EVERSENSE®
CONTINUOUS GLUCOSE MONITORING SYSTEM

SPONSOR EXECUTIVE SUMMARY

FDA ADVISORY COMMITTEE MEETING OF THE CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES ADVISORY COMMITTEE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CMC	Chemistry, manufacturing, and controls
DMS	Data management system
DXA	Dexamethasone acetate
EU	European Union
FDA	Food and Drug Administration
GEE	Generalized estimating equations
HbA1c	Glycosylated hemoglobin
HCP	Health care provider
IDE	Investigational device exemption
LC-MS/MS	Liquid chromatography tandem-mass spectrometry
LED	Light-emitting diode
MARD	Mean absolute relative difference
MMA	Mobile medical application
NFC	Near field communication
PMA	Pre-market approval
PMMA	Poly-methyl methacrylate
RF	Radio frequency
SAE	Serious adverse event
SD	Standard deviation
SMBG	Self-monitoring blood glucose
US	United States
YSI	Yellow Springs Instrument

1 SYNOPSIS

1.1 Introduction

The Eversense® Continuous Glucose Monitoring (CGM) system is a new device consisting of a fully implantable glucose sensor, a removable smart transmitter, and a mobile medical application. The system uses a novel glucose measuring technology to provide accurate glucose measurements using a long-lasting subcutaneously-placed glucose sensor. Unlike currently available CGM systems which require replacement of the transcutaneous glucose sensor approximately every 6 to 10 days, the Eversense sensor functions for up to 90 days, offering patients with diabetes a long-lasting sensor without the need for frequent sensor changes that may better accommodate patients' preferences and lifestyles. The Eversense CGM system also includes several other unique safeguards, as well as user-friendly features designed to enhance patient adherence.

Senseonics is seeking Food and Drug Administration (FDA) approval for use of this prescription device to continually measure glucose levels in adults (age 18 and older) with diabetes for the operating life of the sensor or up to 90 days. Eversense is intended to be used as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices. The system is designed to provide real-time glucose readings, glucose trend information, and alerts for the detection and prediction of episodes of low and high blood glucose.

The accuracy and safety of the Eversense CGM system has been assessed in multiple clinical studies. These include a pivotal study (PRECISE II) and a supplemental study (PRECISION) in the United States (US), a European Union (EU) CE marking approval study (PRECISE), and a post-market patient registry study in Europe (hereon referred to as "European patient registry"). The major findings from the US studies, along with data from the supportive studies, are summarized in this briefing document.

Results from the pivotal PRECISE II study demonstrate the following:

- Eversense provides accurate glucose measurements, with an overall mean absolute relative difference (MARD) of 8.5%, system agreement of 87% at a threshold of 15 mg/dL or 15% of the reference glucose values, and reliable alerts for hyperglycemic and hypoglycemic excursions, with a 98% and 96% detection rate for high glucose alerts at 180 mg/dL and low glucose alerts at 70 mg/dL, respectively.
- The system is easy to wear and the sensor functions reliably up to 90 days, with 91% of sensors lasting 90 days.
- 100% of sensor insertions were successful on the first attempt and sensor removals were completed successfully on the first attempt in 99% of patients, demonstrating that the insertion and removal procedures were performed effectively by health-care providers with no prior Eversense experience. Adverse events associated with sensor insertion and removal were not different from those anticipated from a comprehensive risk assessment

of these procedures. Follow-up approximately 10 days after sensor removal confirmed normal healing for 100% of procedures.

- Adverse events associated with Eversense were infrequent, generally mild and transient in nature, and consistent with other CGM systems.

In addition to supporting the above findings in the PRECISE II study, the European patient registry also demonstrated:

- Over 1,600 patients in a real-world setting, including 443 patients who have undergone multiple repeat insertions, have confirmed that the safety profile of the device and insertion/removal procedure remains the same.

The results from the clinical studies and registry confirm that the Eversense CGM system provides safe, accurate, and reliable continuous glucose monitoring for up to 90 days. For patients who face diabetes on a daily basis over a lifetime, it is reasonable to conclude that the medical benefits of continued CGM use prevail over the very limited safety risks with this device. With the Eversense CGM system, more patients may be able to receive the benefits of glycemic control using a longer term CGM that fits their lifestyle needs.

1.2 Unmet Need and Background on CGM

The goal for treating diabetes is to maintain glucose within as normal a range as possible, known as euglycemia, by minimizing the periods of hyperglycemia while avoiding episodes of hypoglycemia. Information about glucose levels and trends over time are the key to achieving this balance.

Despite recent improvement in therapies, type 1 and type 2 diabetes continue to be difficult medical conditions to manage. The challenge remains to achieve desired glycemic control, preventing both short-term consequences (severe hypoglycemia and diabetic ketoacidosis) and long-term complications (retinopathy, neuropathy, nephropathy, and cardiovascular disease).

The current standard of care for glucose monitoring involves using a small portable meter to obtain a capillary fingertip glucose measurement, known as Self-Monitored Blood Glucose (SMBG), multiple times a day. Unfortunately, patient adherence with obtaining these SMBG values remains a challenge. Further, since a blood glucose meter collects and displays only a single point-in-time glucose level, even patients who monitor frequently cannot capture trend information and may miss significant hypoglycemic and hyperglycemic excursions.

CGM systems address SMBG short-comings by dramatically increasing the amount of actionable information available to the patient. CGM systems offer continual access to glucose values that can alert the patient when glucose is trending too low or too high, as well as provide prospective alerts before hypoglycemic or hyperglycemic conditions occur. Data from multiple randomized controlled studies have demonstrated the benefits of CGM use (Grunberger, 2010; Beck, 2017; Bergenstal, 2017; Ruedy, 2017; Vigersky, 2012). These include improvements in glycosylated hemoglobin (HbA1c), reduced risk of hypoglycemia, and increased time spent in

euglycemia (Juvenile Diabetes Research Foundation, 2011). In addition, quality of life improvements associated with CGM use have been reported (Polonsky and Hessler, 2013; Polonsky, 2017). The extent of these benefits in public health terms depends upon both accurate glucose measurements and patients' acceptance and adoption of the technology.

The use of CGM has significantly expanded in recent years primarily due to the improvement in analytical accuracy of the devices, as well as the associated improvements in the accuracy of glucose alerts. Current CGM systems provide patients with information that can reduce the extent of glycemic excursions before patients experience them. This has been a key benefit and attribute of CGM systems.

Despite this progress, the currently available CGM systems have not been widely adopted and are only used by a small minority of people who could benefit from them, such as people with type 1 diabetes and people with type 2 diabetes on intensive regimens using insulin. Less than 25% of the people with type 1 diabetes utilize CGM as a tool in the management of their diabetes (Wong, 2014; Miller, 2015; Type 1 Diabetes Exchange Registry, 2017). In addition, utilization in type 2 diabetes is significantly lower than that of type 1.

One limitation with current CGM technology is the requirement for repeated, frequent transcutaneous insertion of a sensor by the patient. Most currently approved sensors must be replaced approximately weekly, resulting in 30-50 sensor insertions and removals each year. Fatigue of use and the complexity of long-term use lead to suboptimal use and adherence. Discomfort, issues with sensor insertion and skin irritations with these systems also lead to discontinuation and low utilization. In one survey assessing CGM device use, the reasons for discontinuation in the first year were as follows: problems with sensor insertion or adhesives for 61% of participants, discomfort when wearing the CGM sensor for 41% of participants, and bulkiness of the device for 28% of participants (Type 1 Diabetes Exchange Registry, 2016). An additional limitation is related to the transmitter unit. For the majority of currently approved systems, the transmitter cannot be temporarily removed without also removing and replacing the sensor. Thus, patients are tethered to their transmitter.

A system that addresses these limitations by allowing for less frequent insertions and removals, reducing discomfort, and providing flexibility would benefit patients and likely expand the population of people using these CGM technologies.

1.3 Product Description

The Eversense CGM system provides continual glucose measurements using a sensor that is fully inserted into the subcutaneous space on the lateral upper arm, a removable transmitter that is worn externally over the sensor, and the mobile medical application (MMA) that displays glucose information on a handheld device (e.g., smartphone, tablet; Figure 1).

The Eversense CGM system has been commercially available in Europe since June 2016.

Figure 1. Components of the Eversense CGM System

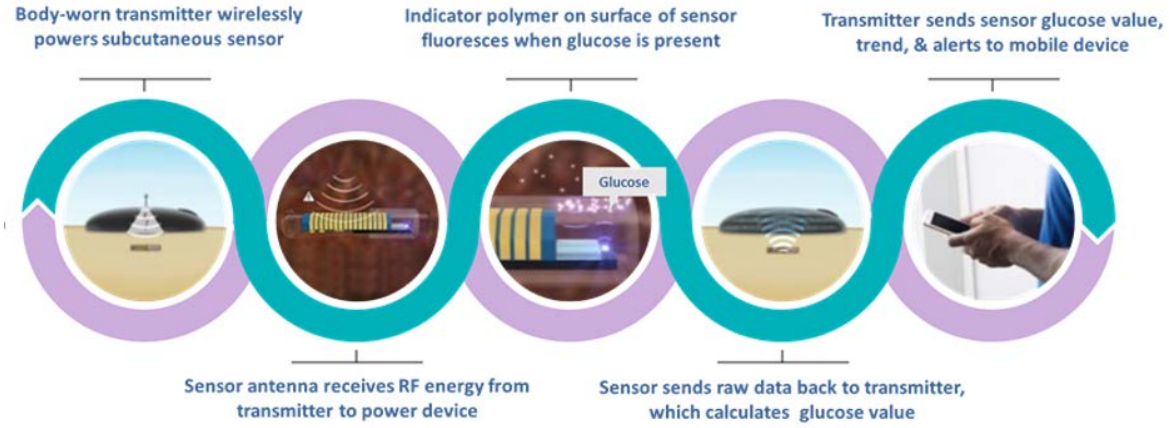
1.3.1 Sensor

The Eversense CGM system was designed to provide a longer lasting sensor to reduce the burden of weekly sensor replacements by the patient. The Eversense sensor is fully implanted in the subcutaneous space of the lateral upper arm below the deltoid. The sensor has a 90-day operating life, requiring only 4 sensor insertions and removals each year.

Eversense sensor technology uses selective, fully reversible binding between glucose and a fluorescent indicator hydrogel to measure interstitial glucose. Glucose binding by the indicator hydrogel results in an increase in fluorescence intensity, which is measured by the sensor's optical system. The sensor has a silicone collar containing 1.75 mg of the steroid dexamethasone acetate to reduce inflammation and enhance sensor longevity.

The sensor is activated to measure interstitial fluid glucose when it receives radio frequency (RF)-power from the transmitter using near field communication (NFC), and this initiates the measurement sequence by powering up the sensor's optical system. The sensor's optical system uses a light-emitting diode (LED) to excite the fluorescent indicator hydrogel and photodiodes to capture the resulting fluorescence intensity. Fluorescence intensity data are sent to the transmitter, which uses the information to produce a glucose reading and to check the integrity of the system (Figure 2, first 4 circles).

Figure 2. Mechanism of Operation of System Components



1.3.2 Smart Transmitter

The Eversense smart transmitter powers the dormant sensor via NFC magnetic coupling; calculates glucose values and trends; and wirelessly transmits glucose information to the MMA using secure Bluetooth Low Energy. It is worn externally on the upper arm over the sensor and held in place using a replaceable silicone-based adhesive patch. Unlike other CGM devices, the transmitter provides distinct vibration signals for alerts (hypoglycemic/hyperglycemic excursions, predictions, no glucose readings) and notifications (reminders and system status information), even when the handheld device with the MMA is absent, turned off, or out of battery power. All alerts and notifications are also repeated on the MMA for duplicate communication purposes.

Unlike other CGM devices, the transmitter is not physically attached to the sensor and can therefore be temporarily removed and then reapplied to the arm without disturbing the sensor. This also means that a strong adhesive is not needed to prevent dislodgement; instead, a gentle daily adhesive patch is used to keep the transmitter in place.

1.3.3 Mobile Medical Application

The MMA is a software application that runs on a handheld device (e.g., compatible mobile iOS or Android device) for display of glucose information provided by the transmitter (Figure 2, fifth circle). The handheld device receives the glucose signal from the transmitter via secure Bluetooth, and the MMA displays the calculated glucose readings, including glucose trend information and alerts. In addition, the MMA enables the user to enter glucose values from SMBG measurements for twice-daily calibrations of the Eversense CGM system.

1.3.4 Sensor Insertion and Removal Procedures

The Eversense sensor is inserted into the lateral upper arm below the deltoid by a physician during a brief, office-based procedure. The insertion procedure starts with determination of the preferred location of the sensor by the patient and the physician. The site is then marked using the provided template and disinfected prior to the injection of a small amount of local anesthetic

(e.g., 1% lidocaine) to the insertion site and tract of the sensor. The area is then disinfected a second time and sterile drapes are positioned with the insertion site accessible. Next, a shallow incision approximately 5 mm long is made with a #15 blade scalpel and the blunt dissector is used to create a subcutaneous pocket. The depth guards and guide marks on the dissector assist in determining the correct pocket depth and length. The sensor is then placed into the pocket using a custom insertion tool that has corresponding guide marks to the ones on the blunt dissector to assist with proper placement. Once the insertion tool (with sensor) is properly positioned in the subcutaneous pocket, the physician retracts a thumb slide on the tool uncovering and depositing the sensor in the subcutaneous pocket. The incision site is then closed with adhesive skin closure (e.g., Steri-Strip®).

When the sensor reaches its end-of-life, it is removed in-office. The physician palpates the sensor and uses the transmitter to identify the location which is then marked. The physician then disinfects and prepares the skin and injects a small amount of local anesthetic (e.g., 1% lidocaine). The area is then disinfected a second time and sterile drapes are positioned with the removal site accessible. Next, a small incision is made at the distal end of the sensor, and a hemostat is used to remove the sensor; this can be the same incision that was used for the insertion procedure. The incision is closed using adhesive skin closure (e.g., Steri-Strip®). Unlike other implantable devices there is no appreciable capsule formation so no additional dissection is typically required for the removal procedure.

A new sensor may be inserted during the same visit using the insertion procedure described above. Rotation of placement site to the other arm is recommended to maximize healing between insertions as is common practice for infusion pumps and other CGM systems.

1.3.5 Physician and Patient Training

A comprehensive training program will be implemented to ensure proper use of the device for patient safety. These training activities will be consistent with those used during the PRECISE II and PRECISION clinical studies as well as the European commercial launch. Both physicians and patients will be trained.

For the required physician training, a multi-modal approach will be taken with didactic instruction via the Eversense CGM Sensor Insertion and Removal Instructions, video instruction, simulated skin insertions and removals of the sensor, and mandatory proctoring of the initial sensor insertions and removals for each physician by a trained observer. Physicians will be certified once he/she has successfully completed the training program.

Patient training on the Eversense CGM system includes use of the Eversense instructions for use, instructional videos, and take-home instructions. A 24/7 Customer Care support line will also be made available, along with the Eversensediabetes.com website, where instructional materials may be found.

1.4 Effectiveness of Eversense CGM System

The PRECISE II study was conducted in the US and serves as the primary source of clinical data in support of US approval. A supplemental study, PRECISION, was also conducted to support approval in the US.

1.4.1 Pivotal PRECISE II Study

Study Design

The PRECISE II study was a non-randomized, single-arm, multi-center study designed to characterize the performance of the Eversense CGM system throughout the 90-day operating life of the sensor. PRECISE II evaluated 90 adults (age ≥18 years old) with type 1 or type 2 diabetes, who are representative of the target population for Eversense use. A subgroup of 15 patients had two sensors inserted, one in each arm, and the remaining 75 patients had one sensor inserted. Patients wore the transmitter and calibrated their sensors using SMBG values twice per day, consistent with normal use, for the duration of the study. Patients remained blinded to all sensor glucose readings, alerts, and notifications.

System accuracy assessments were conducted at clinic visits on Days 1, 30, 60, and 90. sensors were removed prior to the Day 100 follow-up visit. In clinic, patients had blood glucose reference measurements taken by the Yellow Springs Instruments (YSI) laboratory glucose analyzer, the standard for glucose quantification, for comparison to Eversense CGM system readings. Study visits at Days 30, 60 and 90 also included glycemic challenges, exercise sessions, and compression testing to assess sensor performance under a range of critical use conditions.

The primary effectiveness endpoint, sensor accuracy and precision, was expressed as the mean absolute relative difference of the sensor values compared to the reference values for all paired sensor and reference measurements through 90 days post-insertion. The MARD value represents the average absolute difference between sensor and reference glucose measurements, expressed as a percentage of the reference value. It is a conservative assessment of error as it accounts for both negative and positive differences from the reference which would otherwise minimize the overall average error.

Results

Despite not experiencing any glucose values, alerts, and trend information from their systems, 87 (97%) patients completed the study to sensor end-of-life with a median transmitter wear time of 23.4 hours per day, indicating a high level of patient-willingness to wear the device during the 90-day study period.

Over the 90-day study, a MARD of 8.5% was achieved based on a total of 15,753 pairs of sensor-reference values. This result was statistically significantly lower than the pre-specified 20% accuracy threshold, which is a performance target consistent with prior CGM studies. The percentage of Eversense readings (87%) that were within 15 mg/dL or 15% (15/15%) of the

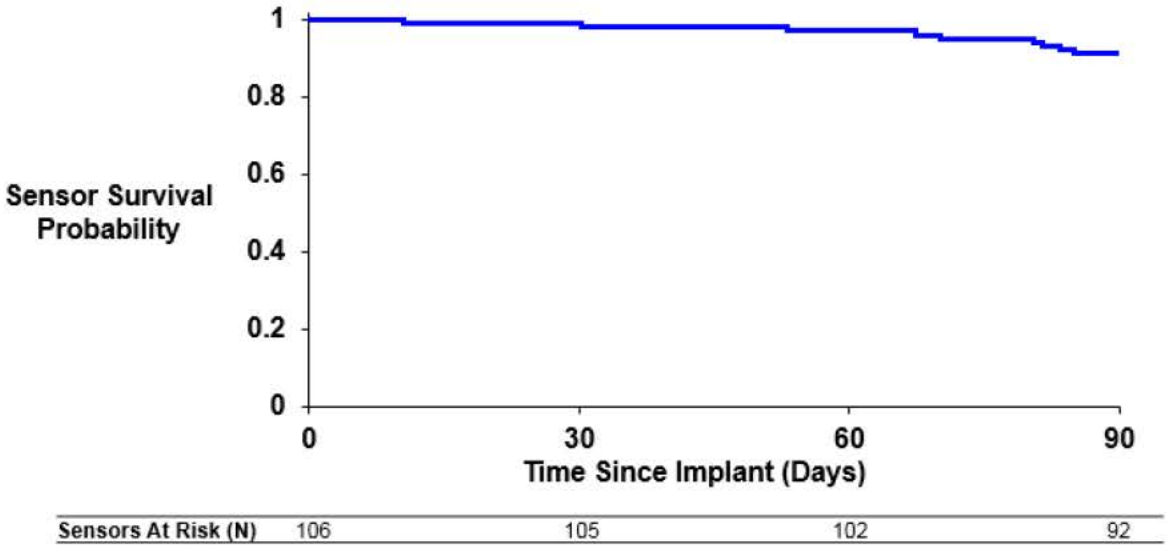
reference values shows that a large proportion of the CGM measurements were highly accurate. Accuracy was maintained over the duration of the study (Table 1) and was stable throughout the 12 hours following each calibration. Furthermore, 91% of sensors were functioning at Day 90, supporting the operating life of the sensor (Figure 3).

Table 1. Accuracy Assessment in PRECISE II at Successive Time Points

Visit	Number of Readings / Unique Patients	Mean Absolute Relative Difference (95% Confidence Interval)	Percentage of Readings within 15 mg/dL or 15%[a]
Day 1	1,708 / 90	10.7% (9.7 – 11.7)	77%
Day 30	5,081 / 88	7.4% (6.8 – 8.1)	91%
Day 60	4,725 / 85	8.2% (7.4 – 9.0)	87%
Day 90	4,239 / 77	9.1% (8.2 – 10.0)	85%
Overall	15,753 / 90	8.5% (8.0 – 9.1)	87%

[a] Sensor readings within 15 mg/dL for reference values ≤80 mg/dL or within 15% of reference for reference values >80 mg/dL

Figure 3. Kaplan-Meier Estimate of Sensor Survival in PRECISE II



Note: Events were sensors that no longer continued to function (i.e., sensor replacement alert was triggered)

Importantly, the Eversense system successfully detected 96% of hypoglycemic excursions and 98% of hyperglycemic excursions, using alert thresholds of 70 and 180 mg/dL, respectively; false positive alerts occurred at rates of 16% and 7%, respectively.

Sensor accuracy was robust and unaffected by exercise of the upper arm or compression of the sensor area. Subgroup analyses by baseline demographics and common concomitant medications also produced similar MARD results.

Overall, the findings from PRECISE II demonstrate that Eversense is an accurate and reliable CGM system; the accuracy achieved with the 90-day sensor is consistent with the results obtained from registrational studies of other available CGM devices.

1.4.2 Supplemental PRECISION Study

Study Design

The PRECISION study was a non-randomized, single-arm, multi-center study designed to provide additional data on 1) the accuracy of the Eversense CGM system within the first 30 days post sensor insertion, 2) plasma dexamethasone levels after sensor insertion, and 3) additional safety and accuracy data for use for up to 90 days. The study enrolled 36 adults, age ≥18 years old, with type 1 or type 2 diabetes. Key differences between the PRECISION and PRECISE II studies are as follows:

- In PRECISION, 27 patients received 2 sensors (one in each arm) and 8 patients were inserted with a single sensor (1 patient did not undergo sensor insertion after enrollment).
- In PRECISION, comprehensive sampling of blood for plasma dexamethasone measurement was conducted and tested using a highly sensitive assay.
- In PRECISION, patients were not blinded to glucose readings while wearing the CGM system (i.e., they experienced the full functionality of the Eversense CGM system).

Results

Based on the Day 1, 7, 14, 30, 60 and 90 visits, a MARD of 9.6% was achieved and 85% of all sensor readings were within 15 mg/dL or 15% (15/15%) of the reference values. Clinically acceptable system agreement was observed from Day 1 onwards with 79% of readings within the 15/15% threshold (Table 2).

Table 2. Accuracy Assessment in PRECISION at Successive Time Points

Visit	Number of Readings / Unique Patients	Mean Absolute Relative Difference (95% Confidence Interval)	Percentage of Readings within 15 mg/dL or 15%[a]
Day 1	2,665 / 35	11.6% (10.0, 13.1)	79%
Day 7	2,926 / 35	9.8% (7.9, 11.7)	86%
Day 14	2,997 / 35	9.0% (7.9, 10.1)	88%
Day 30	2,284 / 35	8.9% (7.5, 10.4)	88%
Day 60	2,133 / 35	8.7% (7.3, 10.0)	87%
Day 90	2,165 / 35	9.7% (8.5, 11.0)	84%
Overall	15,170 / 35	9.6% (8.9, 10.4)	85%

[a] Sensor readings within 15 mg/dL for reference values ≤80 mg/dL or within 15% of reference for reference values >80 mg/dL

Results from PRECISION demonstrate the accuracy of the Eversense CGM system during the initial 30 days post sensor insertion with glucose detection stabilizing prior to 7 days after sensor insertion. The 90-day data (MARD, 9.6%; 85% within 15/15% threshold) further support the findings from PRECISE II that accurate and precise measurements are provided throughout the 90-day sensor operating life. Finally, of the 62 sensors inserted in the PRECISION study, 100% continued to function until Day 90.

1.5 Safety of Eversense CGM System

The pivotal PRECISE II study provided the primary safety data for Eversense in the US. Supplementary safety data in the US is provided by the PRECISION study. Furthermore, the safety data from the two US studies (PRECISE II and PRECISION) and the European pivotal study (PRECISE) were pooled for a comprehensive evaluation of safety from all clinical studies. Finally, data from the EU patient registry was analyzed to further support the long-term safety profile of the Eversense CGM system.

1.5.1 Pivotal PRECISE II Study

The primary safety endpoint in PRECISE II was the incidence of device-related or insertion/removal procedure-related serious adverse events (SAEs) in the clinic and during home use through 10 days after sensor removal. Adverse events were reviewed and adjudicated by an independent medical monitor.

During the study, there was one procedure-related SAE in 90 patients (1.1%, 95% confidence interval [CI] = 0.0% to 6.0%) which was related to sensor removal. In this instance, an initial attempt to remove the sensor was unsuccessful, and the patient was referred to a surgeon who elected to remove the sensor under general anesthesia rather than under local anesthesia, resulting in the SAE adjudication. The sensor was removed without incident. Analysis of this event revealed that the sensor was initially placed deeper than recommended. To mitigate the risk of unsuccessful removal requiring additional interventions, physician training has increased the emphasis on proper depth of placement to facilitate removal and includes instructions for management of difficult to remove sensors. In addition, to further mitigate the risk of deep insertions, the blunt dissector used during sensor insertion has been modified with the addition of depth guards to aid with placing the sensor more consistently at a controlled depth, as proper sensor depth facilitates removal.

A total of 14 device or procedure-related adverse events (AEs) (including the single SAE reported above) were reported in 7 (7.8%) patients (Table 3):

- 8 events in 4 patients of bruising (2), erythema (2), or pain/discomfort (4) at the sensor insertion site
- 1 event of delayed post-removal pain at the sensor insertion site
- 2 events of possibly retained device fragments (sensor end caps made of poly-methyl methacrylate [PMMA])
- 1 event of syncope and 1 event of tingling, both following sensor insertion
- 1 event of unsuccessful sensor removal on first attempt (SAE described above)

All but 2 of the AEs were of mild severity. Two AEs of moderate severity included 1 complaint of pain and 1 instance of difficulty removing the sensor in the patient with the SAE. All but one AE resolved by study completion, and the remaining event of delayed post-removal pain was reported to have completely resolved post-database lock.

The risk of potentially retained device fragments did not necessitate intervention in the study for the following reasons: 1) it was uncertain whether the end caps were retained during removal, 2) the very small size of the end caps (3.2 mm in diameter by 0.8 mm thick), and 3) the recognition that PMMA is a well-known biocompatible permanent implant material. This risk was addressed with an immediate Corrective and Preventative Action plan to implement improved quality control of the cap attachment step in manufacturing. To further mitigate the risk, a design

modification was made to the end cap of the sensor to prevent possible detachment during sensor removal.

Table 3. Adverse Events Related to the Device or Insertion/Removal Procedure in PRECISE II

Adverse Event	Number of Events	Number (%) of Patients (N=90)
All Events	14	7 (8%)
Pain/discomfort	4	3 (3%)
Bruising	2	1 (1%)
Erythema	2	1 (1%)
Device fragment not recovered	2	2 (2%)
Syncope	1	1 (1%)
Tingling	1	1 (1%)
Delayed post-removal pain	1	1 (1%)
Unsuccessful sensor removal on first attempt	1	1 (1%)

There were no unanticipated adverse events and no deaths. Of note, there were no infections related to the device or insertion/removal procedures and no adhesive patch skin reactions (a frequent complaint with other CGM devices), despite a median transmitter wear time of 23.4 hours/day over the 90-day study. Furthermore, there was no observable impact of dexamethasone exposure; no patients exhibited poor healing of the incision following either the insertion or removal procedure, skin thinning over the sensor, or systemic infections.

1.5.2 Supportive PRECISION Safety Results

In the US PRECISION study, 35 patients received a total of 62 sensors. Safety data through 90 days post-insertion showed a similar AE profile for the Eversense CGM system as compared to the PRECISE II study. No insertion/removal procedure-related infections were observed. There were 3 SAEs unrelated to the study device or study procedure (gastroenteritis, a hypoglycemic episode, and a cellulitis infection in the patient's foot).

1.5.3 Integrated Safety Results

The PRECISE II, PRECISION, and PRECISE clinical trials were pooled and together comprise 206 adult patients with type 1 and type 2 diabetes who underwent identical insertion and removal procedures with very similar models of the device. The integrated analysis provides the broadest

review of all safety data collected to date from multicenter, registrational studies of Eversense with over 22,500 patient-days (61 years) of device exposure.

The PRECISE study was a non-randomized, single-arm, multicenter study in the EU that evaluated 81 adults (age ≥18 years old) with type 1 or type 2 diabetes who each had 2 sensors inserted, one in each arm, for up to 180 days. Compared to the US studies (PRECISE II, PRECISION), the EU PRECISE study investigated an earlier design of the Eversense CGM system, which had a marginally shorter sensor that contained the same DXA collar in a different position and an earlier version of software[1]. Despite these differences, safety data from the PRECISE study provide relevant information for the pooled safety analysis.

The types and frequency of AEs from the pooled analysis of the 3 studies were all anticipated for the device or the insertion/removal procedure (Table 4). Importantly, there were no additional SAEs related to the device or the insertion/removal procedure, no unanticipated adverse events, and no cases of infection requiring sensor removal. Of the 3 reports of infection (all reported in PRECISE), 2 cases resolved without intervention, 1 resolved with oral antibiotics, and none required device removal. Modified training on insertion site care including leaving the dressing undisturbed for 48 hours instead of 24 hours to allow for improved early incision healing was implemented in PRECISE II and PRECISION and no infections were reported in these latter trials.

[1] After completion of PRECISE, changes were made to the glucose determining software algorithms to improve system accuracy and slight dimensional changes were made to the sensor to improve manufacturing efficiency. These minor changes are expected to have negligible effects on the safety of the device; therefore, the earlier version of the device provides direct evidence of Eversense safety.

Table 4. Adverse Events Related to the Device or Insertion/Removal Procedure from Integrated Studies

Event Physiologic System and Category[a]	Number of Events	Patients[b] (N=206)
Dermatological	**24**	**16 (7.8%)**
Pain/Discomfort	8	6 (2.9%)
Redness/Erythema	6	5 (2.4%)
Infection	3	3 (1.5%)
Dermatitis at Patch Location	3	2 (1.0%)
Bruising	2	1 (0.5%)
Skin Hyperpigmentation	2	1 (0.5%)
Neurological	**6**	**6 (2.9%)**
Neuropathy - Left Hand	1	1 (0.5%)
Vertigo	1	1 (0.5%)
Excessive Sleep Disturbance	1	1 (0.5%)
Headache	1	1 (0.5%)
Paresthesia	1	1 (0.5%)
Syncope-vasovagal	1	1 (0.5%)
Musculoskeletal Rheumatologic	**2**	**2 (1.0%)**
Pain	2	2 (1.0%)
Cardiovascular	**1**	**1 (0.5%)**
Hypertension	1	1 (0.5%)
Hematologic/immunologic	**1**	**1 (0.5%)**
Hematoma	1	1 (0.5%)
Gastrointestinal Hepatic	**1**	**1 (0.5%)**
Nausea	1	1 (0.5%)
Other	**6**	**5 (2.4%)**
Device Fragment[c] Not Recovered upon Sensor Removal	2	2 (1.0%)
Additional Procedure to Remove Sensor Following First Attempt	4	3 (1.5%)
TOTAL	**41**	**26 (12.6%)**

[a] Some events have been re-categorized for clarity
[b] Patients may experience more than one AE in each category
[c] Sensor cap

1.5.4 Repeat Insertions

A detailed risk analysis of repeat sensor use concluded that the potential risks have been sufficiently characterized through data from premarket clinical studies in the US and EU in combination with real world data from the post-approval study in Europe.

A European patient registry was initiated following approval of the Eversense CGM system in Europe to collect safety data on long-term use of the device, specifically with repeated sensor insertions, in up to 20 countries in Europe and in South Africa. In these countries, every patient who receives an Eversense CGM system is enrolled and will be followed until 100 patients have completed 4 insertion/removal cycles, after which all active patients will continue to be followed for another 12 months.

This post-market study included active, prospective patient follow-up according to defined procedures for evaluation, follow-up, and reporting of adverse events. Study endpoints include the incidence of AEs associated with the device, insertion or removal procedure, and dexamethasone.

As of February 2, 2018, a total of 1,686 patients have enrolled at 350 trained sites from 14 countries. These patients have received a total of 2,386 sensor insertions under real-world use conditions, with approximately 173,658 total days (~475 years) of exposure to the commercial version of the device. Of the 1,686 patients enrolled in the ongoing European patient registry, 443 have received a second sensor, 143 have received a third sensor, 58 have received a fourth sensor, 39 have received a fifth sensor, 14 have received a sixth sensor, and 3 have received a seventh sensor.

Based on the ongoing results, the safety profile following repeat insertions indicates that there are no additional or new risks identified to be associated with long-term use (Table 5). There have been no serious adverse events related to the device or the insertion/removal procedure and no unanticipated adverse events. None of the AEs observed at repeat insertions were unique and all AEs considered potentially related to the device or insertion/removal procedure were infrequent (Table 5). All related AEs were not medically serious and were transient in nature.

Table 5. Adverse Events Related to the Device or Insertion/Removal Procedure in European Patient Registry

Number of Patients (%)	Post 1st Insertion N=1,686	Post 2nd Insertion N=443	Post 3rd Insertion N=143	Post 4th Insertion N=58	Post 5th Insertion N=39	Post 6th Insertion N=14	Post 7th Insertion N=3
SAEs	-	-	-	-	-	-	-
Device, Procedure Related AEs							
Infection	8 (0.5%)	4 (0.9%)	2 (1.4%)	-	-	-	-
Unable to remove sensor on first attempt	7 (0.4%)	2 (0.5%)	-	-	-	-	-
Irritation at adhesive patch location	5 (0.3%)	-	2 (1.4%)	-	-	-	-
Skin thinning (atrophy) over sensor with discoloration	2 (0.1%)	1 (0.2%)	-	-	-	-	-
Bruising	1 (0.1%)	1 (0.2%)	-	1 (1.7%)	-	-	-
Prolonged wound healing after procedure	3 (0.2%)	-	-	-	-	-	-
Skin discoloration	1 (0.1%)	2 (0.5%)	-	-	-	-	-
Sensor broke during removal	3 (0.2%)	-	-	-	-	-	-
Sensor site redness/reaction to dressing	3 (0.2%)	-	-	-	-	-	-
Pain/discomfort	1 (0.1%)	-	-	-	-	-	-
Skin thinning (atrophy) over sensor	1 (0.1%)	-	-	-	-	-	-
Syncope during procedure	1 (0.1%)	-	-	-	-	-	-
Hematoma	-	-	-	1 (1.7%)	-	-	-

These data demonstrate that the risks of repeat sensor insertions and removals have been successfully mitigated to provide a reasonable assurance of device safety. On the basis of this information, and in discussion with the FDA, it was determined that any residual risks associated with repeat insertions are best studied in a post-approval setting (see Section1.6).

1.5.5 Release of Dexamethasone Acetate

A silicone collar, containing 1.75 mg of dexamethasone acetate, is attached to the PMMA encasement adjacent to the indicator hydrogel. This anti-inflammatory steroidal drug elutes slowly, reducing local tissue inflammation and enhancing sensor longevity. Corticosteroids have been successfully used to help manage inflammatory reactions in the medical field for over 6 decades, and also in combination with implanted medical devices.

In PRECISION, plasma dexamethasone concentration was measured using a highly sensitive liquid chromatography tandem-mass spectrometry (LC-MS/MS) assay (lower limit of quantification of 0.05 ng/mL) in 8 patients prior to sensor insertion and after sensor insertion at 30 minutes, 1 hour, and 4 hours, then daily through the Day 7 visit, and at regular study visits thereafter (Days 14, 30, 60, and 90). Dexamethasone levels were measured in the remaining 27 study patients at scheduled clinic visits (screening, Days 0, 1, 7, 14, 30, 60, and 90). At Day 1, 7 and 14 visits, dexamethasone was measured on two successive days since the visits crossed midnight.

All dexamethasone levels through 90 days post sensor insertion were below the 0.05 ng/mL quantification limit of the assay in patients with 1 sensor inserted.

Among patients who were inserted with 2 sensors, 18 out of 27 (66%) had a detectable level of plasma dexamethasone within the first week. The maximum level of dexamethasone measured was 0.114 ng/mL and all decreased to below the quantification limit by Day 9. Given that patients will only receive one sensor at a time under normal use, the findings from PRECISION indicate that patients will generally be exposed to dexamethasone levels of less than 0.05 ng/mL, which is far below the level of 1 ng/mL that has been shown to have a systemic effect (Meikle, 1982; Ueland, 2017; Loew, 1986; Menke, 2016; Zirker, 1976).

Furthermore, explanted sensors from the clinical studies were analyzed for residual DXA content and found to have eluted approximately 15% of their original DXA content on average over 90 days (n=147). According to this analysis, the fraction of embedded DXA that was released into the local environment *in vivo* was 0.26 mg over 90 days of sensor exposure.

Overall, plasma dexamethasone levels remained below 0.05 ng/mL in patients who had one sensor. Such low levels of dexamethasone are not expected to be associated with any pharmacological response beyond the immediate implant area or systemic adverse events.

1.6 Post-Approval Plans

Based on ongoing discussions with the FDA, a US post-approval study will collect data on repeat sensor insertions through 2 years (8 cycles of sensor insertions/removals) in 175 patients providing up to an additional 350 patient-years of experience on repeat insertions to the European patient registry to confirm the ongoing safety profile of Eversense. The primary safety endpoint of this study will be the rate of device-related and insertion and removal procedure-related SAEs through 12 months post-first sensor insertion, with a hypothesis that the rate will be no greater than a performance goal of 7%. The primary effectiveness endpoint will be the time in range, defined as glucose values between 70 mg/dL and 180 mg/dL, at 12 months post-first sensor insertion compared to the first month post-first sensor insertion. In addition, the post-approval study will evaluate the effectiveness of physician training, patient-reported outcomes, and overall rate of AEs through 2 years.

1.7 Conclusions

The benefits of any continuous glucose monitoring system are highly dependent upon the accuracy of CGM measurements and the usability of the device from a patient perspective. As demonstrated in the PRECISE II study, the Eversense CGM system has a high degree of accuracy and precision, with a MARD of 8.5% over the operational life of the sensor. With 91% of sensors reaching 90 days, the Eversense reduces the burden of frequent sensor replacement inherent with other CGM systems and will potentially improve adoption and adherence among diabetes patients. The system also provides accurate detection of hypoglycemic and hyperglycemic excursions. The PRECISE II study results are supported by the findings of the PRECISION and PRECISE studies, offering evidence of the robustness of the data.

The risks of the Eversense CGM system include those related to sensor insertion and removal, those related to sensor performance, those related to wearing the transmitter, and those related to the presence of the sensor *in situ*. The PRECISE II, PRECISION, and PRECISE studies have demonstrated that adverse events related to the device and insertion and removal procedures were relatively infrequent and generally mild and transient in nature, with most resolving within 2 weeks. The anti-inflammatory agent eluted from the device, dexamethasone acetate, was undetectable at levels of <0.05 ng/mL in plasma and is therefore not expected to be associated with any systemic pharmacological response, which is consistent with the safety profile observed in Eversense clinical trials. Long-term safety results from the European patient registry with 2,386 insertions in 1,686 individuals indicate that local tissue response to the sensor was minimal following repeated insertions. In addition, there have been no unanticipated adverse events in any of the clinical trials or in the post-market setting, suggesting that appropriate understanding and mitigation of risks has been established and that overall safety under repeated sensor insertions is maintained. Risks associated with the intended use of Eversense have been mitigated as low as possible by device design, labeling, and training programs and materials.

In terms of sensor performance, the risk of inaccurate results related to the use of Eversense is no greater than that of other CGM systems on the market, as demonstrated by the accuracy achieved in PRECISE II and PRECISION. Furthermore, the risk of inaccurate CGM readings with Eversense is no greater than using an SMBG meter alone, which is how the majority of patients manage their diabetes today. Importantly, the accuracy of the Eversense CGM system, with an overall MARD of 8.5%, is consistent with other commercially available continuous monitoring systems.

The benefits of the Eversense CGM system include continuous and real-time glucose values and trend information as well as real-time alerts for high and low glucose excursions. The Eversense CGM system offers alternatives to current technology by providing a sensor that lasts up to 90 days. This requires only 4 sensor insertions and removals each year. In addition to expected improvements in patient comfort and satisfaction, a longer lasting sensor reduces the amount of time lost to equilibration by limiting the number of insertions. Additionally, unique from other CGM systems and extremely important in notifying the user of impending hypoglycemia, the Eversense transmitter provides vibrations in a recognizable pattern in addition to the audible and

visual alerts issued from the handheld device. These vibratory alerts provide users with important glucose information even when the handheld device with MMA is absent or turned off. Eversense also gives users the ability to temporarily remove the transmitter when desired, without disturbing the sensor, providing patients more flexibility for times when discretion is preferred.

The ready availability of glucose readings and alerts may lead to long-term adherence to CGM technology, better understanding of glucose trends related to food, exercise, stress, and other factors. As with other CGM systems, Eversense, when used in combination with SMBG readings, may lead to improved glucose control, lower HbA1C values, and a reduction in long-term complications of diabetes. The potential risks of the Eversense system are expected and manageable and are outweighed by the potential benefits of adherence to CGM use. As such, Eversense, with its longer-wear sensor and other unique features, represents a new CGM option with a demonstrated positive benefit-risk profile that may meet the needs of patients with diabetes.

2 BACKGROUND ON CONTINUOUS GLUCOSE MONITORING IN DIABETES

Summary

- The current standard of care for glucose monitoring involves obtaining SMBG values multiple times a day. Each blood glucose meter measurement only provides a single point-in-time glucose level, and even patients who monitor frequently may miss significant hypoglycemic and hyperglycemic excursions.
- CGM Systems provide patients and health care providers continual glucose values, trend data, and alerts about high and low glucose excursions, important information that would otherwise be missed in diabetes management.
- Data from multiple controlled, randomized studies have demonstrated the benefits of CGM use including improvements in glycosylated hemoglobin (HbA1c), reduced risk of hypoglycemia, and increased time spent in euglycemia.
- These benefits depend upon accurate glucose measurements and patients' acceptance and adoption of the technology.
- At least 75% of patients who could benefit from CGM systems are not using the technology (Type 1 Diabetes Exchange Registry, 2017).
- Many patients discontinue CGM due to problems with sensor insertion, the adhesive patch, and discomfort when wearing the sensor.
- A system that addresses some of the barriers to CGM use is needed to promote wider adoption and improve patient adherence.

2.1 Overview of Continuous Glucose Monitoring in Clinical Management of Diabetes

Despite recent improvement in therapies, diabetes mellitus continues to be a difficult medical condition to manage. The challenge remains to achieve desired glycemic control and to prevent both short-term consequences (severe hypoglycemia and diabetic ketoacidosis) and long-term complications (retinopathy, neuropathy, nephropathy, and cardiovascular problems). Patient monitoring of blood glucose is one of the key tools of diabetes self-care. The current standard glucose monitoring regimen involves using a small portable meter to obtain a capillary fingertip glucose measurement multiple times a day. According to the International Society of Pediatric and Adolescent Diabetes (ISPAD), "successful application of intensified diabetes management with multiple injection therapy or insulin infusion therapy requires frequent SMBG (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan" (Rewers, 2014).

However, since an SMBG collects and displays only a single, point-in-time glucose level, even patients who monitor frequently may miss significant hypoglycemic and hyperglycemic

excursions. In contrast, continuous glucose monitoring (CGM) devices measure interstitial glucose levels on an ongoing basis; its use with SMBG has been associated with improved glycemic control in adults with type 1 diabetes. CGM dramatically increases the amount of glucose information available to the patient. CGM systems offer continual access to glucose values and trend information and provide alerts when hypoglycemic or hyperglycemic values occur or when glucose is trending too low or too high. These alerts are particularly important at night, when patients are asleep, or in individuals who have hypoglycemic unawareness. In addition, review of detailed glucose history allows the physician and patient to refine the treatment regimen. As a result, patients using CGM systems exhibit increased time in euglycemia, fewer and shorter glycemic excursions, and reduced risk of hypoglycemia, avoiding the consequences of dangerously low or high episodes.

2.2 Current Continuous Glucose Monitoring Options and Limitations

The first continuous glucose monitoring system was approved almost 20 years ago (FDA SSED, 1999). Since that time, the functionality of these systems has evolved, and their accuracy has continued to improve. Accordingly, the utility and benefit of these systems has continued to grow. Data from multiple controlled, randomized studies have demonstrated the benefits of CGM use (Grunberger, 2010; Beck, 2017). These include improvements in glycosylated hemoglobin (HbA1c), reduced risk of hypoglycemia, and increased time spent in euglycemia (Juvenile Diabetes Research Foundation, 2011; Lind, 2017). In addition, quality of life improvements associated with CGM use have been reported (Polonsky and Hessler, 2013; Polonsky, 2017; Lind, 2017). The extent of these benefits in public health terms depends both upon accurate glucose measurements and patients' acceptance and adoption of the technology.

Despite this progress, the currently available CGM systems do not meet the needs of all patients. While the CGM utilization rates have increased from 7% in 2010-2012 to 24% in 2015-2017 among patients seen at centers involved in the type 1 diabetes exchange registry, at least 75% of people with type 1 diabetes do not use CGM in the management of their diabetes (Type 1 Diabetes Exchange Registry, 2017). One limitation is the requirement for repeated, frequent insertion of a sensor by the patient and discomfort associated with wearing a sensor. In a recent survey assessing CGM device utilization, 27% of participants who used CGM discontinued within one year. Problems with sensor insertion or adhesive were cited by 61% of participants who discontinued use, discomfort with wearing a CGM sensor was reported by 41% of participants, and the bulkiness of the CGM device was cited by 28% of participants (Type 1 Diabetes Exchange Registry, 2016; Table 6 below). Most currently approved sensors must be replaced approximately weekly, resulting in 30-50 sensor insertions and removals each year. With each insertion, the new sensor must be initialized. Finally, a receiver unit or handheld device is required to enable glucose alerts and alarms; if the receiver is absent, no alerts are provided.

Table 6. Reasons for CGM Discontinuation and Limitations which the Eversense CGM System has been Designed to Address

Reason for Discontinued CGM Use	Participants in T1D Exchange Registry[a] n=262	Consideration of Eversense CGM System Design
CGM not working properly or not accurate enough	71%	✓
Problems with sensor insertion or adhesive	61%	✓
Using a CGM was too expensive or not covered by insurance	58%	
CGM sensor was uncomfortable to wear	41%	✓
Using a pump and did not want two sites on body	33%	
CGM was too big	28%	

[a] Type 1 Diabetes Exchange Registry, 2016

The Eversense CGM System addresses a limitation of current technology by providing a sensor that lasts up to 90 days. This requires only 4 sensor insertions and removals each year. In addition to expected improvements in patient comfort and satisfaction, a longer lasting sensor reduces the amount of time lost to initialization by limiting the number of insertions. Unlike other CGM sensors, the Eversense sensor is fully inserted subcutaneously in the upper arm, reducing the risks associated with having an open wound and the risk of sensor dislodgement. In addition, the Eversense transmitter may be temporarily removed when desired without disturbing the sensor for times when discretion is preferred. It is secured to the skin using daily, silicone-based adhesive patches, which are more gentle on the skin compared to adhesives on other marketed transmitters. Finally, the Eversense transmitter provides vibratory alerts even when the handheld device with MMA is absent or turned off. Each of these device elements have been developed with the user in mind in order to improve adoption and acceptance of CGM by patients with type 1 or type 2 diabetes.

3 PRODUCT DESCRIPTION

3.1 Proposed Indication and Intended Use

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

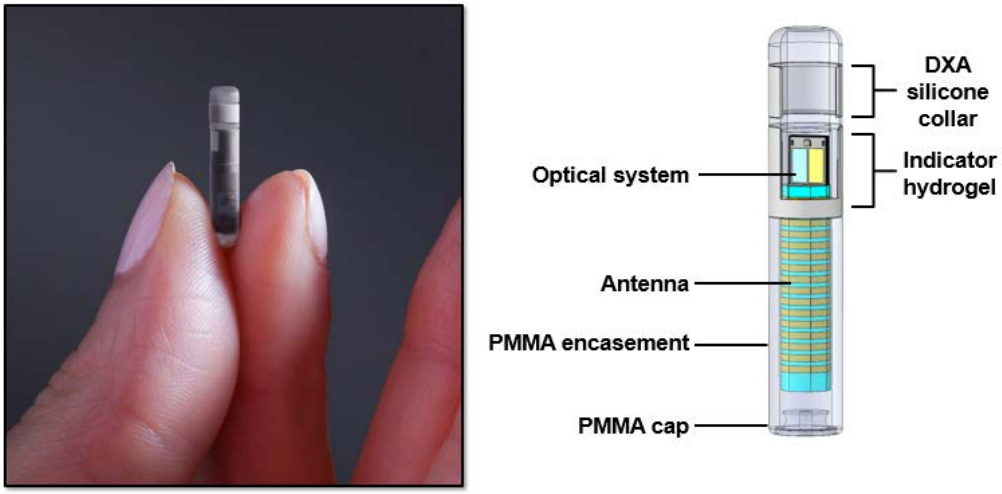
3.2 Device Components and Mechanism of Action

The Eversense CGM system provides continual glucose measurements using three principal components: a sensor that is inserted into the subcutaneous space just underneath the skin in the lateral upper arm, a removable transmitter that is worn externally over the sensor, and the mobile medical application (MMA) that displays glucose information on a handheld device. In addition to these principal components, the Eversense CGM system is also supplied with insertion tools, which are described in Section 3.3, and other accessories (e.g., charging system).

3.2.1 Sensor

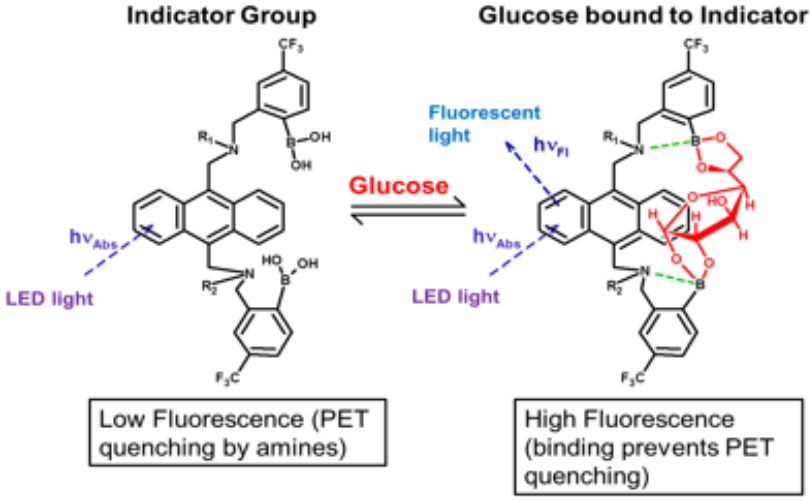
The Eversense sensor (approximately 3.5 mm [0.138 inches] in diameter and 18.3 mm [0.720 inches] in length) is designed to be subcutaneously inserted into the upper arm where it measures interstitial glucose. The sensor contains core electronics that are sealed in biocompatible epoxy within a poly-methyl methacrylate encasement (Figure 4). The sensor is activated to measure interstitial fluid glucose when it receives radio frequency (RF)-power from the transmitter every five minutes.

Figure 4. Eversense Sensor



A 100-micrometer thick, copolymer matrix is grafted to the outside of the PMMA encasement. This layer, the indicator hydrogel, is fluorescent and uses selective, fully reversible binding between glucose and the covalently attached molecular complex to detect changes in glucose concentrations (Figure 5). Glucose binding results in an increase in fluorescence intensity, which is measured by the sensor's optical system.

Figure 5. Eversense Fluorescence Technology (Photoinduced Electron Transfer)



The optical system contained within the PMMA encasement includes an LED and two photodiodes, powered by a ferrite antenna substrate. These act as a miniaturized spectrofluorometer to measure the generated fluorescent intensity. This information is then used to produce a glucose reading and to check the integrity of the system.

A silicone collar, containing 1.75 mg of dexamethasone acetate, is attached to the PMMA encasement adjacent to the indicator hydrogel. This anti-inflammatory steroidal drug elutes slowly, reducing local tissue inflammation and enhancing sensor longevity.

The materials used in the sensor are biocompatible and have been used historically in a wide range of permanent implantable devices. Dexamethasone acetate has also been used in implantable devices (i.e., pacemaker leads). The sensor is provided sterile for single use in a sensor holder and is inserted in the doctor's office using the provided insertion tools (Section 3.3). The sensor operating life is up to 90 days or until the device reaches insufficient sensitivity to glucose upon which a sensor replacement alert is provided from the sensor's integrity checks, whichever occurs earlier.

3.2.2 Smart Transmitter

The transmitter is a device with a rechargeable battery that powers, communicates, and captures information from the sensor, calculates glucose values and trends, and transmits information to the MMA. It is approximately 1.5 by 1.9 inches across and 0.3 inches thick and worn externally over the inserted sensor using a replaceable, silicone-based adhesive patch (Figure 6). Every five minutes, the transmitter sends power via NFC magnetic link to activate the sensor, and then uses this same magnetic link to capture the readings. The transmitter is responsible for calculating all glucose values and trends for transmission to the MMA. The glucose information is sent to the MMA, using secure Bluetooth Low Energy, for display on the handheld device.

Because the transmitter is not physically connected to the sensor, it can be removed and reapplied to the upper arm, without the need for sensor replacement. As such, a gentle daily silicone-based adhesive patch is used to keep the transmitter in place. The transmitter also directly provides vibrations for alerts (hypoglycemic excursions [3 short vibrations x3], hyperglycemic excursions [1 long vibration then 2 short vibrations]), notifications (noncritical and system status information [all 1 short vibration]), and when no glucose can be displayed (3 long vibrations), irrespective of whether the handheld device with the MMA is in the vicinity.

The transmitter is charged with USB connection via a charging cradle in approximately 15 minutes. One charge lasts up to 36 hours of operation. The transmitter can be reused with multiple sensors.

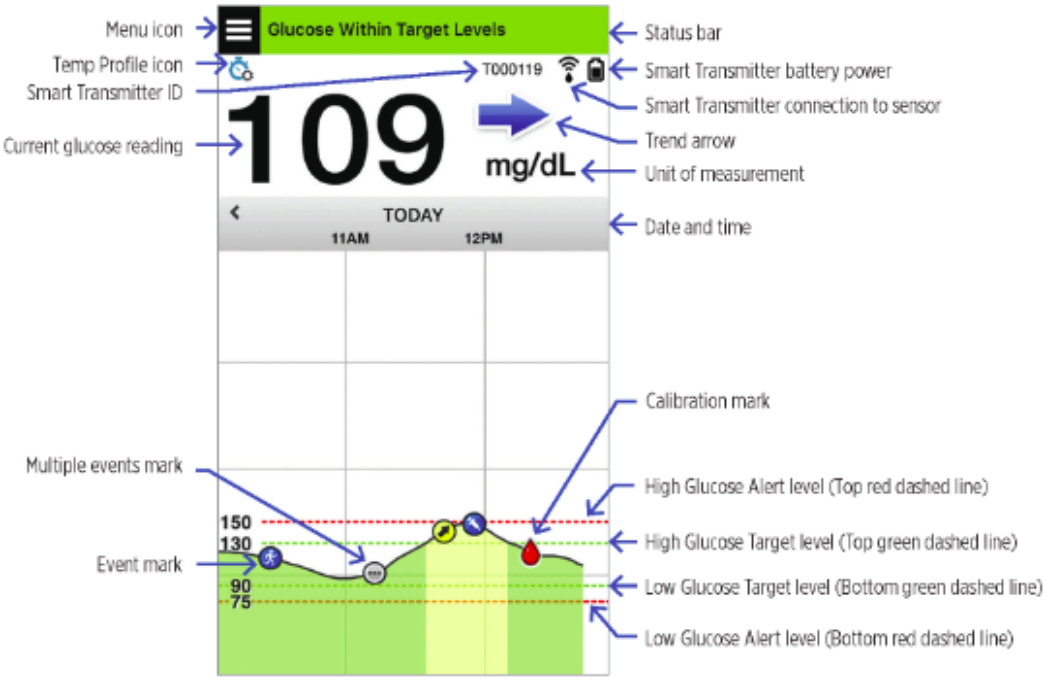
Figure 6. Eversense Smart Transmitter

3.2.3 Mobile Medical Application

The MMA is a software application that runs on a handheld device (e.g., compatible mobile iOS or Android device) for display of glucose information provided by the transmitter (Figure 7). The MMA receives and displays the calculated glucose information from the transmitter, including glucose trend information and glucose alerts. In addition, the MMA enables the user to enter glucose values from SMBG measurements to calibrate the Eversense CGM system. See Section 3.4 for additional information on the functionality of the MMA.

The MMA communicates with the Senseonics server for a one-time download of operational parameters specific for each sensor. It also provides the user an option to upload the data to the Senseonics Data Management System (DMS) for historic viewing and storing of glucose data. Historic glucose information from the DMS may be accessed by individuals in the patient's support circle (i.e., caregiver, guardian, etc.) as authorized.

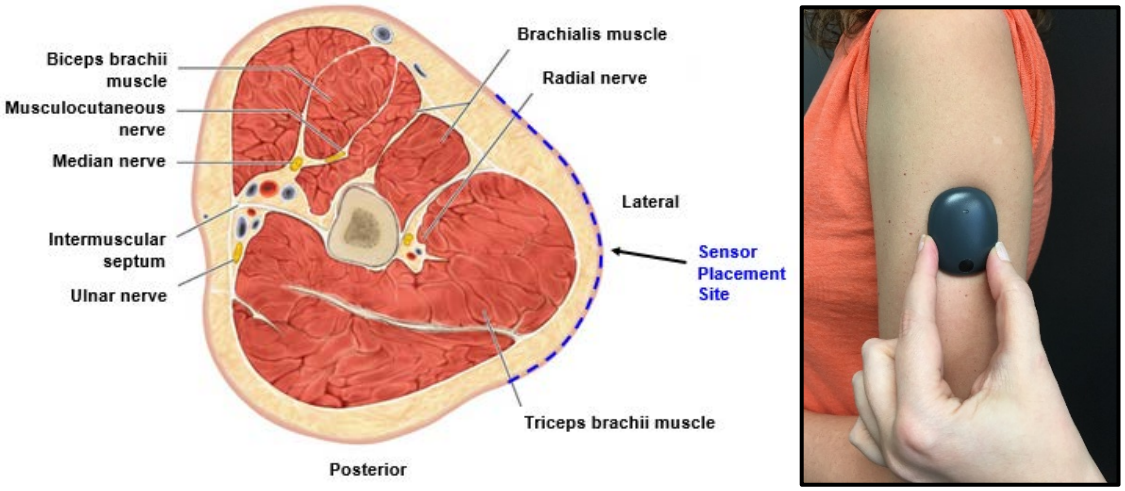
Figure 7. Eversense Mobile Medical Application



3.3 Device Insertion Procedure

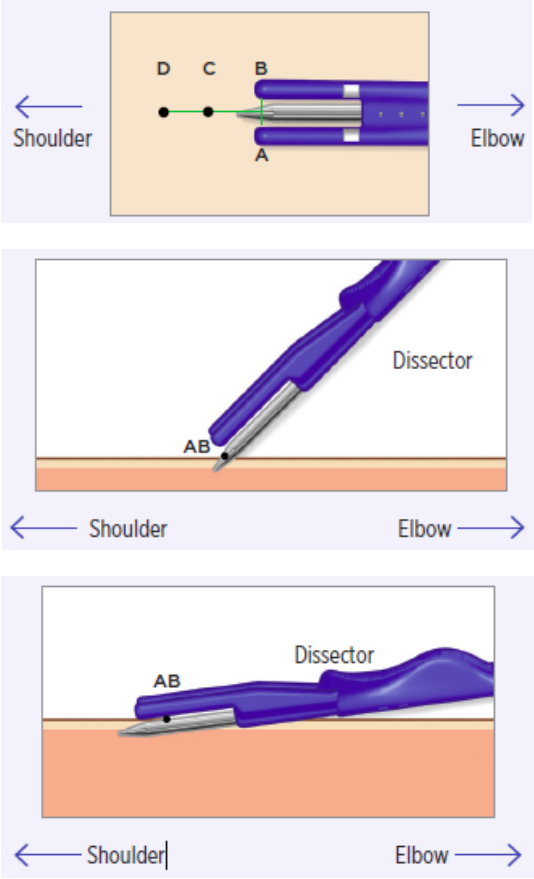
The Eversense sensor is inserted into the lateral upper arm below the deltoid (Figure 8) by a physician during a brief, office-based procedure. Placement in the lateral upper arm avoids the major vasculature and nerves in the medial arm. The insertion procedure starts with determination of the preferred location of the sensor by the patient and the physician. The site is then marked using the provided template and disinfected prior to the injection of a small amount of local anesthetic (e.g., 1% lidocaine) to the insertion site and tract of the sensor. The area is then disinfected a second time and sterile drapes are positioned with the insertion site accessible. Next, a shallow incision approximately 4 mm deep and 5 mm long is made with a #15 blade scalpel and the blunt dissector is used to create a subcutaneous pocket (Figure 9). The depth guards and guide marks on the dissector assist in determining the correct pocket depth (about 4 mm deep) and length (approximately 30 mm long). The sensor is then placed into the pocket using a custom insertion tool (Figure 10), which protects the sterility and integrity of the sensor until it is placed. There are guide marks on the insertion tool that correspond to guide marks on the blunt dissector to assist with proper placement. Once the insertion tool (with loaded sensor) is properly positioned in the subcutaneous pocket, the physician retracts a thumb slide on the tool uncovering and depositing the sensor in the subcutaneous pocket. The incision site is then closed with adhesive skin closure (e.g., Steri-Strip®).

Figure 8. Sensor Placement Site



Source: adapted from https://clinicalgate.com/radial-nerve/

Figure 9. Creation of Subcutaneous Pocket Using the Dissector Tool



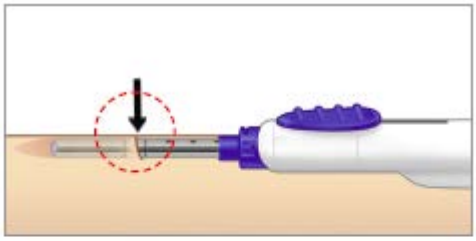
A ~5 mm long incision is made (marked AB in the top figure) at the sensor insertion site.

The blunt dissector is introduced at a 45° entry angle until the depth guards touch the skin (middle figure).

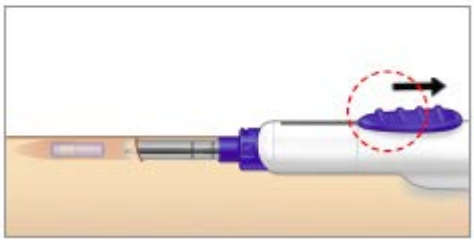
The angle of entry is lowered to approximately parallel to the skin (5-10°) and the dissector is advanced while maintaining the depth guards and handle in close contact with the skin to create a pocket 3-5 mm deep and ~30 mm long, parallel to the skin (lower figure).

The dissector is advanced until the incision lies within the white guide marks on the depth guards (shown in top figure).

Figure 10. Sensor Placement Using the Sensor Insertion Tool



The sensor is loaded into the insertion tool and hydrated before the incision is made. Once the pocket has been prepared, the insertion tool is advanced into the pocket until the incision is between the two lines on the tool (black arrow in top figure).



The insertion tool thumb slider is retracted (black arrow in lower figure), uncovering and leaving the sensor in the subcutaneous pocket.

3.4 Calibration and Functionality

Following the 1-day initialization period, calibration is performed twice daily via user-entered SMBG measurements. The user can customize a calibration schedule during setup, which then determines when the user is prompted with calibration notifications allowing flexibility with the user's lifestyle. If a routine calibration entry is missed, no additional CGM readings will be displayed after 16 hours have elapsed since the last calibration. Routine calibration corrects for changes in baseline signal that may occur as a result of changes in the local optical environment around the inserted sensor and changes due to moderation of the fluorescent indicator.

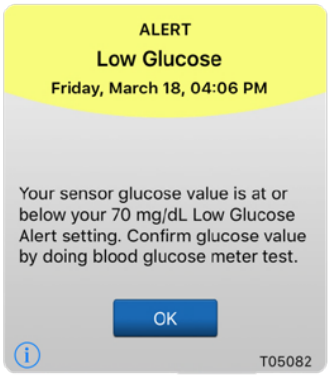
During daily use, patients will most often use the My Glucose Screen (Figure 7), which is the main screen, to track glucose levels. This screen displays the current glucose level and trend arrow along with other system states (e.g., transmitter battery and sensor connection strength) and historical data. As with other CGM products, events such as meals and exercise can be entered into the application to help patients track glucose trends throughout the day. During daily use, the transmitter may be removed for charging or for patient-specific reasons and reattached to the arm as needed.

The Eversense CGM system produces three kinds of alerts, as follows:

- ***Threshold Alerts:*** Identify glucose levels below or above pre-set levels. The high and low glucose alerts remind users that they should confirm the CGM's glucose value by performing a blood glucose meter test.
- ***Predictive Alerts:*** Provide an early indication that a glucose Alert Level is expected to be reached in the immediate future (e.g., 30 minutes prior to an Alert Level).
- ***Rate of Change Alert:*** Identify rising or falling glucose levels that exceed a pre-set rate of change.

When any of these alerts are triggered, the handheld device issues both an audible alert and a visual message (Figure 11). Importantly, the transmitter will vibrate in a defined pattern regardless of whether the handheld device MMA is active, or in the vicinity.

Figure 11. Example of Threshold Alert on Mobile Medical Application



A number of safeguards have been built into the Eversense CGM system to promote use within the limits of the system. A few key notifications include:

- Prompts for calibration, as described above. The system will no longer display glucose readings 16 hours after the last calibration.
- Reminders to schedule an appointment to replace the sensor as the sensor end-of-life approaches. The system will no longer display glucose readings once the sensor reaches the end of its operating life when its sensitivity to glucose in no longer sufficient.

3.5 Removal and Subsequent Sensor Insertion Procedure

When the sensor reaches its end-of-life, it is removed in-office. The physician palpates the sensor and uses the transmitter to identify the location, which is then marked. The physician then disinfects and prepares the skin and injects a local anesthetic (e.g., 1% lidocaine). The area is then disinfected a second time and sterile drapes are positioned with the removal site accessible. Next, a small incision is made at the distal end of the sensor; this can be the same incision that was used for the insertion procedure. A hemostat is then used to remove the sensor. During removal, the proximal portion of the sensor is palpated and gentle pressure applied to facilitate grasping of the distal end. The incision is closed using adhesive skin closure (e.g., Steri-Strip®). Unlike other implantable devices there is no appreciable capsule formation so no additional dissection is typically required for the removal procedure.

A new sensor may be inserted during the same visit using the insertion procedure described above. Rotation of placement site to the other arm is recommended to maximize healing between insertions, as is common practice for infusion pumps and other CGM systems.

4 REGULATORY AND DEVELOPMENT HISTORY

4.1 Regulatory Milestones

Senseonics has collaborated with FDA throughout the development of the Eversense CGM system. Multiple Pre-Submission meetings were held to seek FDA input on clinical study design, product bench testing, chemistry manufacturing, and controls (CMC) requirements, human factors studies, and clinical data submission. Prototype versions (different designs than the final version) of the Eversense CGM system were evaluated in the United States under Investigational Device Exemption (IDE) starting in 2008 and the IDE for the US pivotal study of the final device configuration was approved in August 2015. A Pre-Market Approval (PMA) application containing the results from the pivotal study (PRECISE II) and earlier testing was submitted to FDA on October 26, 2016 and clinical data from the supplemental study (PRECISION) was submitted to FDA on December 11, 2017.

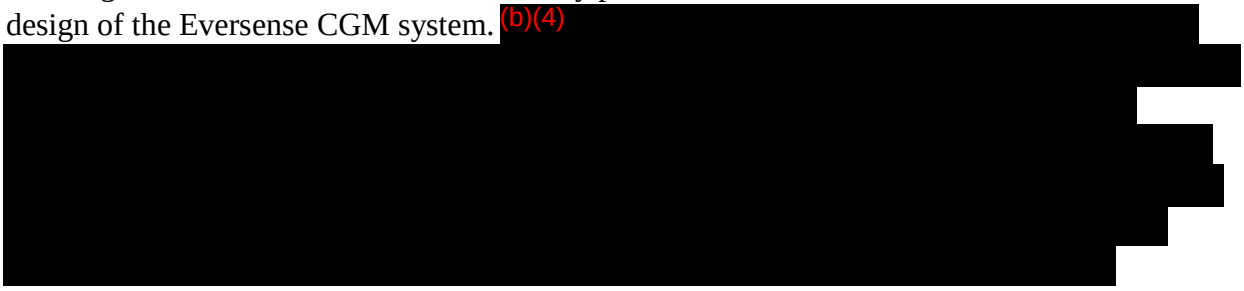
In Europe, a similar version of the Eversense CGM system received CE Marking authorization in May 2016 and has been commercially available in Europe since June 2016. The US version of the Eversense CGM system received CE Marking authorization in September 2017.

4.2 Clinical Development Program

Clinical studies performed on the Eversense CGM system are summarized in Table 7. The PRECISE II study serves as the primary source of clinical data in support of US marketing approval. PRECISE II was a single-arm, 90-day trial conducted in 90 patients at 8 sites in the US. The objective of this study was to demonstrate the safety and effectiveness of the Eversense CGM system. As the clinical benefits of CGM use are well-established (Section 2.1), the effectiveness of the Eversense CGM system relies on its ability to perform accurate glucose measurements. Thus, the primary effectiveness endpoint was glucose detection accuracy over the life of the sensor.

The PRECISION study was a single-arm study at 3 sites in the US with 35 patients. This study provides supplemental data on the accuracy of the device at additional time points from insertion through the first 30-days of use. Results from PRECISION also provide additional effectiveness and safety data on the use of the system through 90 days.

The PRECISE study provides supportive safety information relevant to US marketing approval. This single-arm, 180-day trial evaluated 81 patients at 7 sites in Europe and supported CE Marking of the Eversense in 2016. This study precedes the US trials and evaluated an earlier design of the Eversense CGM system. (b)(4)



(b)(4) [redacted]

In addition, a European patient registry, which specifically collects data on repeat sensor insertions was initiated to characterize the long-term use of the Eversense CGM system. The objectives of this registry and planned analyses are discussed in Section 7.5. Initial data available from the registry support the safety of the device in real-world use.

(b)(4) [redacted]

Table 7. Overview of Clinical Studies with the Eversense CGM System

Study	Key Design Element	Sites	Patients	Role
Registrational Studies				
PRECISE II	90 days	8 US	90	Pivotal Effectiveness Safety
PRECISION	90 days	3 US	35	Supportive Effectiveness Safety
PRECISE	180 days	7 EU	81	Supportive Safety[a]
Registries				
European Patient Registry	24 months	350 EU and South Africa	1,686[b]	Post-Market Safety
Other Studies				
Feasibility Studies	Varied	10 Worldwide	332	Pilot

[a] PRECISE was the pivotal effectiveness and safety study for territories outside the US.
[b] All patients in the EU and South Africa who receive an Eversense CGM system will be enrolled in the registry and followed until the first 100 patients have undergone 4 sensor insertions and 4 sensor removals and reached 24 months follow-up.

(b)(4) [redacted]

(b)(4)

5 NON-CLINICAL STUDIES

5.1 Interference Studies

Chemical interference studies were conducted to evaluate how the performance of the Eversense CGM system is affected by common concomitant medications in patients with diabetes or substances that have the potential to interfere with the mechanism of action of the sensor. The interference studies were conducted in accordance with the following standards:

- CLSI Standard EP7A2 – Interference Testing in Clinical Chemistry, Approved Guideline – Second Edition.
- ISO 15197: 2013 – *In Vitro* Diagnostic Test Systems – Requirements for Blood-Glucose Monitoring Systems for Self-testing in Managing Diabetes Mellitus Annex A.

The test method involved comparing sensor glucose measurements from samples containing the substance to samples without that added substance (i.e., paired-difference method). Potential interferents were tested at concentrations either specified in the standards or at concentrations 3 times the therapeutic dose. Substances were tested at 2 glucose concentrations – a low concentration of 72 mg/dL and a high concentration of 324 mg/dL. The ISO 15197:2013 acceptance criteria (i.e., bias >10 mg/dL for glucose values of <100 mg/dL and bias >10% for glucose ≥100 mg/dL) were used for determining if a substance had an interfering effect.

Of the 41 substances were tested, 39 did not have an interfering effect (Table 9).

Table 9. Interference Test Results

Substances Tested with No Interfering Effect			Substances Tested with Interfering Effect
Acetominophen	Sorbitol	Xylitol	Mannitol
Amoxicillin trihydrate	Galactose, D-	Naproxen	Tetracycline
Ascorbic acid	Gentisic acid	Piroxicam	
Caffeine	Glutathione	Pralidoxime iodide (PAM)	
Dreatinine	L-Dopa	Quinidine	
Dopamine	Lactate	Ribose	
EDTA	Lactose	Salicylic acid	
Ephedrine	Levofloxacin	Tolazamide	
Fructose, D-	Maltose, D-(+)	Tolbutamide	
Glyburide (glibenclamide)	Mannose, D-(+)	Urea	
Heparin	Metformin	Xylose, D-(+)	
Ibuprofen	Methyl-DOPA	Erythritol	
Lactitol	Maltitol	Isomalt	

Mannitol and tetracycline were the only agents that had an effect on Eversense readings at concentrations associated with therapeutic doses; in addition, sorbitol was also identified as a potential interferent under certain conditions of use:

- Mannitol and sorbitol, when administered intravenously or in irrigation solution, may afford concentrations that could produce a positive bias in Eversense glucose readings. A positive bias introduces the possibility that a user may inappropriately dose with insulin, which could have severe negative clinical consequences. The potential interfering effects of mannitol for CGM systems are well known (Klonoff, 2011), and a statement regarding the potential for mannitol or sorbitol to cause falsely elevated readings when administered intravenously, or as a component of an irrigation solution or peritoneal dialysis solution is included in the proposed Eversense labeling.
- Tetracycline, which both absorbs and fluoresces light over wavelengths that overlap with the sensor's fluorescent, glucose indicating polymer, introduced a negative bias in glucose reading from the Eversense CGM system. A negative bias may create a situation in which a user inappropriately increases their carbohydrate intake or does not dose with insulin during a time in which their blood glucose concentration is respectively euglycemic or hyperglycemic. The proposed Eversense labeling informs users that the

use of tetracycline may falsely lower sensor glucose readings and that a blood glucose meter should be used if they are taking tetracycline.

Overall, the interference studies demonstrated that the glucose detection mechanism in the Eversense CGM system is highly specific to glucose and unaffected by many potentially interfering substances. Mannitol, an interferent common to all current CGM systems, sorbitol, and tetracycline and their potential to falsely elevate or lower glucose readings is explicitly stated in Eversense labeling. Of note, interference from acetaminophen, a recognized limitation of some CGM systems (e.g., Guardian® Sensor (3) [Medtronic MiniMed, Inc.], Dexcom G5® Mobile CGM System [Dexcom]) (Medtronic MiniMed, 2017; Dexcom, 2018), is not an issue with the Eversense system.

6 CLINICAL EFFECTIVENESS

Summary

- Eversense is highly accurate as demonstrated in the PRECISE II pivotal study, the supplemental PRECISION study, and a supporting study, PRECISE.
- In PRECISE II (N=90 patients), the overall MARD was 8.5%, meeting the study's primary endpoint to achieve a MARD of less than 20%.
    - Over 90% of sensors were still operating after 90 days and accuracy was maintained over the duration of use.
    - 87% of readings with the Eversense were within 15 mg/dL or 15% of reference glucose readings, and 94% were within 20 mg/dL or 20% of the reference.
    - The system detected 96% and 98% of hypoglycemic and hyperglycemic excursions, with false alert rates of 16% and 7%, respectively.
    - Accurate measurements were obtained throughout the 12 hours following each calibration on a twice per day calibration schedule.
    - Exercise of the upper arm, and compression of the sensor area, did not affect sensor accuracy.
    - Similar sensor accuracy was achieved in any subgroup examined, with a MARD of 6.1% to 10.3% in any subgroup.
- In PRECISION (N=35), high accuracy was achieved through 90-days post sensor insertion, consistent with results obtained in PRECISE II.
    - 85% of sensor readings were within 15 mg/dL or 15% of reference values overall with 79%, 86%, 88%, 88%, 87%, and 84% agreement at the 15/15% threshold on Days 1, 7, 14, 30, 60, and 90, respectively.
    - Hypoglycemic and hyperglycemic excursions were detected 95% and 99% of the time, respectively; detection rates were consistent on Days 1, 7, 14, 30, 60, and 90.
    - Sleep assessments demonstrated that sensor accuracy was maintained at night with 83% of readings falling within 15 mg/dL or 15% of reference values.
- These results show that the Eversense CGM system reliably provides accurate glucose measurements over the 90-day operating life of the sensor.

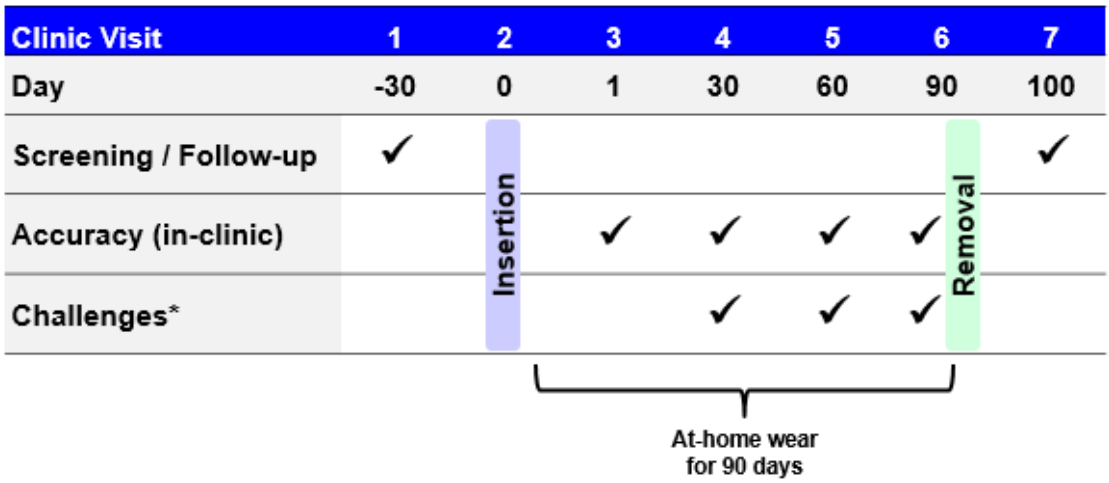
6.1 PRECISE II

6.1.1 Study Design

The PRECISE II study was a non-randomized, single-arm, multi-center study designed to evaluate the effectiveness, specifically accuracy, and safety of the Eversense CGM in adult patients with diabetes mellitus. This study was conducted at 8 US sites with no prior experience with the Eversense CGM system. A total of 90 adult patients (18 years of age or older) with

either type 1 or type 2 diabetes were inserted and were to be followed through 90 days of device use, as shown in Figure 12. Patients were disqualified from study enrollment if they had a history of severe hypoglycemia in the previous 6 months; had a history of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months; were pregnant; or had a condition preventing or complicating the placement, operation, or removal of the sensor or wearing transmitter, including upper extremity deformities or skin conditions.

Figure 12. PRECISE II Study Design



* Glycemic, exercise, and compression challenges

Fifteen health care providers (HCPs), including 13 physicians, 1 nurse practitioner, and 1 physician assistant, were trained on the use of the Eversense CGM system and qualified to perform the sensor insertion and removal procedures at the start of the study. On Day 0, patients were inserted with sensors. A total of 15 patients had 2 sensors inserted, 1 in each arm. The remaining 75 patients each had 1 sensor inserted. At home, patients calibrated their sensors according to the Eversense instructions for use using home blood glucose meter values obtained from commercially-available FDA-approved SMBG meters and strips provided as part of the study. However, they were blinded to sensor glucose readings, alerts and notifications during the study.

Clinic visits occurred on Day 1, 30, 60, and 90. At each visit, sensor accuracy was evaluated by comparing Eversense glucose measurements to reference plasma glucose values obtained by the YSI laboratory analyzer, the FDA gold standard for measuring plasma glucose to assess CGM and SMBG systems. Reference glucose measurements were collected every 15 minutes or 5 minutes when levels were 75 mg/dL or lower. During the Day 30, 60, and 90 visits, patients underwent different tests to characterize sensor performance across the reporting range of the device and under anticipated use conditions:

- ***Glycemic challenges***: These evaluated the performance of the Eversense at high and low glucose ranges in all qualifying patients in a safe and monitored setting. For hyperglycemic challenges, patient glucose was raised using carbohydrates to induce

hyperglycemia of >180 mg/dL for 2 hours, including 30 minutes at levels >350 mg/dL. For hypoglycemic challenges, patient glucose was lowered using insulin to induce hypoglycemic levels of <75 mg/dL for 1 hour including 15 minutes at levels <60 mg/dL. Detailed insulin/glucose administration and safety guidelines were implemented.

- ***Upper arm exercise sessions***: This test characterized sensor performance during significant user arm movement. All patients with a single inserted sensor and capable of performing 30 minutes of anaerobic upper arm exercises with bar bells were evaluated while in euglycemic, hypoglycemic, and hyperglycemic glucose ranges. Reference glucose measurements were collected every 5 minutes during this period.
- ***Compression tests of the Sensor site***: This test simulated conditions likely to trigger nocturnal sensor attenuation, a known issue with transcutaneous CGM systems. Patients inserted with two sensors participated in a 30-minute period of sensor compression, during which they lied directly on the primary sensor/transmitter arm with the transmitter sandwiched between the arm and the bed. Reference glucose measurements were collected every 5 minutes during this period.

After Day 90, or earlier if the sensor end-of-life was reached, the patient returned to the office to have the sensor removed. A post sensor-removal follow-up visit occurred at Day 100.

The primary effectiveness endpoint was a measure of sensor accuracy known as Mean Absolute Relative Difference, or MARD. MARD captures measurement accuracy by comparing the test measurements to the reference glucose readings. In PRECISE II, a glucose reading from the sensor was compared with the corresponding reference glucose values taken within 5 minutes before the sensor reading. It is a commonly reported measure of accuracy for CGM systems and is calculated as follows:

$$MARD\ (\%) = \frac{\sum(|Sensor - YSI|/YSI)}{n} * 100;$$

where *sensor* and *YSI* are the corresponding glucose readings from the Eversense and reference devices – a matched pair – and *n* is the total number of matched pairs. A smaller value of MARD represents a lower error in the sensor reading, and therefore greater accuracy.

The primary analysis tested a superiority hypothesis. In order to be deemed a success, the trial 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 (106 implanted sensors). This performance goal was pre-specified and was selected based on prior studies of other CGM systems. 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.

Numerous exploratory analyses were pre-specified and performed. Key analyses that are described include:

- Sensor accuracy at each visit

- Sensor accuracy over time between calibrations
- Duration of sensor function
- Proportion of sensor readings within pre-set accuracy limits
- Detection accuracy for low and high glucose (i.e., threshold alerts)

In addition, results from the exercise and compression tests as well as analyses by patient characteristics are included as subgroup analyses. Within patient precision was also calculated (Appendix 11.3).

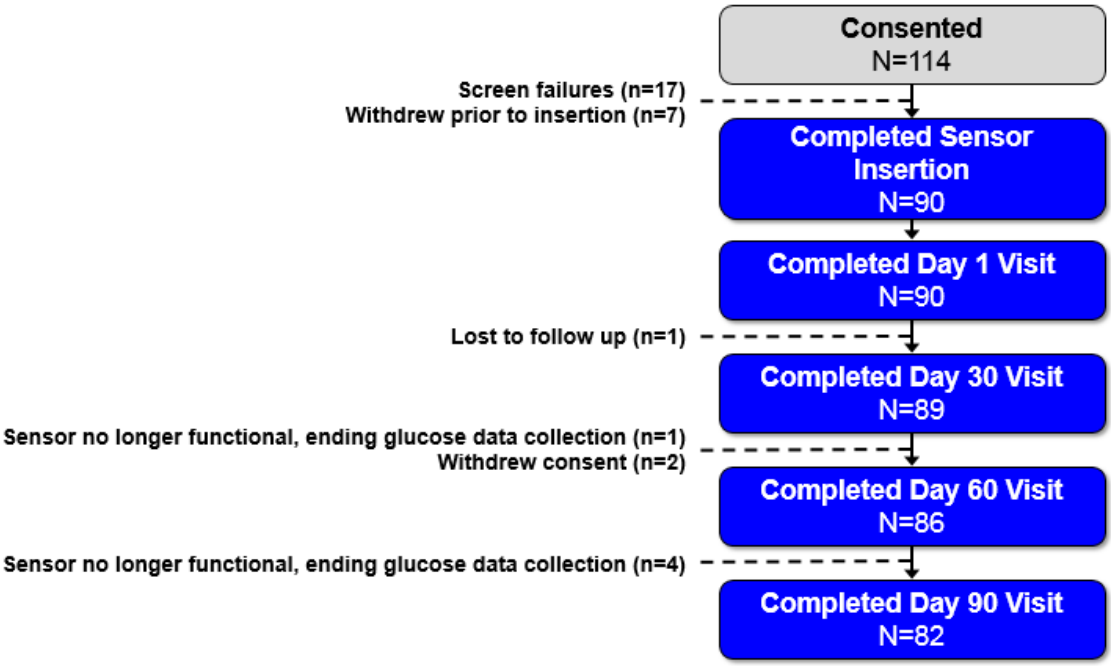
6.1.2 Patient Disposition and Population

A total of 114 patients were consented and 90 were inserted. The most common reason for screen failure was unstable cardiovascular status (e.g., symptomatic coronary artery disease, uncontrolled hypertension, etc.).

During the course of the study, one patient was lost to follow-up and two patients withdrew consent. Five patients, or 6% of the study sample, received a sensor replacement alert which ended glucose data collection; the remaining 82 patients completed the Day 90 visit. A total of 15,753 matched pair readings were collected over the entire study.

Patients in PRECISE II wore their transmitters a median of 23.4 hours over the 3-month study time period; 87% of the patients wore the system more than 20 hours per day.

Figure 13. Patient Disposition in PRECISE II



The sample of 90 patients was representative of the target population for Eversense use. As shown in Table 10, patients had a mean age of 45 years and a mean body mass index (BMI) of 29 kg/m^2.

Table 10. Patient Demographics in PRECISE II

Parameter		N=90
Sex, n (%)	Male	54 (60%)
Age, years	Mean (SD)	45 (16)
Race, n (%)	Caucasian	77 (86%)
	Black or African American	7 (8%)
	Asian	3 (3%)
	Other	3 (3%)
Body Mass Index, kg/m^2	Mean (SD)	29 (6)

At baseline, the average HbA1c was 7.6%, and patients had been diagnosed with diabetes for an average of 20 years (Table 11). Two-thirds of the patients had type 1 diabetes. One-half of patients in the study were using an insulin pump to treat their diabetes and one-quarter were using multiple daily injections.

Table 11. Baseline Disease Characteristics in PRECISE II

Parameter		N=90
HbA1c	Mean (SD)	7.6% (1.2%)
Time since diabetes diagnosis, years	Mean (SD)	20 (14)
Diabetes type, n (%)	Type 1	61 (68%)
	Type 2	29 (32%)
Type of diabetes therapy, n (%)	Insulin pump	43 (48%)
	Multiple daily injections	24 (27%)
	Oral or diet/exercise	22 (24%)
	Long acting insulin	1 (1%)

6.1.3 (b)(4)

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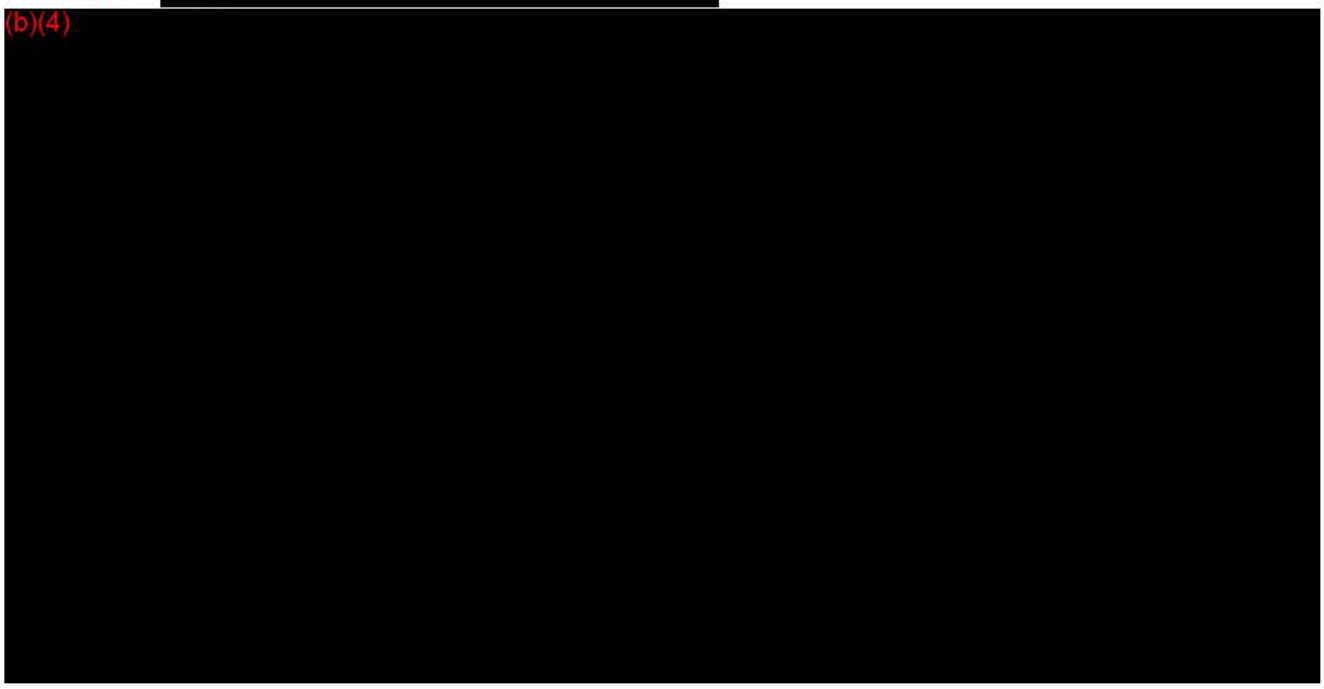


6.1.4 Primary Endpoint – MARD From Day 1 to Day 90

A MARD of 8.5% was achieved based on a total 15,753 matched pair readings (Table 13). This result was statistically significantly lower than the 20% threshold, a performance target consistent with prior similar studies. These results demonstrate system accuracy and precision across the reporting range of the device.

Table 13. MARD Through 90 Days in PRECISE II

	Number of Readings / Unique Patients	Mean Absolute Relative Difference	95% Confidence Interval[a]	P-value Compared to 20% Performance Target[b]
Overall	15,753 / 90	8.5	8.0 – 9.1	<0.0001

[a] Estimated using bootstrap resampling
[b] Based on between-patient and within-patient variance components estimated from a random effects regression model

As shown in Appendix 11.1, the total mean bias based on the difference of all 15,753 matched pair readings was -3.1 mg/dL (95% limits of agreement interval = -40.1, 33.9 mg/dL), indicating a general balance between elevated and low Eversense sensor readings.

6.1.5 Secondary Endpoints

6.1.5.1 Percentage within Predefined Ranges

Another important measure of accuracy with CGM devices is the likelihood of individual accurate and inaccurate glucose readings. Table 14 shows the proportion of Eversense readings that fell within 4 pre-established accuracy limits that are commonly used for assessing CGM accuracy. The majority of sensor readings fell within the pre-established accuracy limits. For example, 94% of sensor readings fell within either 20% of the reference values (for glucose concentrations >80 mg/dL) or 20 mg/dL (for glucose concentrations ≤80 mg/dL) and 87% of sensor readings were within 15% or 15 mg/dL of the reference values.

Table 14. Proportion of Sensor Readings within Pre-Set Limits in PRECISE II

Accuracy Limits: Comparison to Reference[a]	Percent of Sensor Readings Within Limit
15 mg/dL or 15%	87%
20 mg/dL or 20%	94%
30 mg/dL or 30%	99%
40 mg/dL or 40%	>99%

[a] Sensor readings within given concentration limit for reference values ≤80 mg/dL or within given percentage of reference for reference values >80 mg/dL

These results are in line with currently available CGM systems including the Dexcom G5® Mobile CGM System (Dexcom). For reference, in a separate study, Dexcom G5® Mobile CGM System readings were within 15 mg/dL or 15%, within 20 mg/dL or 20%, within 30 mg/dL or 30%, and within 40 mg/dL or 40% of the reference value 86%, 93%, 98%, and 99% of the time, respectively (FDA SSED, 2014).

When evaluating the accuracy of individual matched pairs, 99.9% of Eversense system readings were within Zones A and B of the Consensus Error Grid (Appendix 11.2).

6.1.5.2 Accuracy at Days 1, 30, 60, 90

Accuracy was maintained over the duration of the study (Table 15), indicating that the sensor operating life of 90 days is supported, and end-of-life was correctly triggered before sensor accuracy was significantly compromised. Sensor differences were slightly higher on Day 1, following initial calibration. Day 1 accuracy is known to be slightly decreased in all CGM systems likely due to the sensor settling process. Although slightly elevated at 10.7% on Day 1 relative to the 7-9% performance for the remainder of the sensor life, an accuracy of 10.7% is clinically acceptable and comparable to many prior and currently marketed continuous glucose monitoring systems.

Table 15. Accuracy Assessment by Time Point in PRECISE II

Visit	Number of Readings / Unique Patients	Mean Absolute Relative Difference (95% Confidence Interval)	Percentage of Readings within 15 mg/dL or 15%[a]
Day 1	1,708 / 90	10.7% (9.7 – 11.7)	77%
Day 30	5,081 / 88	7.4% (6.8 – 8.1)	91%
Day 60	4,725 / 85	8.2% (7.4 – 9.0)	87%
Day 90	4,239 / 77	9.1% (8.2 – 10.0)	85%
Overall	15,753 / 90	8.5% (7.9 – 9.0)	87%

[a] Sensor readings within 15 mg/dL for reference values ≤80 mg/dL or within 15% of reference for reference values >80 mg/dL

6.1.5.3 Accuracy at Different Reference Glucose Levels

At reference glucose levels of 80 mg/dL and lower, Eversense had a reasonable mean error of 8.4 mg/dL (absolute difference). Above 80 mg/dL, Eversense achieved a MARD of 7.9%, with similar performance in the euglycemic and higher glucose ranges.

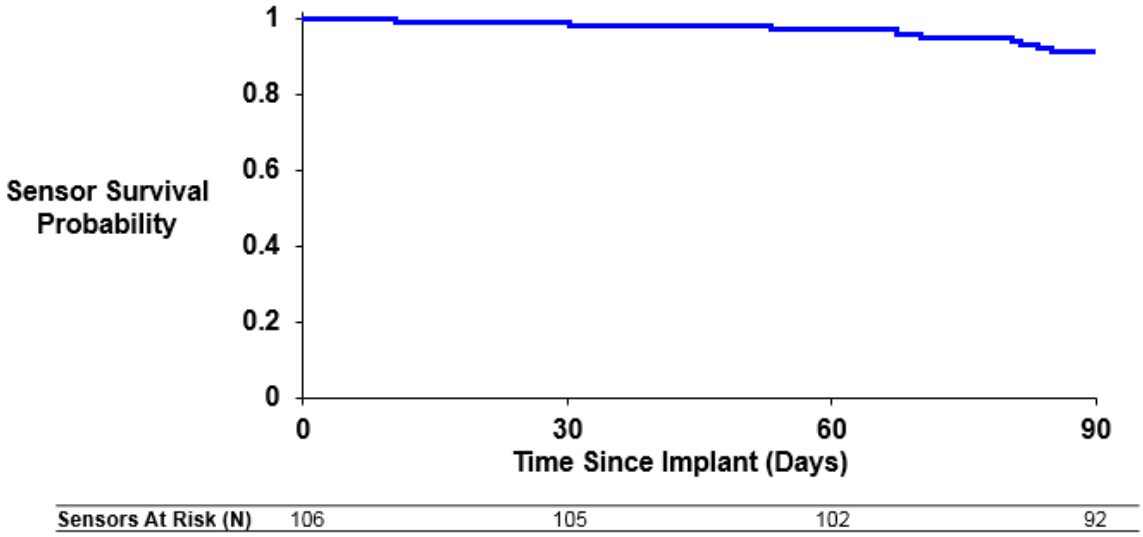
Table 16. Accuracy for Different Glucose Ranges in PRECISE II

Parameter	Reference Glucose Level	Number of Readings	Results
Overall MARD	All	15,753	8.5%
Mean Absolute Difference	≤80 mg/dL	1,654	8.4 mg/dL
MARD	>80 mg/dL	14,099	7.9%
	81-180 mg/dL	7,540	8.2%
	181-300 mg/dL	5,378	7.6%
	301-350 mg/dL	820	7.9%
	351-400 mg/dL	326	7.5%
	>400 mg/dL	35	8.3%

6.1.5.4 Sensor Functionality at Day 90

Kaplan-Meier estimates were generated to analyze sensor survival. In this analysis, an event was defined as a sensor that no longer continued to function as indicated by a sensor replacement alert. Ninety-one percent (91%) of sensors were functioning at Day 90, supporting the intended operating life of the sensor (Figure 14).

Figure 14. Kaplan-Meier Estimate of Sensor Survival in PRECISE II



Note: Events were sensors that no longer continued to function (i.e., sensor replacement alert was triggered)

Nine (9) sensors had an event (i.e., replacement alert triggered) and 6 sensors were censored over the 90-day follow-up period for reasons other than the triggering of the sensor replacement alert. These 6 censored sensors were from 2 patients who were lost to follow-up or withdrew consent, 2 patients who had transmitter errors, and 2 patients who completed the Day 90 visit outside of the visit window. Of the 9 sensors that triggered a sensor replacement alert, 3 occurred in the first 2 months post insertion and the remaining 6 occurred between 60 and 90 days after sensor insertion. Overall, 99% of sensors were functional through 30 days, and 97% functioned through 60 days.

6.1.5.5 Accuracy of Alerts

The Eversense CGM system also demonstrated accuracy in providing alerts for high and low glucose values. Threshold alerts were set to trigger when a reading was ≤70 mg/dL, indicating low glucose, or ≥180 mg/dL, indicating high glucose. Low glucose levels determined by the reference analyzer were successfully detected 96% of the time by the Eversense (Table 17). Similarly, 98% of high glucose concentrations were detected by the Eversense alert. For nearly all missed alerts, the sensor glucose readings were within 20 mg/dL of the alert level. False alert rates of 16% and 7% were observed; these typically occurred when sensor measurements were within 20-30 mg/dL of the alert level.

Table 17. Accuracy of Threshold Alerts for Low and High Glucose Level Detection in PRECISE II

Alert Setting	Detection Rate	False Alert Rate
Low Glucose (≤70 mg/dL)	96%	16%
High Glucose (≥180 mg/dL)	98%	7%

As a point of reference, Dexcom G5® Mobile CGM System has a detection rate of 91% for glucose concentrations ≤70 mg/dL and a false alert rate of 3% for glucose concentrations ≥180 mg/dL (FDA SSED, 2014). These performance characteristics were considered to be acceptable for the Dexcom G5® Mobile CGM System to achieve approval for use as a replacement for SMBG in making treatment decisions. Thus, the detection and false alert rates achieved with Eversense are comparable to those attained by a non-adjunctive CGM.

6.1.5.6 Calibration Stability

Accuracy was maintained throughout the 12-hour period following a home calibration based on in-clinic measurements. As shown in Table 18, a high percentage of Eversense readings in any 2-hour interval following an SMBG calibration entry was within pre-set accuracy limits.

Table 18. Accuracy of Sensor Readings Following Calibration in PRECISE II

Hours After Calibration	Percent of Sensor Readings Within 15 mg/dL or 15%[a]	Percent of Sensor Readings Within 20 mg/dL or 20%[a]
(0, 2)	85%	92%
[2, 4)	88%	95%
[4, 6)	86%	94%
[6, 8)	88%	96%
[8, 10)	88%	96%
[10, 12)	89%	96%

[a] Sensor readings within given concentration limit for reference values ≤80 mg/dL or within given percentage of reference for reference values >80 mg/dL or

6.1.6 Subgroup Analyses Including Exercise and Compression Testing

The MARD was calculated separately for multiple subgroups, to determine if demographic or patient characteristics influenced the performance of the device. As can be seen by the similar MARD values across subgroups (Table 19, Table 20, and Table 21), there were no significant changes in accuracy as a result of compression, exercise, gender, age, dominant hand, BMI,

race/skin color, or use of medications for diabetes, hypertension, thyroid, or cholesterol management.

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6.2 PRECISION

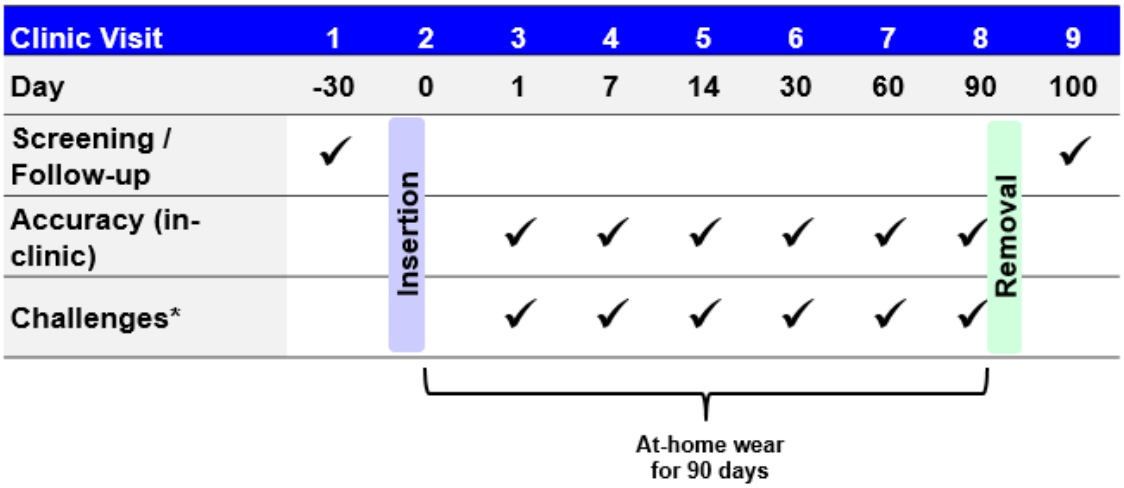
6.2.1 Study Design

The PRECISION study was a non-randomized, single-arm, multi-center study designed to evaluate the effectiveness, or accuracy, and safety of the Eversense CGM system in adult patients with diabetes mellitus. The main objective of this study was to provide additional data on both the accuracy and plasma dexamethasone concentration profiles of the Eversense up to 90 days post-sensor insertion, with an emphasis on the performance in the first 30 days. A total of 35 adults (age ≥18 years old) with type 1 or type 2 diabetes were inserted with Eversense sensors at 3 US sites with HCPs who had previous experience with the Eversense CGM system.

Patients were disqualified from study enrollment if they had a history of severe hypoglycemia in the previous 6 months; had a history of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months; were pregnant; or had a condition preventing or complicating the placement, operation, or removal of the sensor or wearing of transmitter, including upper extremity deformities or skin condition.

On Day 0, a subset of 8 patients had one sensor inserted, and the remaining 27 patients had two sensors inserted, one in each arm. Patients were instructed to wear the transmitter and calibrate their sensors using SMBG values twice per day, consistent with normal use, for the duration of the study. Commercially-available FDA-approved SMBG meter and strips were provided for use during the study. Patients who had two sensors received two transmitters to wear, one for each arm. All transmitters collected and stored raw data from the sensor throughout the duration of the study.

Figure 15. PRECISION Study Design



* Sleep assessments at Visits 4 and 5; glycemic challenges at all marked visits

Unlike the PRECISE II study, patients in PRECISION received live information provided by the Eversense CGM system including glucose readings, alerts, and notifications. Consistent with the intended use of the Eversense as an adjunctive device, all diabetes care decisions were based on reference blood glucose values or SMBG as appropriate.

System accuracy assessments were conducted at clinic visits on Days 1, 7, 14, 30, 60, and 90. At each visit, sensor accuracy is evaluated by taking reference glucose values using the YSI laboratory analyzer for comparison to Eversense glucose measurements. Reference glucose measurements are collected every 15 minutes at levels >75 mg/dL and <325 mg/dL, and every 5 minutes otherwise. Glycemic challenges and sleep assessments are also conducted during clinic visits.

- ***Glycemic challenges***: These tests are similar to those performed in PRECISE II (Section 6.1.1); however, in PRECISION, the target duration of induced hyperglycemia was 2 hours at levels >180 mg/dL, including 1 hour at levels >325 mg/dL, and the target duration of induced hypoglycemia was 2 hours at levels <75 mg/dL, including 30 minutes at levels <60 mg/dL.
- ***Sleep assessments***: This test is intended to evaluate sensor attenuation, a phenomenon observed with other CGM systems while the user is sleeping. At the overnight visits,

patients with bilaterally inserted sensors were instructed to sleep on one side to mimic compression of the sensor site that may occur during sleep.

Patients returned to the office to have the sensor removed after Day 90. A post sensor-removal follow-up visit occurred approximately 10 days after removal.

For all effectiveness measures, descriptive statistics were planned, and no inferential statistical analyses were specified.

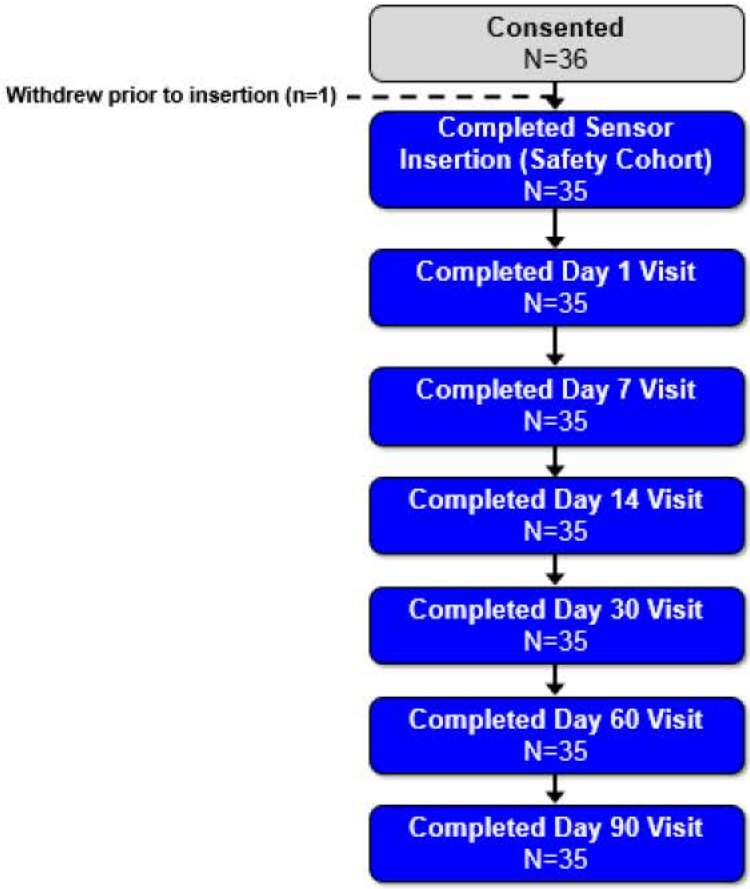
The effectiveness analysis and exploratory effectiveness endpoints were based on all data from all patients with at least one paired glucose reading (one sensor with one reference glucose reading within 5 minutes prior).

6.2.2 Patient Disposition and Population

Of the 36 patients enrolled in the study, 35 received one (n=8) or two (n=27) sensors. All 35 patients completed all study visits through Day 90 (Figure 16).

Similar to PRECISE II, patients in PRECISION wore their transmitters a median of 23.4 hours over the duration of the study; 91% of individual patients wore the system more than 20 hours per day.

Figure 16. Patient Disposition in PRECISION



As shown in Table 22, patients in PRECISION were predominantly Caucasian, had a mean age of 52 years, and had a mean BMI of 28 kg/m^2.

Table 22. Patient Demographics in PRECISION

Parameter		N=35
Sex, n (%)	Male	18 (51%)
Age, years	Mean (SD)	52 (16)
Race, n (%)	Caucasian	32 (91%)
	Black or African American	1 (3%)
	Asian	2 (6%)
Body Mass Index, kg/m^2	Mean (SD)	28 (5)

At baseline, the average HbA1c was 7.8%, and patients had been diagnosed with diabetes for an average of 26 years (Table 23). Over 70% of the patients had type 1 diabetes. One-half of patients in the study were using an insulin pump to treat their diabetes and one-third were using multiple daily injections.

Table 23. Baseline Disease Characteristics in PRECISION

Parameter		N=35
HbA1c	Mean (SD)	7.8% (1.3%)
Time since diabetes diagnosis, years	Mean (SD)	26 (14)
Diabetes type, n (%)	Type 1	25 (71%)
	Type 2	10 (29%)
Type of insulin therapy, n (%)	Continuous insulin infusion pump	19 (54%)
	Multiple daily injections	11 (31%)
	None	5 (14%)

6.2.3 Sensor Insertion and Removal Procedures

In PRECISION, 100% of sensors were successfully inserted in under 5 minutes and 97% of sensors were successfully removed on the first attempt with an average removal procedure time of 4.3 minutes (Table 24). Two sensors in one patient were not successfully removed on the first attempt; these were subsequently removed without incident after referral to a surgeon (Section 7.4.2.3).

Table 24. Sensor Insertion and Removal Procedures in PRECISION

	Insertion N=62	Removal N=62
Successfully Completed on First Attempt, n (%)	62 (100%)	60 (97%)
Procedure Time (minutes)		
Average	1.9	4.3
Median (range)	2.0 (0, 5.0)	1.0 (0, 80)

6.2.4 Effectiveness Endpoints

6.2.4.1 Accuracy at Day 1, 7, 14, 30, 60, and 90

In PRECISION, a MARD of 9.6% was achieved based on a total 15,170 matched pair readings over the entire study. In addition, 85% of sensor readings were within 15 mg/dL or 15% of reference measurements.

As can be seen in Table 25, sensor readings had clinically acceptable accuracy starting from Day 1, with 79% of sensor readings falling within the 15 mg/dL or 15% pre-established accuracy limit. Sensor accuracy further improved by Day 7, when 86% of sensor readings fell within the 15/15% threshold.

Table 25. Accuracy from Day 1 to Day 90 in PRECISION

Visit	Number of Readings / Unique Patients	Mean Absolute Relative Difference 95% Confidence Interval	Percentage of Readings within 15 mg/dL or 15%[a]
Day 1	2,665 / 35	11.6% (10.0, 13.1)	79%
Day 7	2,926 / 35	9.8% (7.9, 11.7)	86%
Day 14	2,997 / 35	9.0% (7.9, 10.1)	88%
Day 30	2,284 / 35	8.9% (7.5, 10.4)	88%
Day 60	2,133 / 35	8.7% (7.3, 10.0)	87%
Day 90	2,165 / 35	9.7% (8.5, 11.0)	84%
Overall	15,170 / 35	9.6% (8.9, 10.4)	85%

[a] Sensor readings within 15 mg/dL for reference values ≤80 mg/dL or within 15% of reference for reference values >80 mg/dL

Relative to the PRECISE II study, Day 1 results in PRECISION demonstrated a slightly higher MARD (11.6% vs 10.7%) but a similar percentage of highly accurate system agreement readings; that is, approximately 78% of sensor readings in both studies were within 15 mg/dL or 15% of reference values. The difference in MARD can be attributed to the increased quantity of samples collected during glycemic challenges in PRECISION on Day 1 (2,665 versus 1,708 matched pairs on Day 1 visit for PRECISION and PRECISE II, respectively) and the higher percentage of data collected in the lower glucose range in PRECISION (26%, 695 readings

≤80 mg/dL) as compared to PRECISE II (6%, 110 readings ≤80 mg/dL). Importantly, both PRECISION and PRECISE II produced consistent results with respect to the proportion of individual sensor readings that were within the 15/15% accuracy threshold. This consistency establishes a link between the two studies and strengthens the conclusion that sensor accuracy is stabilized prior to Day 7, as observed in PRECISION.

6.2.4.2 Percentage within Predefined Ranges

As shown in Table 26, a high percentage of Eversense sensor readings were within the more stringent pre-established accuracy limits (15/15% and 20/20%) at all study visits. The system agreement observed in PRECISION is consistent with the findings of the PRECISE II study.

Table 26. Proportion of Sensor Readings within Pre-Set Limits Through 90 Days in PRECISION

Accuracy Limits:	Percent of Sensor Readings Within Limit						
Comparison to Reference[a]	Day 1	Day 7	Day 14	Day 30	Day 60	Day 90	Overall
15 mg/dL or 15%	79%	86%	88%	88%	87%	84%	85%
20 mg/dL or 20%	89%	93%	95%	94%	94%	92%	93%
30 mg/dL or 30%	96%	98%	99%	99%	99%	99%	98%
40 mg/dL or 40%	99%	99%	>99%	100%	>99%	99%	99%

[a] Sensor readings within given concentration limit for reference values ≤80 mg/dL or within given percentage of reference for reference values >80 mg/dL

6.2.4.3 Accuracy of Alerts at Each Study Visit

In PRECISION, increased sampling was conducted during glycemic challenges in the hypoglycemic and hyperglycemic glucose range providing robust data on the accuracy of low and high glucose alerts. At all study visits, the detection rate for low and high glucose values was 94% and 97% or better, respectively, and the rate of false alerts was 2-16% (Table 27), reinforcing the results observed in PRECISE II.

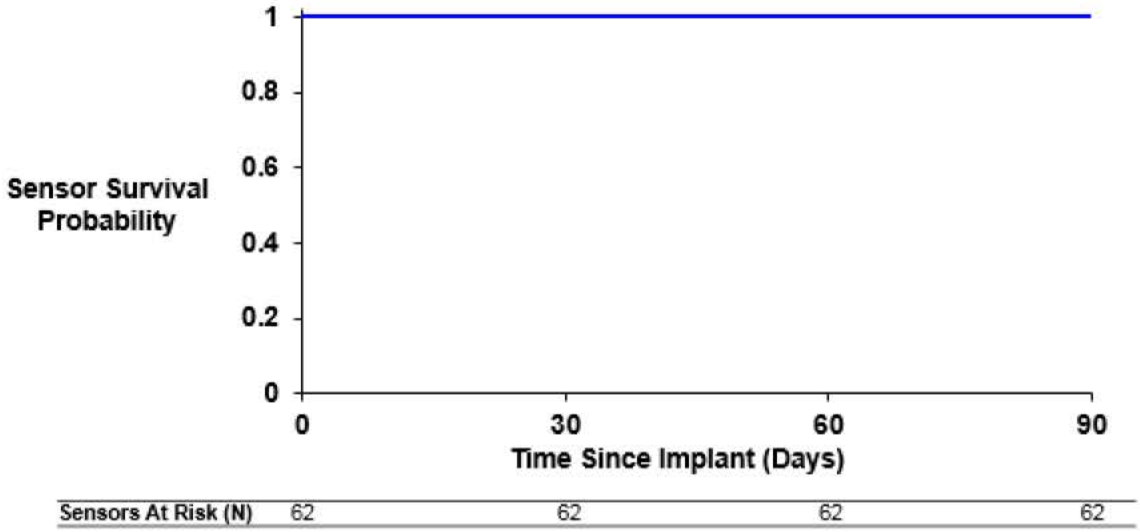
Table 27. Accuracy of Threshold Alerts for Low and High Glucose Level Detection Through 90 Days in PRECISION

	Low Glucose (≤70 mg/dL)		High Glucose (≥180 mg/dL)	
Visit	**Detection Rate**	**False Alert Rate**	**Detection Rate**	**False Alert Rate**
Day 1	95%	16%	99%	8%
Day 7	94%	9%	100%	6%
Day 14	97%	8%	100%	4%
Day 30	96%	3%	99%	8%
Day 60	98%	2%	98%	9%
Day 90	94%	5%	97%	7%
Overall	**95%**	**8%**	**99%**	**7%**

6.2.5 Sensor Functionality at Day 90

Of the 62 sensors inserted in the PRECISION study, 100% continued to function until Day 90 (Figure 17).

Figure 17. Kaplan-Meier Estimate of Sensor Survival in PRECISION



6.2.6 Sleep Assessments and Within Patient Precision

During sleep assessments on Days 7 and 14, patients laid on their sensors while they slept during the overnight visits. Collected blood glucose measurements were then used to calculate nighttime (midnight to 7 am) accuracy and precision and compared to daytime (7 am to midnight) accuracy and precision, when patients were upright. The percent of the sensor readings within 15 mg/dL or 15% of reference values was similar during the sleep challenge as compared to during the day:

83% of sensor readings were within the 15/15% threshold at night compared to 89% during the day.

Within patient precision was assessed by calculating the absolute relative difference between bilateral sensor readings. Readings from both the night and the day showed good within patient agreement with paired absolute relative difference of 10.8% and 9.7%, respectively.

6.3 Effectiveness Conclusions

As demonstrated in the pivotal study, PRECISE II, the Eversense CGM system produces accurate glucose values and low or high glucose alerts that are clinically relevant for up to 90 days of use. The results from PRECISION mirror the high degree of system agreement achieved in the PRECISE II and support the effectiveness findings of the pivotal trial.

Over the duration of use, the Eversense system achieved a MARD well below the 20% pre-specified threshold. In addition, 87% of sensor readings were within 15 mg/dL or 15% of reference measurements and 94% of readings were within 20 mg/dL or 20% of reference measurements. Detection rates for low and high glucose alerts were over 96% in PRECISE II and over 95% in PRECISION. Finally, 91% of sensors functioned through 90 days of use in PRECISE II, and 100% of sensors functioned through 90 days of use in PRECISION. The various conditions tested in PRECISE II and PRECISION have demonstrated that the performance of the Eversense CGM system is robust. These results support the conclusion that the Eversense CGM system is effective for its intended use as an adjunctive CGM device.

7 CLINICAL SAFETY

Summary

- The premarket safety database for the Eversense CGM system includes 206 patients who were inserted with a total of 335 sensors for up to 90 days (PRECISE II and PRECISION) or up to 180 days (PRECISE).
- In the pivotal PRECISE II study, the incidence of SAEs related to the device or insertion/removal procedure was low (1.1%; 95% CI = 0.0% to 6.0%).
    - A sensor that could not be removed on the first attempt was referred to a surgeon who elected to perform the removal under general anesthesia (triggering SAE designation).
- There were no device or procedure related SAEs in PRECISION or PRECISE.
- Adverse events associated with the Eversense were generally mild and transient.
    - In PRECISE II, 7 (7.8%) patients experienced AEs related to the device or insertion/removal procedure. There were no infections, and no adhesive patch skin reactions. Common AEs included bruising, erythema, pain/discomfort. There were 2 events of possible failure to recover the PMMA sensor cap during removal.
    - In PRECISION, where most patients received 2 sensors, 5 (14.3%) patients experienced AEs related to the device or procedure, which were generally similar to AEs observed in PRECISE II; all AEs resolved. There were 2 AEs in one patient whose 2 sensors could not be removed by the investigator; the sensors were later successfully removed by a surgeon using local anesthesia (lidocaine injection).
    - In the integrated PRECISE II, PRECISION, and PRECISE pool, device or insertion/removal procedure related AEs occurred in 26 (12.6%) out of 206 patients. There were 3 infections, 2 of which resolved without antibiotic treatment; all 3 infections resolved without sensor removal.
- Proactively collected post-market safety data from the European patient registry (including 1,686 patients receiving a total of 2,386 sensors) show a similar safety profile following repeated sensor insertions.
- No unanticipated AEs and no deaths have been reported to date.
- Multiple risk mitigation measures have been implemented and include 1) additional emphasis during training on insertion site preparation and optimal placement depth, 2) a design change to the blunt dissector to facilitate proper placement depth, and 3) a design change to modify the sensor cap to prevent detachment.
- Levels of plasma dexamethasone were less than 0.05 ng/mL (assay limit of quantification) in patients with a single sensor. Limited local AEs and no systemic AEs have been reported in association with the DXA collar.
- Overall, the safety profile of Eversense is consistent with the risks associated with a CGM system and those anticipated for a subcutaneously-placed device.

7.1 Treatment Exposure

The premarket safety database for Eversense comprises 206 patients from the non-randomized PRECISE II, PRECISION, and PRECISE clinical trials. In this population, 123 patients received 2 sensors, one in each arm, and 83 received a single sensor; 6 patients received replacement sensors. Thus, a cumulative 335 insertion procedures and 335 removals were documented under these studies (Table 28).

Furthermore, a total of 1,686 patients enrolled in the ongoing European patient registry have received a total of 2,386 sensor insertions as of February 2, 2018. Of these patients, 443 have received a second sensor, 143 have received a third sensor, 58 have received a fourth sensor, 39 have received a fifth sensor, 14 have received a sixth sensor, and 3 have received a seventh sensor.

Collectively, the 3 studies with the European patient registry include over 537 patient-years of device exposure.

Table 28. Overview of Safety Database for the Eversense CGM System

Safety Datasets	Duration of Sensor Use	Patients	Sensor Insertions	Total Exposure (patient-days)
Regulatory Registrational Studies				
PRECISE II	90 days	90	106	8,289
PRECISION	90 days	35	62	3,450
PRECISE	180 days	81	167	10,790
Integrated (PRECISE II, PRECISION, PRECISE)	Up to 180 days	206	335	22,529
Registries				
European Patient Registry	Varied	1,686	2,386	173,658
Total	-	**1,892**	**2,721**	**196,187**

7.2 PRECISE II

7.2.1 Primary Safety Endpoint – Serious Adverse Events

The primary safety endpoint in PRECISE II was the incidence of device-related or insertion/removal procedure-related SAEs in the clinic and during home use through 10 days after sensor removal. Adverse events in the study were reviewed and adjudicated by an independent medical monitor.

The incidence of SAEs related to the device or insertion/removal procedure was low (1.1%, 95% CI = 0.0% to 6.0%). There was a single SAE related to device removal, in which an initial attempt to remove the sensor was unsuccessful. At the planned removal visit, two incisions were made, and an ultrasound was used in an attempt to locate the sensor. The sensor could not be located, likely due to the fact that the sensor was originally placed deeper than recommended.

The patient was referred to a surgeon, who elected to use general anesthesia and visualize the sensor using fluoroscopy. The sensor was removed intact, without incident, and the patient had an uneventful recovery. The use of general anesthesia resulted in the SAE adjudication. A full narrative is located in Appendix 11.4.

To mitigate the risk of unsuccessful removal requiring additional interventions, physician training has increased the emphasis on proper depth of placement to facilitate removal and includes instructions for management of difficult to remove sensors. These risk reduction measures have been implemented for European commercialization and will continue to be addressed through post-approval training and monitoring. To further mitigate the risk of deep insertions, the blunt dissector used during sensor insertion has been modified with the addition of depth guards to aid with placing the sensor at a more consistent and controlled depth, as proper sensor depth facilitates removal.

7.2.2 Adverse Events Related to Device and Insertion/Removal Procedures

A total of 14 device- or procedure-related AEs (including the single SAE reported above) were reported in 7 (7.8%) patients (Table 29). The majority of these events were dermatological and mild, and all resolved, most without the need for intervention.

There were two events involving the possible retention of sensor fragments after removal. In each case, the small cap of the sensor was missing when returned to the Sponsor for explant analysis and may have been lost on transfer to the return vial or may have been retained in the sensor site. It is important to note that the cap is made of PMMA, a biocompatible material that has been successfully tested for permanent implant. Due to the small size of the fragment (3.2 mm in diameter by 0.8 mm thick), and the uncertainty of whether it was retained during removal, the investigators decided not to make any attempts to locate or remove the cap.

Table 29. Adverse Events Related to the Device or Insertion/Removal Procedure in PRECISE II

Patient	Adverse Event (Severity)	Time of Onset	Outcome	Intervention
1	Bruising, x2 bilateral (mild) Erythema, x2 bilateral (mild)	3 days after removal	Resolved	Hydrocortisone cream
2	Pinpoint tenderness (mild)	2 days after insertion	Resolved	None
3	Device fragment[a] not recovered (mild)	Day of removal	Resolved	None
	Insertion site pain (mild)	Day of removal		None
	Discomfort (mild)	18 days after removal	Resolved[b]	None
4	Musculoskeletal pain (mild)	45 days after insertion (patient had performed heavy lifting)	Resolved	None
5	Intermittent burning and tingling (mild)	9 days after insertion	Resolved	None
	Unsuccessful removal of sensor (moderate, SAE)	9 days prior to successful removal of sensor on second attempt		Removal by general surgeon using general anesthesia and fluoroscopy
	Pain (moderate)	1 day after unsuccessful removal		Pain medication
6	Device fragment[a] not recovered (mild)	Day of removal	Resolved	None
7	Syncope (mild)	Day of insertion	Resolved	Lying down with feet elevated

[a] Sensor cap
[b] Resolved, per telephone contact post-database lock

All AEs related to the device or the procedure were considered anticipated and common for a subcutaneous implant. Furthermore, all AEs reported during the trial resolved fully.

7.3 PRECISION

Similar to the PRECISE II Study, adverse events in PRECISION were reviewed and adjudicated by an independent medical monitor.

In the PRECISION study, there were 3 SAEs, all of which were unrelated to the device or insertion/removal procedure. The SAEs were gastroenteritis, a hypoglycemic episode, and a cellulitis infection in the patient's foot.

A total of 8 device or procedure-related AEs were reported in 5 (14.3%) patients in the PRECISION study (Table 30). Note that 27 patients had 2 sensors inserted in this study. The types AEs were similar to those reported in PRECISE II and are categorically described in the integrated safety analysis below.

Table 30. Adverse Events Related to the Device or Insertion/Removal Procedure in PRECISION

Patient	Adverse Event (Severity)	Time of Onset	Outcome	Intervention
1	Dermatitis, x2 bilateral (mild)	55 days after insertion	Resolved	None
2	Pain (moderate)	Day of removal	Resolved	None
3	Pain/Discomfort (mild)	Day of insertion	Resolved	None
4	Skin hyperpigmentation, x2 bilateral (mild)	Day of removal	Resolved	None
5	Unsuccessful removal of sensor, x2 bilateral (mild)	93 and 105 days after insertion	Resolved	Removal by surgeon using local anesthesia (lidocaine injection)

7.4 Integrated Safety Analyses

An integrated safety analysis was conducted using pooled data from all registrational studies of the Eversense CGM system. This included 2 US studies (PRECISE II and PRECISION) and 1 EU study (PRECISE), which all enrolled similar patient populations and followed similar safety evaluation procedures through 90 days (PRECISE II and PRECISION) or 180 days (PRECISE) post-insertion.

The PRECISE study design and patient population is detailed in Appendix 11.5. Briefly, PRECISE was a non-randomized, single-arm, multi-center study in the EU that evaluated the effectiveness and safety of the Eversense CGM system to support product approval in the CE Marking territories. As described in Section 4.2, PRECISE evaluated an earlier design of the Eversense CGM system, which is not expected to impact the safety profile of the device. PRECISE enrolled 81 adult patients who had type 1 or type 2 diabetes and used insulin therapy and followed them at scheduled clinic visits through 180 days of device use or until the sensor end-of-life was reached.

The increased sensor exposure from bilateral sensor insertions (i.e., 2 sensors per patient in all or a subset of patients in the 3 studies) and for up to 180 days of continuous wear-time (PRECISE) provides more rigorous safety data on patient exposure outside that of the proposed intended use for the US. The integrated analysis provides the broadest review of all safety data collected to date from multicenter, registrational studies in adults with type 1 and type 2 diabetes with over 22,500 patient-days of sensor exposure.

7.4.1 Serious Adverse Events

There were no additional SAEs related to the device or the insertion/removal procedure in PRECISE. Thus, the integrated incidence of device or insertion/removal procedure-related SAEs across the 3 studies was 0.5% (1 out of 206 patients).

7.4.2 Adverse Events Related to Device and Insertion/Removal Procedures

In the integrated analysis, there were 41 device or insertion/removal-related AEs occurring in 26 patients for an overall incidence rate of 12.6% (Table 31).

Overall, while there were minor differences in the types of AEs observed across the 3 studies all were AEs anticipated for the device or the insertion/removal procedure (a list of AEs from PRECISE is provided in Appendix 11.6), all were transient and none were medically serious. Importantly, there were no unanticipated adverse events or deaths.

Infections, common insertion site reactions, AEs where a secondary procedure was required to remove the sensor, and potential AEs related to dexamethasone are detailed below.

Table 31. Adverse Events Related to the Device or Insertion/Removal Procedure from Integrated Studies

Event Physiologic System and Category[a]	Number of Events	Patients[b] (N=206)
Dermatological	**24**	**16 (7.8%)**
Pain/Discomfort	8	6 (2.9%)
Redness/Erythema	6	5 (2.4%)
Infection	3	3 (1.5%)
Dermatitis at Patch Location	3	2 (1.0%)
Bruising	2	1 (0.5%)
Skin Hyperpigmentation	2	1 (0.5%)
Neurological	**6**	**6 (2.9%)**
Neuropathy - Left Hand	1	1 (0.5%)
Vertigo	1	1 (0.5%)
Excessive Sleep Disturbance	1	1 (0.5%)
Headache	1	1 (0.5%)
Paresthesia	1	1 (0.5%)
Syncope-vasovagal	1	1 (0.5%)
Musculoskeletal Rheumatologic	**2**	**2 (1.0%)**
Pain	2	2 (1.0%)
Cardiovascular	**1**	**1 (0.5%)**
Hypertension	1	1 (0.5%)
Hematologic/immunologic	**1**	**1 (0.5%)**
Hematoma	1	1 (0.5%)
Gastrointestinal Hepatic	**1**	**1 (0.5%)**
Nausea	1	1 (0.5%)
Other	**6**	**5 (2.4%)**
Device Fragment[c] Not Recovered upon Sensor Removal	2	2 (1.0%)
Additional Procedure to Remove Sensor Following First Attempt	4	3 (1.5%)
TOTAL	**41**	**26 (12.6%)**

[a] Some events have been re-categorized for clarity
[b] Patients may experience more than one AE in each category
[c] Sensor cap

7.4.2.1 Infections

A conservative approach was taken to collect and report infections across the 3 studies, such that symptoms indicative of an infection were reported as infections, regardless of whether the patient received treatment for an infection.

There were 3 infections among 206 patients, resulting in a low infection rate (1.5% of patients; less than 0.5% of 670 total insertion and removal procedures). All 3 cases resolved without removal of the sensor and are summarized below:

- In one case, the infection, which the patient self-reported, was clinically insignificant as the infection resolved without antibiotic treatment and laboratory values (metabolic chemistry) were within normal ranges.
- In the second case, the patient was prescribed oral antibiotics and laboratory values (metabolic chemistry) reflected that a systemic infection could be excluded.
- The third patient was described as having a "superficial wound infection" associated with an ingrown hair caused by shaving the area prior to sensor insertion. The area was cleaned, and the ingrown hair was removed, and no antibiotics were prescribed.

Notably, these infections occurred in PRECISE, and no additional cases of infection occurred in PRECISE II or PRECISION, presumably due to improvements in patient training that were implemented in these latter studies. In PRECISE II and PRECISION, patients were instructed to leave bandages over the insertion site for a longer period of time following the insertion procedure before changing the bandage (48 hours compared to 24 hours in PRECISE).

The rate of infection in the integrated safety pool of Eversense (1.5%) is comparable to that of other subdermally implanted products, including contraceptive and opioid use disorder implants. As an example, Probuphine (buprenorphine, Braeburn Pharmaceuticals, Inc.) is a rod-shaped, drug-eluting nonbioresorbable product that is implanted, 4 rods at a time, for 6 months in the upper arms. Implant site infections (including AE terms of cellulitis, purulent discharge, implant site pruritus, incision site infection, and wound infection, implant site abscess, and subcutaneous abscess) were reported at a rate of 4.0% with Probuphine (FDA, 2016c).

7.4.2.2 Insertion Site Adverse Events

Dermatologic AEs including pain/discomfort, redness/erythema, bruising, and dermatitis were the most commonly reported events that were related to the device or insertion/removal procedure; 24 dermatologic AEs, occurring in 16 patients (7.8%), were reported among the 206 patients in the integrated safety pool. These insertion site reactions were generally mild and transient and are common to all CGM systems. Notably, AEs related to the adhesive patch (3 AEs in 2 [1.0%] patients) were infrequent, especially considering the duration of the studies (90 or 180 days).

As a point of reference, 12 AEs in 9 patients[2] due to sensor insertion and adhesive area irritations were reported for the Dexcom G4® PLATINUM Continuous Glucose Monitoring System in a study of 51 patients over the 7-day sensor wear period for a rate of 17.6% (FDA SSED, 2014). With the Freestyle Libre Pro Flash Glucose Monitoring System (Abbott), 26 of 72 patients in the 14-day clinical study reported skin irritation AEs for a rate of 36% (FDA SSED, 2016b). In a 10-day study of the Freestyle Libre Flash Glucose Monitoring System (Abbott), 5 out of 48 patients (10%) experienced a reaction at the sensor application site (FDA SSED, 2017).

7.4.2.3 Removal Procedure Adverse Events

There were 4 instances where a second removal procedure was required following a first attempt that was unsuccessful:

- One event occurred in PRECISE II and the SAE is described in Section 7.4.1.
- Two events were reported in PRECISION for the same patient. After an unsuccessful first attempt to remove one sensor, the physician attempted to remove both sensors under ultrasound guidance. This attempt was also unsuccessful, and the patient was referred to a general surgeon who removed the sensors without complication using local anesthesia (lidocaine injection) and ultrasound guidance.
- The last case was reported in PRECISE and occurred with the first patient entered in the study at one of the sites. The patient was referred to a surgeon for removal of the sensor after the initial attempt was unsuccessful. As with the previously described cases, the sensor in this patient was inserted deeper than recommended, which likely caused the difficulties with removal. The surgeon successfully removed the sensor following the recommendations in the instructions for use with local anesthesia (lidocaine injection).

The integrated incidence rate for unsuccessful removals across all 3 studies is 1.9% of patients (or 1.2% [4/331] of removal procedures). This incidence is lower than that of other subdermally implanted products requiring similar removal procedures. Removal complications with Probuphine (including removals that required a second procedure to remove all rods) occurred in 4.1% of patients.

The Eversense CGM system training program and labeling will specifically address depth of sensor insertion. Additional training material is being included in the training program to provide the necessary device and procedure overview in the event that the assistance of an additional medical professional such as a surgeon, is requested to aid with a difficult removal. As detailed in Section 7.2.1, design modifications to the blunt dissector have also been made to facilitate proper sensor placement depth.

[2] A total of 13 AEs were reported in 10 patients. One AE was deemed study-related and the other 12 were related to the device. A conservative calculation including 9 patients was used to obtain an event rate.

7.4.2.4 Potential Adverse Events Related to Dexamethasone Exposure

Potential risks related to dexamethasone exposure that were identified before study initiation included systemic infections as well as local effects at the sensor insertion site. Therefore, across all 3 studies, investigators were instructed to examine the sensor site at all visits for skin anomalies over the sensor placement site and poor healing of the incision following both the insertion and removal procedure.

One patient in the integrated safety analysis had 2 events of mild hyperpigmentation that were related to the device and resolved upon removal of the sensors. No systemic AEs from the 3 studies were attributed to dexamethasone, consistent with the negligible levels of plasma dexamethasone.

7.5 Safety of Repeat Sensor Insertions

7.5.1 European Patient Registry

7.5.1.1 Study Design

The European patient registry is an ongoing post-marketing study that was initiated in June 2016 following approval of the Eversense CGM system in Europe. The purpose of this registry is to confirm the long-term safety of the Eversense CGM system after repeat sensor insertions in up to 20 countries in the EU and in South Africa. Data from this study represent real world evidence of long-term safety and were provided to FDA in support of the marketing application for Eversense.

The registry is enrolling all patients inserted with a sensor until 100 patients have undergone 4 insertion/removal cycles, after which all enrolled patients will be followed for another 12 months. Participants must have diabetes and be older than 18 years of age. Exclusion criteria include a planned magnetic resonance imaging over the next 12 months, critical illness or current hospitalization, known contraindication to dexamethasone or dexamethasone acetate, requirement of IV mannitol or mannitol irrigation solutions, or pregnancy.

Follow-up visits are anticipated at intervals of approximately 3 months. sensor removal and replacement is scheduled once the current sensor reaches or approaches its end of life at approximately 90 days. Tracking of the devices inserted and removed will be maintained for all patients in the registry. In addition, safety data are collected in an active, prospective manner according to procedures for patient follow-up, adverse event evaluation and follow-up, and reporting of adverse events. Safety evaluations include examination of all previous and recent sensor sites at each in-clinic visit and documentation of adverse events occurring in the clinic and during home use.

The primary endpoint is the rate of serious device-related, procedure-related, or drug (dexamethasone acetate)-related adverse events through approximately 2 years post-first insertion which includes 3 reinsertions by design.

To demonstrate long-term safety, the rate of serious device or procedure related adverse events at 2 years post-first insertion will be tested using the following hypothesis:

H_o: Rate of serious device or procedure related AE at 360 days ≥3% + M

H_a: Rate of serious device or procedure related AE at 360 days <3% + M

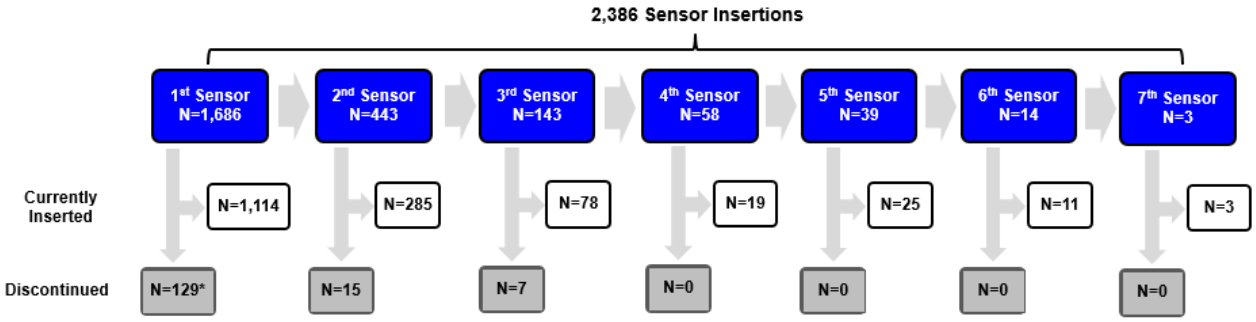
A one sample, 1-sided, non-inferiority margin (denoted as M in the above hypothesis statements) based on binary (proportion outcome) was used to determine the sample size. Patients who have the sensor removed prior to 12 months will be followed up for safety events for an additional ten days after the removal of the sensor. The safety data from these patients through 10-days post removal will be included in the safety analysis. An underlying rate of serious device or insertion/removal related AEs was assumed to be 3%. Based on a non-inferiority margin of 6%, 80% power, and a one-sided alpha of 0.025, a sample size of 131 patients was deemed adequately powered to test the hypothesis. Currently there are no implantable devices for continuous glucose monitoring that would be sufficiently similar to appropriately compare to the Eversense CGM system. The non-inferiority margin of 6% was selected to ensure an adequate minimum sample size of at least 100 patients at 1 year.

Interim analyses were planned for the European patient registry to provide an ongoing and current safety profile.

7.5.1.2 Interim Safety Results

As of February 2, 2018, a total of 1,686 patients enrolled across 350 sites have received a total of 2,386 sensor insertions. Of the 1,686 patients, 1,114 are currently on their first sensor, 443 have received a second sensor, 143 have received a third sensor, 58 have received a fourth sensor, 39 have received a fifth sensor, 11 have received a sixth sensor, and 3 have received a seventh sensor (Figure 18). The majority of discontinuations to date were due to coverage issues impacting the patients' access to the product. Approximately 9% of patients discontinued for non-reimbursement reasons after the first sensor removal. Subsequently, approximately 10% of patients discontinued after the second sensor and third sensor removals, and no patients discontinued after their fourth, fifth, or sixth sensor removal.

Figure 18. Number of Sensors Insertions in European Patient Registry



* Of the 129 patients who discontinued following their first sensor removal, 85 discontinued due to coverage issues impacting the patients' access to the product.

The safety profile following 700 total subsequent insertions revealed no additional or new risks associated with long-term use of the Eversense CGM system. As shown in Table 32, there have been no SAEs related to the device or the insertion/removal procedure and no unanticipated adverse events.

Table 32. Adverse Events Related to the Device or Insertion/Removal Procedure in European Patient Registry

	Number of Events	Incidence Rate[a] N=1,686	Rate per 100 Patient-Years of Exposure[b]
SAEs	0	0%	0
Device, Procedure, or Drug Related AEs	52	3.4%	10.9
Infection	14	0.8%	2.9
Unable to remove sensor on first attempt	9	0.5%	1.9
Irritation at adhesive patch location	7	0.4%	1.5
Skin thinning (atrophy) over the sensor with discoloration[c]	3	0.2%	0.6
Bruising	3	0.2%	0.6
Prolonged wound healing after procedure	3	0.2%	0.6
Skin discoloration	3	0.2%	0.6
Sensor broke during removal	3	0.2%	0.6
Sensor site redness/reaction to dressing	3	0.2%	0.6
Pain/discomfort	1	0.1%	0.2
Skin thinning (atrophy) over the sensor	1	0.1%	0.2
Syncope during procedure	1	0.1%	0.2
Hematoma	1	0.1%	0.2

[a] Rate determined using number of events as the numerator and total number of patients enrolled as the denominator
[b] Rate determined using number of events as the numerator and 475.8 years as the denominator, multiplied by 100
[c] Relatedness unable to be determined for 2 cases of skin thinning (atrophy) over the sensor with discoloration

Sixteen (16) cases of infection have been reported. Two of these cases were designated by the independent medical monitor as not related to the device or procedure, but due to other implicating factors:

- One patient had a severe bacterial infection in the leg involving the upper dermis and extending into the superficial cutaneous lymphatics, which the physician believed was the origin of the infection with secondary seeding of the sensor via translocation of bacteria

from the patient's hands to skin lesions near the healed insertion site of the sensor. This was reported as a possible delayed secondary infection which was unrelated to the device or procedure. A blood dexamethasone measurement was obtained, and the level was undetectable.

- The second infection was confounded by extended hospitalization with intravenous antibiotics for tonsillitis. No blood level of dexamethasone was obtained in this case as the sponsor was notified after the event.

Both of these patients were on their first sensors and in both cases, the sensor was successfully removed, and the placement site healed.

Fourteen (14) cases of infection related to the device or procedure occurred within days of insertion and were adjudicated to be definitely or possibly/probably related to the sensor insertion procedure. Four of the 14 cases occurred in 2 patients who had 2 separate occurrences of infection after placement of each of their first and second sensors. Both patients were treated with proper incision care and a short course of antibiotics after their first infection. The sensors went on to function as intended for the full life of the sensor. The subsequent occurrence of the second infection led to sensor removal by the treating physician. Insufficient information was provided by the clinic to determine the reason for repeat infections in the first patient. The second patient demonstrated noncompliance to the post-procedure incision care instructions after their first insertion (i.e., taking multiple showers on post-procedure Day 1 and removing both the dressing and Steri-Strip®) allowing the edges of the incision to separate, resulting in an infection. During the second sensor insertion in this patient, the physician proactively used a suture to close the incision. There is no further information regarding adherence to post-procedure instructions and the patient developed an infection within days of insertion. Of the remaining 10 infections, 7 resulted in sensor removal with no further complications or progression of infection. Of the other 3 reported infections, one appeared to have resolved with no antibiotic treatment without sensor removal, one had no follow up information despite queries, and one is under current investigation.

A total of 7 AEs involved skin changes. These have been reported as skin atrophy (N=1), skin thinning (atrophy) with skin discoloration (N=3), and skin discoloration (N=3). The case of isolated thinning (atrophy) is under current investigation. One case of skin thinning (atrophy) with discoloration resolved and no follow up is available for the other 2 cases. Of the cases of isolated skin discoloration, 1 resolved and 2 have not had further follow up. Importantly, no delayed healing of the insertion site or systemic infections were reported in association with dexamethasone. The 3 AEs of prolonged wound healing were investigated and attributed to poor Steri-Strip® placement.

There have been 7 reported cases of adhesive patch irritation. These irritations were mild and of limited duration. All patients reported resolution of the irritation and continued use of the CGM system.

There were 3 events where the body of the sensor broke during removal; in each case, all parts of the sensor were successfully removed. One case occurred when the physician used a clamp that had teeth (i.e., kocher clamp). These clamps are not recommended in the Eversense CGM system labeling for sensor removal. For the other 2 cases, little information is available on the removal procedure and no follow-up investigations could be performed as the sites disposed of the damaged sensors. Senseonics is currently updating physician training material to further emphasize the use of proper instruments and procedures.

No trends were observed following subsequent sensor insertions to suggest a worsening of patient risk with prolonged use of the Eversense CGM system (Table 33).

Table 33. Adverse Events Related to the Device or Insertion/Removal Procedure in European Patient Registry

Number of Patients (%)	Post 1st Insertion N=1,686	Post 2nd Insertion N=443	Post 3rd Insertion N=143	Post 4th Insertion N=58	Post 5th Insertion N=39	Post 6th Insertion N=14	Post 7th Insertion N=3
SAEs	-	-	-	-	-	-	-
Device, Procedure Related AEs							
Infection	8 (0.5%)	4 (0.9%)	2 (1.4%)	-	-	-	-
Unable to remove sensor on first attempt	7 (0.4%)	2 (0.5%)	-	-	-	-	-
Irritation at adhesive patch location	5 (0.3%)	-	2 (1.4%)	-	-	-	-
Prolonged wound healing after procedure	3 (0.2%)	-	-	-	-	-	-
Sensor site redness/reaction to dressing	3 (0.2%)	-	-	-	-	-	-
Sensor broke during removal	3 (0.2%)	-	-	-	-	-	-
Skin thinning (atrophy) over sensor with discoloration	2 (0.1%)	1 (0.2%)	-	-	-	-	-
Skin thinning (atrophy) over sensor	1 (0.1%)	-	-	-	-	-	-
Skin discoloration	1 (0.1%)	2 (0.5%)	-	-	-	-	-
Pain/discomfort	1 (0.1%)	-	-	-	-	-	-
Bruising	1 (0.1%)	1 (0.2%)	-	1 (1.7%)	-	-	-
Syncope during procedure	1 (0.1%)	-	-	-	-	-	-
Hematoma	-	-	-	1 (1.7%)	-	-	-

7.5.2 Risk Assessment

In line with FDA guidance, Senseonics conducted a comprehensive risk assessment of the Eversense CGM system to systematically evaluate the potential for long-term, chronic risks associated with continual use of Eversense. This assessment focused on clinical issues surrounding repeat sensor insertion (i.e., removal of the Eversense sensor and insertion of a new Senor in the contralateral arm for multiple cycles) and prolonged wear of the transmitter and included a systematic evaluation of potential risks, how each risk has been mitigated based on premarket initiatives (device design, preclinical testing, clinical testing), and corresponding post-market controls.

The risk assessment concluded that each potential risk has been sufficiently characterized through data from premarket clinical studies in the US and EU in combination with real world data from the post-approval study in Europe. Moreover, the risks of repeat sensor insertions and removals and chronic wear of the transmitter have been successfully mitigated to provide a reasonable assurance of device safety. On the basis of this information, and in discussion with the FDA, it was determined that any residual risks associated with repeat insertions are best studied in a post-approval setting (see Sections 8.2 and 8.3).

7.6 Release of Dexamethasone Acetate

7.6.1 Plasma Level

(b)(4)

(b)(4)

[redacted]

7.6.2 In Vivo Elution

(b)(4)

[redacted]

7.7 Safety Conclusions

The overall safety profile of the Eversense CGM system was as expected for a device of this type. The safety findings from PRECISE II, PRECISION, and PRECISE were generally consistent, supporting the robustness of each study and providing confidence in the safety database of the Eversense CGM system.

The integrated safety analysis, based upon 206 patients treated at multiple sites in the United States and Europe, demonstrated that the incidence of device or insertion/removal procedure-

related adverse events was limited to a rate of 13% over 90 and 180 days of use. There was one SAE related to the removal procedure that resolved fully. All AEs reported during the trials also resolved fully. Infections occurred following less than 0.5% percent of insertion and removal procedures (~1.5% of patients), and there were limited adhesive skin reactions. Finally, there was limited systemic dexamethasone exposure and no associated AEs across the 3 registrational studies.

Available post-market safety data from the European patient registry demonstrated a similar safety profile following repeat sensor insertions.

Taken together, these safety findings support the conclusion that the Eversense CGM system is safe for its intended use as a continuous glucose monitoring system. Importantly, the clinical data provided a well-controlled means and sufficient patient experience to characterize the risks associated with the Eversense CGM system to allow patients in consultation with their health care providers to make an informed decision regarding use of this new CGM system.

8 POST-APPROVAL PLAN

8.1 Training

A comprehensive training program will be implemented to ensure proper use of the device. These training activities will be consistent with those used during the PRECISE II and PRECISION clinical studies as well as the European commercial launch. Both physicians and patients will be trained.

For the required physician training, a multi-modal approach will be taken with didactic instruction via the Eversense CGM sensor Insertion and Removal Instructions, video instruction, simulated skin insertions and removals of the sensor using artificial skin in a prosthetic training arm, and mandatory proctoring of the initial senor insertions and removals for each physician by a trained observer. These activities and materials are designed to reinforce proper sterile technique, sensor placement, and appropriate sensor removal procedures, including instructions for challenging removals. A physician will be certified once he/she has successfully completed the training program.

As of February 2, 2018, 350 sites outside the US have been trained on the Eversense CGM system; the certification program is rigorous, and 94% and 86% of clinicians were authorized by the trainer to independently perform insertions and removals, respectively, after one in-person training session.

Patient training includes use of the Eversense instructions for use, instructional videos, and take-home instructions. A 24/7 Customer Care support line will also be made available, along with the Eversensediabetes.com website where instructional materials will be made available.

8.2 European Patient Registry

The European patient registry will continue to monitor the clinical performance and safety of the Eversense CGM system.

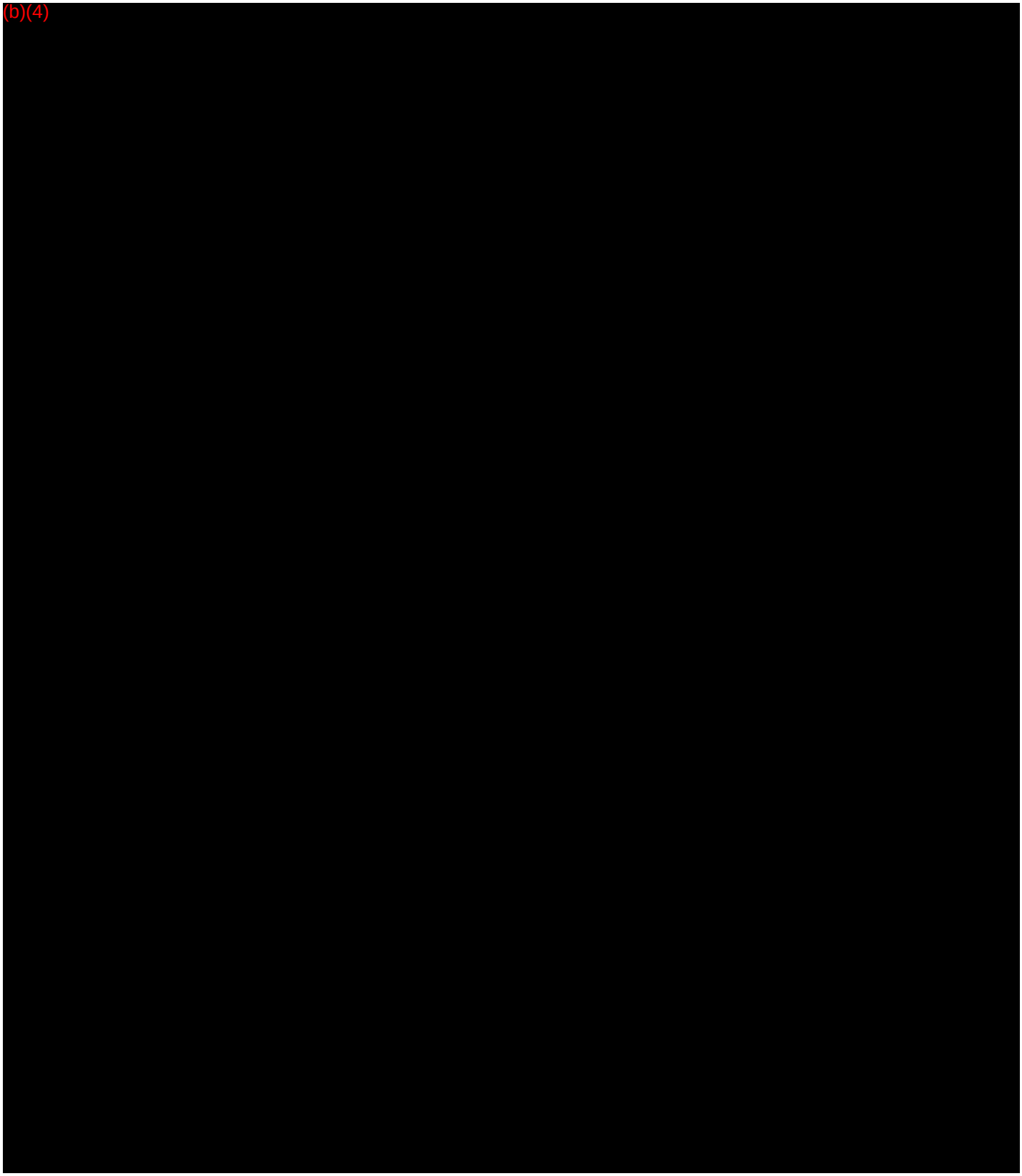
8.3 US Post-Approval Study

Senseonics is working in collaboration with FDA on the design of a US post-approval study to evaluate the long-term safety and effectiveness of the Eversense CGM system over repeat insertion and removal cycles. The post-approval study will be a 2-year, prospective, multi-center study at up to 20 sites in the US enrolling up to 175 adults with diabetes. Study visits will occur at 3-month intervals over the 2-year study duration, during which patients will received up to 8 consecutive sensors.

(b)(4) [redacted]

8.3.1 Study Endpoints and Analyses

(b)(4)



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8.3.2 Study Procedures

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9 BENEFIT RISK ANALYSIS

The benefits of any continuous glucose monitoring system depend upon both accurate glucose measurements and patients' acceptance and adoption of the technology. Currently available CGM systems do not meet the needs of all patients. One limitation is the requirement for repeated, frequent insertion of a sensor by the patient. Most currently approved sensors must be replaced approximately weekly, resulting in 30-50 sensor insertions and removals each year. The Eversense CGM system addresses this limitation by providing a sensor that lasts up to 90 days requiring only 4 sensor insertions and removals each year. In addition to expected improvements in patient comfort and satisfaction, a longer lasting sensor reduces the amount of time lost to first day wear inaccuracy by limiting the number of insertions. Furthermore, as the Eversense sensor is placed subcutaneously, there is no open wound or risk for dislodgement. This allows for the Eversense transmitter to be temporarily removed when desired without disturbing the sensor, such as for times when discretion is preferred, and to be secured to the skin using gentle silicone-based adhesives. Importantly, the Eversense transmitter provides vibratory alerts even when the receiving handheld device is absent or turned off. Each of these elements adds additional flexibility and functionality for people with diabetes who choose to monitor their glucose levels continuously.

As demonstrated in the PRECISE II study, the Eversense CGM system has a high degree of accuracy, with a MARD of 8.5% over the extended life of the sensor. With 91% of sensors reaching 90 days, the Eversense system eliminates the need for frequent sensor replacement inherent with other CGM systems, while maintaining similar glucose measurement accuracy (Table 35). Eversense also provides accurate detection of low and high glucose to help alert patients to impending hypoglycemic and hyperglycemic episodes. In particular, the low glucose detection rate and high glucose false alarm rate observed in PRECISE II are similar to the rates attained by devices used to guide treatment decisions. Furthermore, the proportion of Eversense readings falling within desired accuracy limits are consistent with those of currently available CGMs. The PRECISE II study results are supported by the findings of PRECISION, offering evidence of the robustness of the data.

Table 35. Accuracy of Commercially Available CGM Systems

Device	Sensor Wear Time	MARD	Hypoglycemic Event Detection	Hyperglycemic Event Detection	Accuracy Limits 15/15%	Accuracy Limits 20/20%
FreeStyle Libre Flash[a] (user-initiated; for non-adjunctive use)	10 days	9.7%	85%	95%[b]	82%	91%
Guardian® Sensor (3)[c] (for optional delivery of basal insulin)	7 days	10.6%	92%	95%	79%	88%
Dexcom G5® Mobile[d] (for non-adjunctive use)	7 days	9.0%	91%	99%	86%	93%
Eversense (PRECISE II Results)	**90 days**	**8.5%**	**96%**	**98%**	**87%**	**94%**
Eversense (PRECISION Results)	**90 days**	**9.6%**	**95%**	**99%**	**85%**	**93%**

[a] FreeStyle Libre Flash Glucose Monitoring System (Abbott) (FDA SSED, 2017)
[b] Hyperglycemic event detection rate with alert threshold of 240 mg/dL
[c] MiniMed® 670G System (Medtronic MiniMed, Inc.); results are based on calibrations every 12 hours (FDA SSED, 2016a)
[d] Dexcom G5® Mobile Continuous Glucose Monitoring System (Dexcom) (FDA SSED, 2014)

The risks of the Eversense CGM system include those related to sensor insertion and removal, those related to sensor performance, those related to wearing the transmitter, and those related to the presence of the sensor *in situ*. The PRECISE II, PRECISION, and PRECISE studies have demonstrated that trained investigators, with limited to no prior experience with insertion or removal of the Eversense sensor, were able to safely perform the office-based insertion and removal procedures with few complications. Across these 3 studies, all 335 sensors were inserted on the first attempt without incident; furthermore, the frequency of AEs where the sensor was not successfully removed on the first attempt was relatively low (1.5%) with a serious adverse event rate of 0.5% (1 out of 206 patients). Importantly, the risks associated with sensor removal can be mitigated through training and device design. Adverse events associated with the device or insertion and removal procedures were generally local, mild, and transient with the most commonly reported adverse events being dermatological in nature (such as bruising, erythema, or pain at the incision site). Overall, the incidence of related AEs (13%) over 90 days of use is comparable to that expected with other CGM devices.

Since Eversense is intended for adjunctive use and only SMBG readings should be used to make diabetes treatment decisions, inaccurate CGM values would only lead to additional finger sticks. The risk of inaccurate results related to the use of the device is no greater than that of other CGM systems on the market; nor is this risk greater than using an SMBG meter alone, which is how the majority of patients manage their diabetes today. Equally important, the accuracy of the Eversense CGM system, with an overall MARD of 8.5%, also mitigates these risks.

Overall, the risks associated with Eversense have been characterized in over 200 patients in the PRECISE II, PRECISION, and PRECISE clinical studies and no unanticipated safety issues have been identified. The identified risks have been mitigated as low as possible by device design, labeling, and training programs and materials.

As with other CGM systems, the benefits of the Eversense CGM system include continuous and real-time glucose values and trend information as well as real-time alerts to high and low glucose excursions. The ready availability of glucose readings and alerts offers the opportunity for longer term CGM adherence, better understanding of glucose trends related to food, exercise, and other factors. As with other CGM systems, Eversense, when used in combination with SMBG readings, may lead to improved glucose control, lower HbA1C values, and a reduction in long-term complications of diabetes. The potential risks of Eversense are minimal and manageable and are outweighed by the potential benefits of adherence to CGM utilization. For patients who lack a CGM device that fits their lifestyle, the Eversense CGM system, with its longer-wear sensor and other unique system features, represents a potentially viable option. Given its positive benefit-risk profile, the Eversense CGM system would serve as an important tool to facilitate improved glycemic control for many patients with diabetes.

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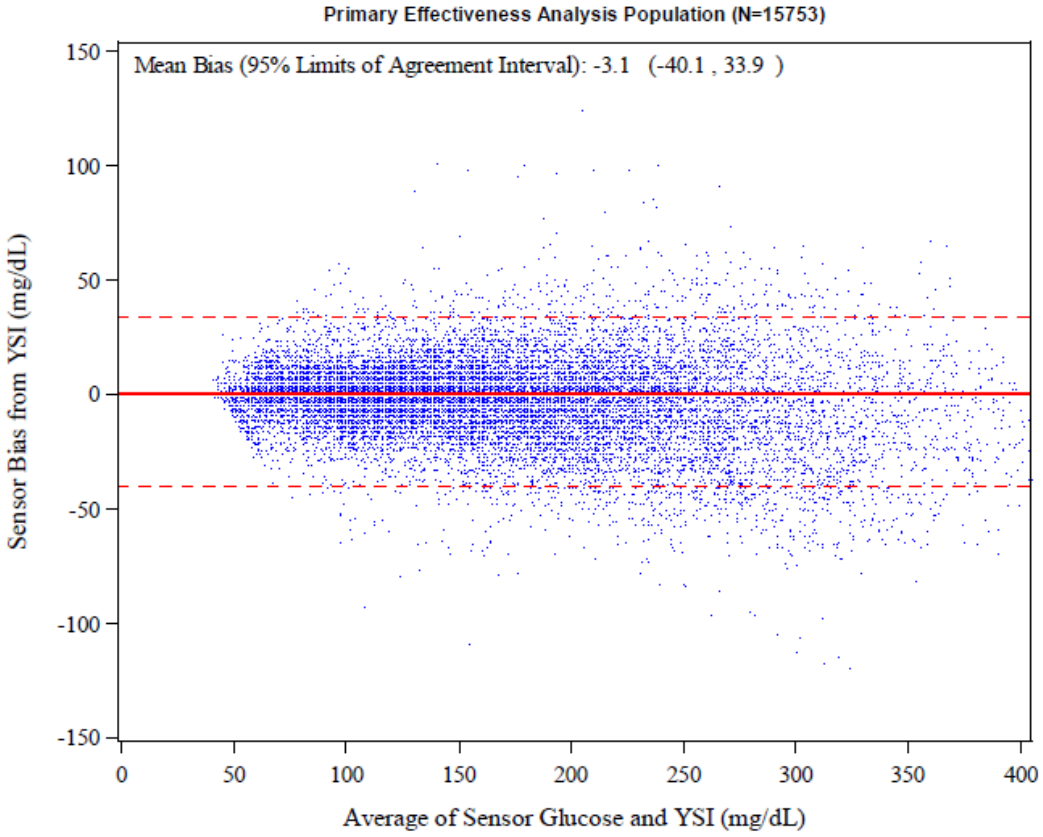
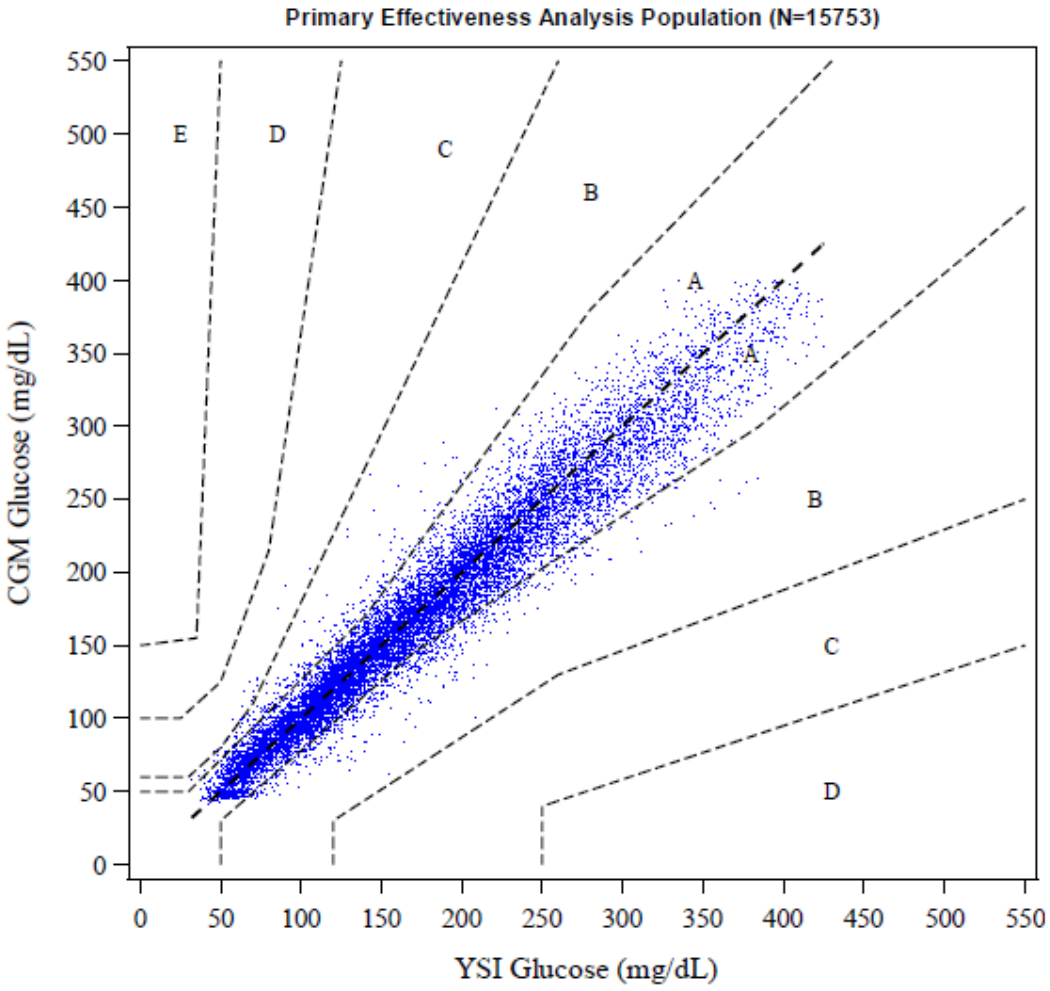
11 APPENDICES

11.1 Bland-Altman Analysis (PRECISE II)



Each blue dot represents one sensor reading.

11.2 Consensus Error Grid Analysis (PRECISE II)



Each blue dot represents one sensor reading.

11.3 Within Patient Precision (PRECISE II)

Within patient precision was assessed by calculating the absolute relative difference in patients with bilateral sensor insertions. The absolute relative difference based on primary-secondary sensor readings was 9.0% with a coefficient of variation of 6.4%.

11.4 Patient Narratives

SAE in PRECISE II Study

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11.5 PRECISE Study Design

The PRECISE study was a non-randomized, single-arm, multi-center study in the EU that evaluated the effectiveness and safety of the Eversense CGM system in adults with diabetes. The primary purpose of PRECISE, an EU registrational trial, was to support product approval in the CE Marking territories. As described in Section 4.2, PRECISE evaluated an earlier design of the Eversense CGM system. The configuration used in PRECISE included a slightly shorter sensor which had the DXA collar in a different location; it also used an earlier version of software to compute glucose values.

Adult patients who had type 1 or type 2 diabetes and used insulin therapy were enrolled and followed through 180 days of device use. Patients were disqualified from study enrollment if they had a history of severe hypoglycemia in the previous 6 months; had a history of diabetic ketoacidosis requiring emergency room visit or hospitalization in the previous 6 months; were pregnant; or had a condition preventing or complicating the placement, operation, or removal of the sensor or wearing of transmitter, including upper extremity deformities or skin condition.

On Day 0, each patient was inserted with 2 sensors, one in each arm. Clinic visits occurred on Day 1, 14, 30, 60, 90, 120, 150, and 180. After Day 180, or earlier if the sensor end-of-life was

reached, the patient returned to the office to have the sensor removed. A post sensor-removal follow-up visit occurred approximately 10 days after removal.

A total of 109 patients were consented, and 81 were inserted; all 81 patients were successfully inserted with sensors on the first attempt. The first patient at 5 sites who were inserted were considered training patients and another 5 patients received an initial configuration of the device, different from the configuration used for the remainder of the study population. These 10 patients were included in the safety analysis.

During the course of the study, 6 patients withdrew consent, and 42 patients had their sensors removed after the sensor stopped operating (11 before Day 90 and 31 after). The remaining 23 patients completed the Day 180 visit.

Patients in PRECISE were representative of the target population with respect to demographics and baseline characteristics.

11.6 Additional Safety Data

Table 36. Adverse Events Related to the Device or Insertion/Removal Procedure in PRECISE

Event Physiologic System and Category[a]	Number of Events	Number of Patients (% of Patients)
Dermatological	**10**	
Dermatitis	1	
Redness	4	8 (9.9%)
Discomfort	2	
Infection	3	
Neurological	**4**	
Neuropathy - Left Hand	1	
Vertigo	1	4 (4.9%)
Excessive Sleep Disturbance	1	
Headache	1	
Musculoskeletal Rheumatologic	**1**	1 (1.2%)
Pain - Left Forearm	1	
Cardiovascular	**1**	1 (1.2%)
Hypertension	1	
Hematologic/immunologic	**1**	1 (1.2%)
Hematoma	1	
Gastrointestinal Hepatic	**1**	1 (1.2%)
Nausea	1	
Other	**1**	
Additional Procedure to Remove Sensor following first attempt	1	1 (1.4%)
TOTAL	**19**	**14 (17.3%)**

[a] Some events have been re-categorized for clarity