Studies

Bench testing that was conducted to support safety and effectiveness of the Eversense® CGM System was provided in the SSED for P160048. Additional testing to support device modifications related to the changes in device design and the Indications for Use is described below:

Transmitter and Mobile App Software: Software verification and validation testing of the transmitter firmware and the Mobile App software was performed 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. Specific test methods, acceptance criteria, and test results were reviewed and found acceptable.

Sensor Biocompatibility Testing: New biocompatibility testing was performed for the modified E3 sensor. Additional cytotoxicity and intracutaneous irritation tests were performed with the modified sensor design in accordance with recognized consensus standards ISO 10993-5 and ISO 10993-10, respectively. 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. A toxicological risk assessment was performed and concluded that the modified sensor design introduced no new toxicological risks.

Sensor Sterilization: The sensor with its holder is provided sterile for single-use and is sterilized using ethylene oxide (EO). Sterilization validation adoption was performed with the modified sensor design following ISO 11135:2014 and testing performed to verify compliance to ISO 10993-7:2002.

Sensor Analytical Performance Testing: Analytical performance testing was conducted using the approved sensor functional test method and demonstrated that sensors met the acceptance criteria.

B. Animal Studies

No new animal studies were needed to support this PMA supplement. Please refer to SSED P160048 for the animal studies supporting the original PMA application.

C. Additional Studies

No additional studies were performed to support this PMA Supplement. Please refer to SSED P160048 for the additional studies supporting the original PMA application.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study (PROMISE) in the United States under IDE # G180235 to evaluate the performance of the Eversense® E3 CGM System to support 180 days of interstitial fluid glucose measurement.

The applicant performed the PROMISE clinical study using transmitter software (which converts the raw data collected by the sensor into glucose readings) referred to as SW602, which is currently used in the approved 90-day product with a modification to extend the wear period to 180 days. After the PROMISE clinical study was completed, the applicant implemented a new version of the software referred to as SW604, which was a glucose algorithm developed and trained based on an independent clinical dataset. SW604 includes a change in the frequency of calibrations required by the system and other design modifications to support 180 days of wear. The Eversense® E3 CGM System with SW604 employs 2-calibrations (cal)/day for the first 21 days following the insertion. The system switches to a reduced calibration scheme on Day 21, where it chooses between 1 or 2 cal/day, depending on sensor signal metrics. At every calibration, the system determines if the next calibration point is needed in 24 hours (1 cal/day) or 12 hours (2 cal/day) and informs the user through the MMA so that the user can plan the next calibration accordingly. The applicant post-hoc processed the raw sensor data from the PROMISE study using the SW604.

The PROMISE study included both the original Eversense® sensor as well as the Eversense® E3 sensor with the modified hydrogel. The original Eversense® sensor was

used as the primary sensor in all subjects enrolled in this study. The Eversense® E3 sensors with the modified indicator hydrogel were evaluated in a subgroup of the subjects to serve as a bridging study to evaluate the design change.

Safety data presented in the SSED is for all subjects since the differences between the original Eversense® and the Eversense® E3 sensors do not affect the procedure of inserting and removing the sensor. Accuracy data are presented separately for the original Eversense® and the Eversense® E3 sensors.

A summary of the clinical study is presented below.

A. Study Design

The PROMISE study was a non-randomized, non-blinded, prospective, multi-center study evaluating 181 adult subjects with diabetes mellitus in the United States at 8 sites. The investigation included both clinic visits and home use of the Eversense® E3 CGM System. Of the 181 subjects who were inserted by trained investigators, 85 subjects were inserted with one sensor only in the left arm and 96 subjects were inserted with two sensors (one in each arm). The subject visit schedule for the 180-day assessment included 12 visits over a period of approximately 8 months. The visits included a screening visit, sensor insertion, 10 accuracy visits, and a follow-up visit after sensor removal. The accuracy of the CGM System was evaluated during clinic visits on days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180 by comparing sensor glucose values and plasma glucose values drawn every 5 to 15 minutes for a period of approximately 8 to 10 hours and measured on a bedside glucose analyzer. During sensor accuracy clinic visits, qualifying subjects participated in hyperglycemia and hypoglycemia challenges.

The first subject was enrolled on December 27, 2018. The last subject was completed on May 8, 2020. One hundred seventy subjects (94%) completed the Day 180 (Visit 11) with accuracy data collection. One subject missed the Day 180 Visit. Ten (10) subjects withdrew from the study (5.5%) after sensor insertion. There were 3 subjects lost to follow-up after sensor removal. These subjects did not return to the clinic for Visit 12, the 10-day post removal follow-up visit.

The CGM glucose values and all glucose-related alerts were not blinded to the subjects or 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.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PROMISE study was limited to patients who met the following inclusion criteria:

   a. Adults, age ≥ 18 years
   b. Clinically confirmed diagnosis of diabetes mellitus for ≥ 1 year

c. Signed an informed consent form and is willing to comply with protocol requirements

Patients were not permitted to enroll in the PROMISE study if they met any of the following exclusion criteria:

a. History of unexplained severe hypoglycemia in the previous 6 months. Severe hypoglycemia is defined as hypoglycemia resulting in loss of consciousness or seizure
b. History of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months
c. Subjects with gastroparesis
d. 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.
e. A condition preventing or complicating the placement, operation, or removal of the sensor or wearing of transmitter, including upper extremity deformities or skin condition
f. Symptomatic coronary artery disease; unstable angina; myocardial infarction, transient ischemic attack or stroke within 6 months; uncontrolled hypertension (systolic>160 mm Hg or diastolic >100 mm Hg at time of screening); current congestive heart failure; history of cardiac arrhythmia (benign PACs and PVCs allowed). Subjects with asymptomatic coronary artery disease (e,g, CABG, stent placement or angioplasty) may participate if negative stress test within 1 year prior to screening and written clearance from Cardiologist documented.
g. Hematocrit <30% or >60%
h. History of hepatitis B, hepatitis C, or HIV
i. Current treatment for a seizure disorder unless written clearance by neurologist to participate in study
j. History of adrenal insufficiency
k. Currently receiving (or likely to need during the study period): immunosuppressant therapy; chemotherapy; anticoagulant/antithrombotic therapy (excluding aspirin); topical glucocorticoids over sensor site only; antibiotic for chronic infection (e.g. osteomyelitis, endocarditis)
l. Known topical or local anesthetic allergy
m. Known allergy to glucocorticoids
n. 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
o. Participation in another clinical investigation (drug or device) within 2 weeks prior to screening or intent to participate during the study period
p. The presence of any other active implanted device

2. Follow-up Schedule

At the end of the Day 180 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 performed approximately 10 days (-3/+7 days) later for evaluation of the sensor site. Study investigators documented any device-related and insertion/removal procedure-related serious adverse events during the study.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAE) through 180 days post insertion and sensor removal and follow-up.

With regards to effectiveness, there were statistically powered endpoints related to effectiveness. The effectiveness data were presented using multiple analyses as described in the Study Results section below.

With regard to success/failure criteria, safety and effectiveness measures were evaluated descriptively; neither inferential analysis nor hypothesis testing was performed.

B. Accountability of PMA Cohort

Two hundred eight subjects were consented and screened for participation in the study. Two subjects withdrew prior to insertion and after enrollment due to their inability to comply with the proposed visit schedule. Twenty-five subjects were documented as Screen Failures. Of the 181 subjects who participated in the study, 85 subjects were inserted with one sensor only in the left arm and 96 subjects were inserted with two sensors (one in each arm). All primary sensors used the original sensor hydrogel formulation.

One hundred seventy subjects (94%) completed the Day 180 visit. Ten subjects withdrew from the study (5.5%) after sensor insertion. There were 3 subjects lost to follow-up after sensor removal. These subjects did not return to the clinic for the 10-day post removal follow-up visit.

Of the 96 subjects who had two sensors inserted, 43 were inserted with the E3 sensor with modified hydrogel formulation as the secondary sensor. Forty of these subjects (93%) completed the Day 180 (Visit 11), and 42 subjects completed the 10-day follow-up after sensor removal (Visit 12). Three (3) E3 subjects withdrew from the study (7.0%) after sensor insertion, and one was lost to follow-up after sensor removal.

C. Study Population Demographics and Baseline Parameters

The demographics of all subjects and the E3 subgroup study population are typical for a study performed in the US. See Tables 1 through 4 for a description of the demographic and baseline characteristics for these subjects inserted with sensors.

Table 1: Study Demographics (n=181); all subjects

Demographic	Value
Gender n (%) Male Female	 85 (47.0) 96 (53.0)
Age (years) [mean (SD)] Min, Max	48.6 (14.9) 18, 77
Ethnicity n (%)	
Hispanic	23 (12.7)
Non-Hispanic	158 (87.3)
Race n(%)	
Caucasian	163 (90.1)
Black or African American	10 (5.5)
Asian	4 (2.2)
American Indian or Alaska Native	2 (1.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)
More than One Race	2 (1.1)
Body Mass Index Class [mean (SD)] kg/m^2 Min, Max	31.4 (7.2) 19.0, 61.0
Normal (<25 kg/m^2) n (%)	28 (15.5)
Overweight (≥25 and <30) n (%)	53 (29.3)
Obese (≥30) n (%)	100 (55.2)

Table 2: Study Demographics (n=43); E3 sensor subgroup

Demographic	Value
Gender n (%) Male Female	 21 (48.8) 22 (51.2)
Age (years) [mean (SD)] Min, Max	48.5 (16.6) 21, 77
Ethnicity n (%)	
Hispanic	7 (16.3)
Non-Hispanic	36 (83.7)
Race n(%)	
Caucasian	38 (88.4)
Black or African American	2 (4.7)
Asian	2 (4.7)
American Indian or Alaska Native	0 (0.0)

Demographic	Value
Native Hawaiian or Other Pacific Islander	0 (0.0)
More than One Race	1 (2.3)
Body Mass Index Class [mean (SD)] kg/m^2 Min, Max	31.8 (7.0) 19.0, 49.0
Normal (<25 kg/m^2) n (%)	4 (9.3)
Overweight (≥25 and <30) n (%)	14 (32.6)
Obese (≥30) n (%)	25 (58.1)

Table 3: Diabetic History (n=181); all subjects

Diabetic History	Value
Years since diabetes diagnosis (years) [mean(SD)] Min, Max	22.0 (13.3) 1,56
Diabetes type n (%) Type 1 Type 2	 126 (69.6) 55 (30.4)
Type of insulin therapy n (%) None (oral diabetes medications only) Multiple daily injections Continuous insulin infusion pump Other (Basal only or 1 injection per day)	 16 (8.8) 65 (35.9) 92 (50.8) 8 (4.4)
History of ketoacidosis in the past 6 months (n/%)	0 (0.0)
History of hypoglycemia in the past 6 months (n/%)	0 (0.0)

Of the 181 subjects, 126 had Type I diabetes. A total of 92 subjects had continuous insulin infusion pump.

Table 4: Diabetic History (n=43); E3 sensor subgroup

Diabetic History	Value
Years since diabetes diagnosis (years) [mean (SD)] Min, Max	19.2 (13.4) 2,54
Diabetes type n (%) Type 1 Type 2	 27 (62.8) 16 (37.2)
Type of insulin therapy n (%) None (oral diabetes medications only) Multiple daily injections Continuous insulin infusion pump	 8 (18.6) 13 (30.2) 17 (39.5)

Other (Basal only or 1 injection per day)	5 (11.6)
History of ketoacidosis in the past 6 months (n/%)	0 (0.0)
History of hypoglycemia in the past 6 months (n/%)	0 (0.0)

Of the 43 E3 sensor subgroup subjects, 27 had Type I diabetes. A total of 17 subjects had a continuous insulin infusion pump.

The E3 sensor subgroup key characteristics with regard to demographics and diabetic history were shown to be consistent with those of the entire study population.

D. Safety and Effectiveness Results

1. Safety Results

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.

The analysis of safety was based on all subjects who were enrolled in the study and had sensor(s) inserted. One eighty-one subjects were successfully inserted with sensor(s), 10 withdrew early, 170 of 171 enrolled completed the 180 day visit and all 181 subjects had their sensor(s) removed per protocol and form the basis of the safety population. Ninety-six subjects had two sensors inserted and 85 subjects had one sensor inserted.

The primary safety endpoint was the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAE) through 180 days post insertion and sensor removal and follow-up. An adverse event (AE) 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 Day 180 post sensor insertion and removal and follow-up as shown in Table 5 for all subjects. The proportion of subjects experiencing a serious adverse event is presented together with the associated 95% confidence interval.

Adverse effects that occurred in the PMA clinical study:

There were no reports of unanticipated serious adverse device effects.
There were no reports of unanticipated non-serious adverse device/procedural effects.
There were no device or sensor insertion/removal procedure-related serious adverse events in either all subjects or for the E3 sensor subgroup.

Table 5: All Related and Unrelated SAEs through Day 180

SAEs by Relationship to Study	Number of SAEs	Number of Subjects with SAEs (%)	95% Confidence Interval
All SAEs	9	7 (3.9)	1.6, 7.8
Device Related SAEs	0	0 (0.0)	0.0, 2.0
sensor Insertion Procedure Related SAEs	0	0 (0.0)	0.0, 2.0
Study Procedure Related SAEs	0	0 (0.0)	0.0, 2.0
Unrelated to Study SAEs	9	7 (3.9)	1.6, 7.8

The other safety endpoints included:

- Incidence of device-related or insertion/removal procedure-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.

The device- and/or insertion/removal procedure-related AEs for the entire study population are listed in Table 6 below. Fifty-nine AEs in 37 subjects (20.4%) were adjudicated to be device and/or insertion/removal procedure related or possibly related through Day 180 and/or post sensor removal.

There were no unanticipated AEs and no unanticipated adverse device effects.

The most commonly reported related AEs were dermatological in nature (such as skin irritation to the adhesive patch, skin atrophy, hypopigmentation, and infection) affecting 9.9% of the subjects. The next most commonly reported related AEs were hematologic in nature such as bruising and bleeding affecting 7.7% of the subjects. Finally, 3.9% of subjects experienced related AEs categorized as neurological in nature such as pain. All sensors were removed on first attempt in all 181 subjects.

In the study overall, there were 279 sensor insertions (85 single sensors + 96 dual sensors + 2 replacements), resulting in 558 insertion/removal procedures. There were 2 infections observed at the insertion/removal site, resulting in an incision infection rate in 1.1% of subjects or in 0.36% of the total insertion and removal procedures performed.

Table 6: Adverse Events Related or Possibly Related to the Study Device or Insertion/removal Procedure through Day 180 (end of Pivotal phase of study); all subjects

Event Physiologic System	Number of Events	Number of Subjects (% of Subjects)
	59	37 (20.4)
Dermatological	27	18 (9.9)
Skin irritation, adhesive patch location (including erythema, pruritus, rash, contact dermatitis)	13	9 (5.0)
Skin atrophy	4	4 (2.2)
Hypopigmentation	4	3 (1.7)
Infection (insertion/removal site)	2	2 (1.1)
Infection (under adhesive patch)	1	1 (0.6)
Contact dermatitis due to drape adhesive	1	1 (0.6)
Erythema, insertion site	1	1 (0.6)
Seroma, removal site	1	1 (0.6)
Hematologic Immunologic	22	14 (7.7)
Bruise (1 w/ serosanguinous drainage)	19	11 (6.1)
Bleeding	3	3 (1.7)
Neurological	9	7 (3.9)
Pain	7	6 (3.3)
Arm Numbness	1	1 (0.6)
Tremor	1	1 (0.6)
Other		
Steristrips did not hold	1	1 (0.6)
	1	1 (0.6)

The analysis of the safety of the E3 sensor subgroup within the PROMISE study supports the findings in the overall safety profile of the PROMISE study.

2. Effectiveness Results

The analysis of effectiveness was based on the observed accuracy of the primary sensors in 181 evaluable patients in the PROMISE who contributed 49,613 CGM-comparator matched glucose data pairs.

All effectiveness analyses presented in this document were performed using the approved glucose determination algorithm, referred to as the "SW604" algorithm.

The following tables show the rate at which the Eversense® E3 CGM System agreed with a laboratory comparator method (CM). The tables are organized by CM system glucose ranges, and they tabulate the percent of CGM system measurements that were within a given range of paired comparator measurements. The ranges included below are 15, 20, 30, 40, and greater than 40. For comparator values below 80 mg/dL, the units of the range value are

mg/dL. For CGM values above 80 mg/dL, the units of the range value are percent.

The data which are tabulated in Table 7 below is a combination of data collected on 10 different days of the PROMISE study: days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180 of sensor wear for all subjects with primary sensor. As stated above, the primary sensors used in this study used the original hydrogel chemistry. The E3 sensors with modified hydrogel chemistry were included as secondary sensors for 43 subjects as a bridging study within the PROMISE study. Performance of the modified E3 sensors was reviewed and found to be comparable to that of the original sensors as described below in the section titled "Performance of Modified E3 Sensor."

Table 7: CGM System Agreement to Reference within CM Glucose Ranges Through 180 Days; all subjects, primary sensor

CM Glucose Range (mg/dL)	Number of Paired CGM and CM	Percent of CGM System Readings Within				
		Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall	49,613	85.6	92.9	98.0	99.3	0.7
< 40	20	55.0	80.0	85.0	100.0	0.0
40 – 60	2,281	83.2	89.4	96.4	98.4	1.6
61 – 80	5,270	84.1	92.2	97.9	99.4	0.6
81 – 180	19,001	82.7	90.9	97.3	99.0	1.0
181 – 300	14,578	87.9	94.7	98.7	99.5	0.5
301 – 350	6,862	90.6	96.5	99.4	99.9	0.1
351 – 400	1,510	87.8	93.9	97.9	99.1	0.9
> 400	91	65.9	83.5	96.7	97.8	2.2

The following table shows the rate of concurrence between the Eversense® E3 CGM System and a laboratory comparator method (CM). The tables are organized by CGM system glucose ranges, and they tabulate the percent of paired CM measurements that were in the identical range (shaded diagonal), as well as those CM measurements that were in glucose ranges above and below the paired CGM readings.

Table 8: CGM System concurrence to Comparator Method organized by CGM glucose ranges; data pooled from accuracy assessments on days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180 combined of all subjects, primary sensor

CGM (mg/dL)	Number of Paired CGM-CM (n)	Percent of Matched Pairs in Each CM Glucose Range for Each CGM Glucose Range CM (mg/dL)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
<40	0	--	--	--	--	--	--	--	--	--	--	0
40-60	2205	1	55	42	2	0	0	0	0	0	0	0
61-80	4623	0	20	70	10	0	0	0	0	0	0	0
81-120	8135	0	2	13	73	12	0	0	0	0	0	0
121-160	8090	0	0	0	16	70	13	1	0	0	0	0
161-200	6334	0	0	0	1	18	65	15	0	0	0	0
201-250	6615	0	0	0	0	1	17	64	16	2	0	0
251-300	6046	0	0	0	0	0	1	16	54	28	2	0
301-350	5676	0	0	0	0	0	0	1	16	71	12	0
351-400	1889	0	0	0	0	0	0	0	3	54	39	3
>400	465	0	0	0	0	0	0	0	1	32	58	9

The following table shows the consistency of sensor clinical performance during the sensor wear period by comparing the CM values to their paired sensor points collected on days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180 of the PROMISE study in all subjects with primary sensor.

Table 9: Sensor stability (accuracy over time); all subjects, primary sensor

Day Number	Number of Paired CGM-CM	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within (95% CI)				
				Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall	49613	9.1	6.7	85.6	92.9	98.0	99.3	0.7
Visit 3 (Day 1)	5584	11.0	8.0	80.0	89.0	96.5	98.3	1.7
Visit 4a (Day 7)	2724	9.6	7.2	83.1	91.3	98.2	99.3	0.7
Visit 4b (Day 14)	2318	9.2	6.8	83.1	91.7	98.2	99.6	0.4
Visit 5 (Day 22)	6198	9.1	6.9	85.3	93.6	98.3	99.4	0.6
Visit 6 (Day 30)	6488	8.4	6.1	88.4	94.8	98.7	99.6	0.4
Visit 7 (Day 60)	6345	7.7	6.0	90.5	95.8	99.1	99.8	0.2
Visit 8 (Day 90)	6039	8.2	6.2	88.7	94.4	98.4	99.6	0.4
Visit 9 (Day 120)	5173	9.2	6.7	85.5	93.3	98.3	99.5	0.5
Visit 10 (Day 150)	4227	9.6	6.9	85.5	92.7	97.9	99.1	0.9
Visit 11 (Day 180)	4517	10.4	7.5	81.0	89.6	96.2	98.3	1.7

The table below provides the percent agreement of the Eversense® E3 CGM system and comparator method (CM) within a specific time range after calibration for all subjects with primary sensor in the PROMISE study. Calibration stability data beyond 12 hours is based on the calibration frequency determined by the SW604 algorithm.

Table 10: Calibration stability; all subjects, primary sensor

Time from Calibration	Number of Paired Senseonics CGM and CM	Percent of CGM System Readings Within				
		Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
0-2 hours	10303	87.4	94.2	98.4	99.4	0.6
2-4 hours	8824	85.8	92.8	98.1	99.3	0.7
4-6 hours	6955	86.8	93.5	98.2	99.3	0.7
6-8 hours	5318	85.0	92.5	97.8	99.2	0.8
8-10 hours	4161	84.5	92.5	98.4	99.5	0.5
10-12 hours	4164	83.7	90.8	97.6	99.2	0.8
12-14 hours	2269	82.9	92.0	97.6	99.1	0.9
14-16 hours	1441	83.3	91.1	96.5	98.0	2.0
16-18 hours	1297	87.7	94.4	97.6	99.2	0.8
18-20 hours	1242	87.2	94.4	98.8	99.8	0.2
20-22 hours	1443	84.2	92.9	97.9	99.4	0.6
22-24 hours	1682	83.2	92.4	97.7	99.0	1.0
24-26 hours	509	82.3	91.4	97.4	98.2	1.8
26-28 hours	5	60.0	100.0	100.0	100.0	0.0

The following table provides data to present sensor accuracy at detecting specific glucose rates of change. These concurrence tables provide the percent of matched CM pairs to CGM values over specific glucose rates of change as observed during the PROMISE study in all subjects with primary sensor.

Table 11: Concurrence of CGM and Comparator Method (CM) rate of change stratified by difference CGM rate ranges; all subjects, primary sensor

CGM Trend (mg/dL/Min)	CM Rate of Change (mg/dL/Min) Percent of Matched Pairs in Each CM Trend Range for Each CGM Trend Range					Total (N)
	< -2	[-2, -1)	[-1, 1]	(1, 2]	> 2	
< -2	17	41	41	1	0	756
[-2,-1)	3	31	66	1	0	2963
[-1,1]	0	4	90	5	1	35777
(1,2]	0	1	52	37	10	3263
> 2	0	0	28	38	33	1635
Total (N)	322	2747	36469	3717	1139	

The following table provides the Eversense® sensor percent difference with respect to comparator method (CM) values.

Table 12: Difference measures between Eversense® E3 CGM System and Comparator Readings (CM); all subjects, primary sensor

CM Glucose Ranges (mg/dL)	Number of Paired CGM-CM	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall	**49613**	**9.1**	**6.7**
<40*	20	16.1	13.0
40-60*	2281	9.4	7.0
61-80*	5270	8.8	7.0
81-180	19001	9.0	6.7
181-300	14578	7.7	5.9
301-350	6862	7.1	5.9
351-400	1510	8.0	6.3
>400	91	13.4	11.2

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

Precision Analysis

Precision of the System was evaluated by comparing the results from two separate sensors worn on the same subject at the same time. During the PROMISE study, a total of 53 subjects contributed 169,347 between-sensor matched pairs for the original Eversense® sensor. The table below tabulates the results from this study, including the Percent Absolute Relative Difference (PARD), standard deviation (SD), and Percent Coefficient of Variation (PCV).

Table 13: System precision statistics; all subjects, primary sensor

Level of Mean Glucose (mg/dL)	Mean Difference (sensor 1 - sensor 2) (mg/dL)	SD of Difference (mg/dL)	N Pairs
< 70	-0.1	12.6	5283
70-180	0.1	17.8	112,206
> 180	0.0	30.3	51858
All	0.1	22.3	169,347
PARD	10.1%		
PCV	7.1%		

Alert Performance

The Eversense® System includes threshold alerts and optional predictive alerts. A threshold alert is issued if measured glucose is below or above the user-defined low or high alert set point. A predictive alert is issued if measured glucose is predicted to go below or above the user-defined low or high alert set point within the next 15 minutes.

Alert performance was evaluated to obtain 'true alert' and 'false alert' rates, and 'confirmed event' and 'missed event' detection rates. The descriptions and tables below describe the alert rate performance of the device within the PROMISE study for all subjects, primary sensor.

- The confirmed event detection rate is the rate that the device alerted when it should have alerted. It is the ratio of the number of times an alert was sounded when blood glucose was below the threshold to the total number of times blood glucose went below the threshold (for hypoglycemic alerts).
- The Missed Event Detection Rate is the rate at which the device did not alert when it should have. It is the rate at which blood glucose, as measured by comparator method, was below the low glucose alert threshold and the device did not sound an alert (for hypoglycemic events). This is the complement of the confirmed event detection rate.
- The true alert rate is the ratio of the number of times an alert was sounded while blood glucose was below the alert threshold to the total number of times an alert was sounded
- The false alert rate is the complement of the true alert rate (i.e., if the true alert rate is 90%, the false alert rate would be 10%).

Table 14: In-Clinic Hypoglycemic Event Detection, Threshold and Predictive Alert Performance; all subjects, primary sensor

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	87%	13%	68%	32%
70	93%	7%	87%	13%
80	96%	4%	90%	10%
90	97%	3%	90%	10%

Table 15: In-Clinic Hyperglycemic Event Detection, Threshold and Predictive Alert Performance; all subjects, primary sensor

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	96%	4%
140	99%	1%	95%	5%
180	99%	1%	94%	6%
200	98%	2%	93%	7%
220	98%	2%	92%	8%
240	98%	2%	92%	8%
300	92%	8%	87%	13%

Number of Readings Provided

The system is capable of providing a reading every 5 minutes (up to 288 readings per day). For a variety of reasons (e.g., sensor failure), the System may not display a glucose reading and readings are "skipped." The number of actual sensor values provided to subjects over the entire 180-day period and the corresponding percentage is summarized in the table below.

Table 16: Eversense® 180 CGM System Reliability from the PROMISE Study; all subjects, primary sensor

% 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%	--	0
76 - 100%	7193 out of 7627, 50086 out of 50086	100

Performance of the E3 Sensor

A modified sensor design, referred to in this document as the E3 sensor, was also evaluated in the PROMISE study. Compared to the original sensor (the primary sensor in all participants and the Secondary sensor in 53 of the 96 participants who wore two sensors), the E3 sensor had a modified hydrogel formulation intended to extend the in vivo functional life of the sensor. The formulation change was not intended to affect the primary mechanism of action of the sensor.

Accuracy of the E3 sensor was assessed in a sub-group of 43 subjects who wore the E3 sensor as the Secondary sensor in the study. This sub-group served as a bridging study to directly compare the performance of the E3 sensor to that of the original sensor.

The table below shows the agreement between the Eversense® E3 sensor to the laboratory comparator method (CM). Performance of the Eversense® CGM system observed in the PROMISE study using the original sensor (primary) is also presented for reference.

Table 17: CGM System Agreement to CM within CM Glucose Ranges Through 180 Days; primary sensor and E3 sensor

Sensor Design	CM Glucose Range (mg/dL)	Number of Paired CGM and CM	Percent of CGM System Readings Within				MARD
			Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	
Original sensor (Primary)	Overall	49,613	85.6	92.9	98.0	99.3	9.1%
E3 sensor	Overall	12,034	87.3	93.9	98.6	99.6	8.5%

The data which are tabulated in Table 18 below is a combination of data collected on 10 different days of the PROMISE study: days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180 of sensor wear for all subjects with the E3 sensor.

Table 18: CGM System Agreement to CM within CM Glucose Ranges Through 180 Days; E3 sensor

CM Glucose Range (mg/dL)	Number of Paired CGM and CM	Percent of CGM System Readings Within				
		Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall	12034	87.3	93.9	98.6	99.6	0.4
< 40	--	--	--	--	--	--
40 - 60	592	92.6	96.5	99.5	99.7	0.3
61 - 80	1221	89.4	96.8	99.3	99.7	0.3
81 - 180	5067	84.6	92.0	97.8	99.5	0.5
181 - 300	3300	87.5	94.2	98.6	99.6	0.4
301 - 350	1457	90.6	95.9	99.9	100.0	0.0
351 - 400	372	94.1	97.0	100.0	100.0	0.0
> 400	25	96.0	100.0	100.0	100.0	0.0

The following tables show the consistency of the E3 sensor performance during the sensor wear period by comparing the CM values to their paired sensor points collected on days 1, 7, 14, 22, 30, 60, 90, 120, 150 and 180.

Table 19: Sensor stability (accuracy over time); E3 sensor

Day Number	Number of Paired CGM-CM	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent 15/15% of CM	Percent 20/20% of CM	Percent 30/30% of CM	Percent 40/40% of CM	Percent Greater than 40/40% of CM
Overall	12034	8.5	6.4	87.3	93.9	98.6	99.6	0.4
Visit 3 (Day 1)	1203	11.2	9.3	78.6	87.4	96.5	99.3	0.7
Visit 4a (Day 7)	792	10.0	5.8	81.9	88.0	94.7	98.5	1.5
Visit 4b (Day 14)	404	7.4	4.9	87.4	95.0	99.0	100.0	0.0
Visit 5 (Day 22)	1436	8.4	6.5	88.9	95.7	99.2	99.9	0.1
Visit 6 (Day 30)	1523	8.2	5.9	85.8	93.4	98.2	99.3	0.7
Visit 7 (Day 60)	1365	8.6	6.7	87.9	94.2	98.6	99.8	0.2
Visit 8 (Day 90)	1418	7.0	5.7	93.1	97.1	99.8	99.9	0.1
Visit 9 (Day 120)	1195	8.4	6.5	89.2	96.1	99.6	99.9	0.1
Visit 10 (Day 150)	1285	8.8	6.5	84.0	91.9	99.5	99.9	0.1
Visit 11 (Day 180)	1413	7.4	6.3	93.1	98.0	99.3	99.7	0.3

E3 Sensor Alert Performance

The following tables provide the alert performance for the Eversense® CGM system when using the E3 sensor as observed in the PROMISE study. See the Alert Performance section above for a description of the detection and alert rates described in these tables.

Table 20: In-Clinic Hypoglycemic Event Detection, Threshold and Predictive Alert Performance; E3 sensor

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	90%	10%	73%	27%
70	94%	6%	84%	16%
80	97%	3%	87%	13%
90	98%	2%	89%	11%

Table 21: In-Clinic Hyperglycemic Event Detection, Threshold and Predictive Alert Performance; E3 sensor

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	99%	1%	96%	4%
140	99%	1%	95%	5%
180	99%	1%	93%	7%
200	99%	1%	93%	7%
220	98%	2%	92%	8%
240	98%	2%	91%	9%
300	92%	8%	87%	13%

The following table provides data to present sensor accuracy at detecting specific glucose rates of change. These concurrence tables provide the percent of matched CM pairs to CGM values over specific glucose rates of change as observed during the PROMISE study in all subjects with the E3 sensor.

Table 22: Concurrence of CGM and Comparator Method (CM) rate of change stratified by difference CGM rate ranges; E3 sensor

CGM Trend (mg/dL/Min)	Reference Rate of Change (mg/dL/Min) Percent of Matched Pairs in Each Reference Trend Range for Each CGM Trend Range					Total (N)
	< -2	[-2, -1)	[-1, 1]	(1, 2]	> 2	
< -2	24	35	41	0	0	163
[-2,-1)	4	36	59	0	0	824
[-1,1]	0	4	90	5	1	8716
(1,2]	0	1	46	42	11	896
> 2	0	0	24	40	35	336
Total (N)	86	737	8923	905	284	10935

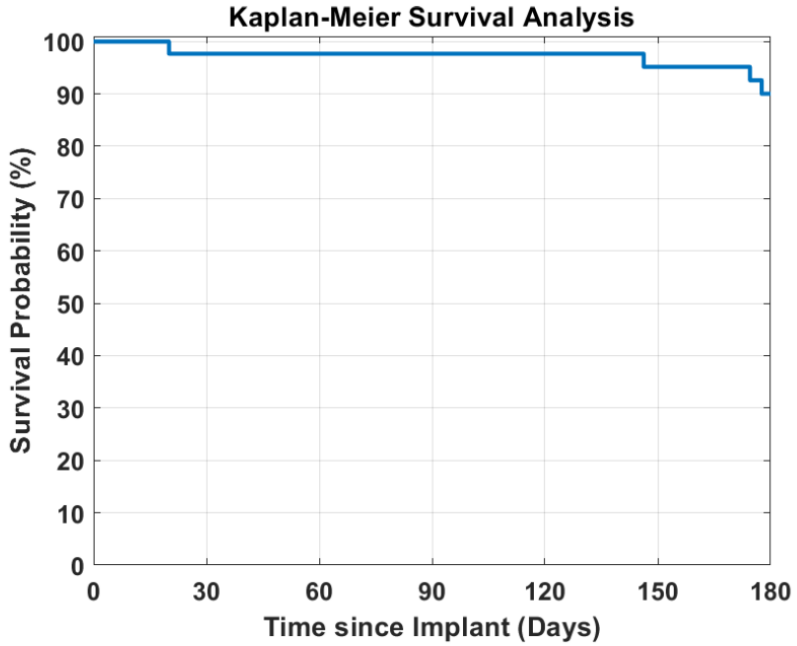
The table below provides the percent agreement of the Eversense® E3 CGM system and comparator method (CM) within a specific time range after calibration for subjects using the E3 sensor in the PROMISE study. Calibration stability data beyond 12 hours is based on the calibration frequency determined by the SW604 algorithm.

Table 23: Calibration Stability; E3 sensor

Time from Calibration	Number of Paired Senseonics CGM and 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
0-2 hours	2638	88.8	94.1	98.7	99.9	0.1
2-4 hours	1905	87.2	94.4	98.5	99.5	0.5
4-6 hours	1404	85.3	93.3	98.1	99.3	0.7
6-8 hours	1043	83.0	91.5	97.7	99.6	0.4
8-10 hours	1041	89.7	93.9	98.8	99.6	0.4
10-12 hours	1091	87.8	94.1	97.7	99.5	0.5
12-14 hours	590	85.8	93.4	99.0	99.3	0.7
14-16 hours	440	82.7	91.8	100.0	100.0	0.0
16-18 hours	379	87.6	93.9	99.5	100.0	0.0
18-20 hours	370	90.0	97.0	98.4	99.7	0.3
20-22 hours	436	88.3	94.5	99.5	99.8	0.2
22-24 hours	522	89.7	96.2	99.4	99.8	0.2
24-26 hours	168	93.5	98.2	99.4	100.0	0.0
26-28 hours	7	100.0	100.0	100.0	100.0	0.0

Sensor Life

In the PROMISE Study, 65% of the primary (original) sensors functioned through 180 days. The E3 sensor design incorporated a formulation change to extend the in vivo functional life of the sensor hydrogel. As a result, 90% of the E3 sensors functioned through 180 days. The survival analysis for the E3 sensors observed in the PROMISE study is presented in the figure below.



3. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The primary clinical studies included eight principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA Supplement was not referred to the Clinical Chemistry and Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the PROMISE clinical study establish a reasonable assurance of effectiveness of the Eversense® E3 CGM System to be used as intended in the intended use population. The primary effectiveness measurements for the clinical studies were based on the performance evaluation of the original sensor used in the Eversense® E3 CGM System compared to the blood glucose values measured by the laboratory glucose analyzer during the in-clinic sessions that spanned the wear period of the device (days 1, 7, 14, 22, 30, 60, 90, 120, 150, and 180). Effectiveness measures for the E3 sensor (evaluated in a sub-group to serve as a bridging study within the larger PROMISE study) demonstrated that the E3 sensor performance is non-inferior to that of the original sensor. The approved version of the device system will use the E3 sensor only.

The clinical performance data are also comparable to currently approved CGM devices approved for non-adjunctive use. The data support acceptable accuracy across the claimed measuring range (40 to 400 mg/dL), precision, sensor life for the intended 180-day wear period, and alert performance.

The clinical and analytical studies demonstrate that the Eversense® E3 CGM System is effective in the study population.

B. Safety Conclusions

The risks of the device are based on the adverse events observed in the clinical study described in **Section X** above, and the potential adverse effects of the device on health as described in the SSED for P160048.

The following related adverse events were observed from using the Eversense® E3 CGM System: bruising, skin irritation, pain, skin atrophy/hypopigmentation, bleeding, infection, erythema, seroma, arm numbness and tremor.

There are potential adverse effects associated with making diabetes treatment decisions when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include

inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

Inaccurate calculation of the rate of change of glucose by the device could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose by the device could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

There are potential adverse effects associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The device also provides glucose alerts; these alerts may cause a user to take action to prevent potential future glycemic events. Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia.

C. Benefit-Risk Conclusions

The probable benefits and risks of the device are based primarily on data collected in clinical and analytical studies conducted to support the approvals of P160048 and P160048/S006, as well as on data collected in the clinical and analytical studies to support approval of the Eversense® E3 CGM System as described above. Potential adverse effects of the device on health are described in Section VIII above.

This submission is for a change to the indications for use to allow the device to be used for up to 180 days, a design change to allow for reduced calibration frequency after day 21 of sensor wear, as well as for a design change to the sensor hydrogel intended to facilitate this longer wear period. A summary of the Benefits and Risks of this device is presented below.

Summary of Benefits:

There is significant patient burden in terms of monitoring diabetes, including psychosocial aspects which include burnout and stigma. Although SMBG remains the most commonly used tool for diabetes management, adherence to SMBG is known to be suboptimal. The Eversense® E3 CGM System has potential advantages associated with a significantly longer wear period (up to 180 days) compared to the wear periods of currently marketed transdermal CGM systems (up to 14 days) and the previously approved Eversense® CGM System (up to 90 days). The longer-term sensor eliminates the need for users to insert a new sensor every 7-14 days and reduces the need of current Eversense® CGM users for repeated sensor removal/insertion. The transmitter which is placed over the sensor and secured in place with adhesive can be removed and replaced without ending sensor life. The use of a mobile device as the primary display is beneficial to patients, as it offers convenience in terms of decreasing the number of devices required to be with the patient to utilize this CGM device. The longer-term sensor in conjunction with a removable transmitter and a mobile display device could result in increased utilization of CGM technology by patients.

An additional benefit of the Eversense® E3 CGM System is the new calibration scheme, which allows for potentially "reduced calibration" beyond 21 days, from 2 times per day to once per day depending on the operating condition of the sensor. This could be expected to provide the benefit of decreased discomfort associated with fingerstick measurements and could lead to improved patient compliance with CGM calibration.

Benefits of non-adjunctive use continuous glucose monitoring in general include real-time knowledge of glucose values and trends, and the identification and/or confirmation of patterns of glycemic excursions throughout the day and night, when patients may be unable to test their blood glucose. Access to retrospective glucose trend information with this device may allow patients to make more informed diabetes treatment decisions rather than relying solely on intermittent glucose point data as provided by self-monitoring blood glucose (SMBG) devices. The extended

wear period of the Eversense® E3 CGM System could further increase adoption of continuous glucose monitor use and provide opportunities for easier and more convenient glucose monitoring to patients with diabetes, while providing the added benefits of this device. The discreet design and long wear period of the Eversense® E3 CGM System may also benefit the current stigma for people with diabetes.

Summary of Risks:

Compared to other marketed CGM Systems with similar indications for use, this device has additional potential risks, which do not differ from the currently marketed version of the Eversense® CGM System (P160048/S006, approved in June 2019). A description of these potential risks is presented below.

There are potential risks relating to the insertion and removal procedures required for use of the Eversense® CGM System, which involves an outpatient based procedure. Designation of specific healthcare providers, required training for the insertion and removal procedures, as well as adequate labeling, is helpful to mitigate these risks. Potential risks relating to insertion and removal procedures include pain, inflammation, infection, and sensor breakage leaving a sensor fragment under the skin in the subcutaneous tissue. There are also risks relating to difficulty with sensor removal, and risks associated with subsequent procedures (i.e., anesthesia, pain, infection) to attempt sensor removal. In addition, there may be potential risks relating to repeated insertion and removal procedures including scar tissue buildup, as the outside side of the upper arms is the only sensor insertion site. A post-approval study is currently in progress to confirm the safety of the insertion and removal procedures relating to the Eversense® CGM System.

The Eversense® CGM System has a drug component, consisting of 1.75mg of dexamethasone acetate (DXA), contained in a dexamethasone eluting silicone collar to the outside of the Eversense® sensor. The sponsor has provided sufficient information and evaluation to reasonably demonstrate that the risks relating to the dexamethasone component of the device are not expected to occur. The sponsor has demonstrated that clinically significant systemic exposure to the dexamethasone component of the device is not expected to occur. The sponsor has also provided information to indicate that wound healing as well as the local area surrounding the device insertion site are not adversely affected. Further, there may be a potential risk relating to repeated exposure to dexamethasone, but these risks seem to be unlikely, given the lack of systemic or local effects relating to a single exposure to dexamethasone.

A post-approval clinical study was required as a condition of approval for P160048/S006 to confirm the safety and effectiveness of the Eversense® CGM System for the non-adjunctive use indication. This was necessary considering the higher-risk, non-adjunctive claim, high-risk patient population intended to use the device, and residual uncertainty relating to real-world performance of this device. As of the time of this approval, this study is still ongoing.

In addition to the above, there is moderate residual uncertainty related to the E3 sensor. The sensor accuracy and survival rate have been evaluated in a relatively small group of 43 subjects. While the results of this evaluation suggest that safety and performance of the SBA sensor is at least equivalent to that of the original sensor, the smaller sample size results in moderate uncertainty regarding whether these results would have been observed in a larger sample of participants inserted with the SBA sensor and whether they are sufficiently representative of the broader intended use population. Further, the rate of adverse events associated with the non-adjunctive use of the E3 version of the sensor, and the potential for adverse events after multiple sensor insertion/removal cycles with the longer 180-day wear period were not evaluated in the clinical study as the output from the E3 sensor was blinded, and multiple sensor wear cycles were not studied. The lack of repeat sensor insertion cycles for the 180-day wear period results in moderate uncertainty regarding whether the rates of adverse events will be comparable to those observed with the approved 90-day device version.

1. Patient Perspective:

Patient perspectives considered during the review included patients' preference for CGMs that can be used non-adjunctively, longer CGM sensor wear times, elimination of frequent self-insertion, and a discreet and fully implantable sensor. The comparatively short sensor life of 7-14 days for other non-adjunctive CGM systems, the need to self-insert the sensor, the need for the transmitter to remain adhered to the skin for the sensor duration, and the inconveniences of wearing a percutaneous sensor that can be dislodged during normal activities have been noted as sources of patient dissatisfaction with other non-adjunctive CGM systems. The benefits of the Eversense® E3 CGM System may result in increased utilization of CGM technology.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits of using the Eversense® E3 CGM System, as discussed above, outweigh the risks.

XIII. CDRH DECISION

CDRH issued an approval order on February 11, 2022. The final clinical conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.