FDA Executive Summary

Prepared for the
March 29, 2018 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel
P160048
Eversense Continuous Glucose Monitoring System
Senseonics, Inc.

I. Introduction

This document is the **FDA Executive Summary** for the meeting of the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel meeting on the Eversense Continuous Glucose Monitoring System (hereafter known as Eversense CGM) from Senseonics, Inc. The sponsor (Senseonics) has submitted an original premarket approval application (PMA number P160048) to obtain marketing approval for the Eversense CGM. The Eversense CGM sensor is a fluorescence-based glucose sensor that is implanted subcutaneously by a physician during a minor office based surgical procedure. The sensor lasts for up to 90 days, after which it must be removed by a physician during another minor office based surgical procedure. The submission is under review by the Division of Chemistry and Toxicology Devices (DCTD), Office of *In vitro* Diagnostics and Radiological Health (OIR), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This document will provide background on continuous glucose monitoring systems (CGMs) and the clinical studies and other information Senseonics has submitted in support of this new device. FDA is seeking the panel's opinion on whether Senseonics has provided adequate information to support the safe and effective use of the Eversense CGM by people living with diabetes.

II. Contents

III. Background on Continuous Glucose Monitors

Diabetes mellitus is a group of metabolic disorders characterized by poor physiological glucose control. Two major classes of diabetes, which differ in etiology, are prevalent in the population: Type I and Type II diabetes. Type I diabetes is predominantly characterized by loss of function of the insulin-producing beta cells of the islets of Langerhans in the pancreas, due to T-cell-mediated autoimmune destruction. Type II diabetes is characterized by the inability of an individual to respond adequately to normal levels of insulin (insulin resistance) and beta cell dysfunction (decreased insulin production). Acute complications of diabetes include hyperglycemia, which when untreated can lead to hyperglycemic emergency, including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS), as well as severe hypoglycemia, which can lead to loss of consciousness, seizures, or death. Long-term complications of diabetes include cardiovascular disease, cerebrovascular disease, peripheral vascular disease, nephropathy, neuropathy, and retinopathy. Long-term prognosis varies according to individual factors, including disease duration and glycemic control.

Most people with diabetes need to monitor their glucose levels on a frequent basis: typically several times a day. These measurements are a means to monitor the user's glucose levels when they are experiencing potential side effects of low or high glucose concentrations, but also when they are asymptomatic, since maintaining glucose levels near optimal levels is essential to prevention of complications. For example, one would test blood glucose, and if the value is too low, they would treat hypoglycemia to raise their blood sugar. For patients with insulin-dependent diabetes, a high blood glucose concentration is used to calculate the insulin dose needed to bring them into a more optimal range (euglycemia). The high frequency of daily glucose determinations can practically only be conducted with devices intended for home-use. There are currently two types of devices intended to help people with diabetes monitor their blood glucose values at home: Self-monitoring blood glucose meters (SMBG) and continuous glucose monitors (CGMs).

SMBGs directly measure blood glucose concentrations in capillary blood collected from the finger. People with insulin dependent diabetes typically monitor by SMBG 3-10 times per day, and in addition to regular monitoring, are advised to do so prior to calculating an insulin bolus (e.g., to correct hyperglycemia, and/or to account for meal carbohydrates). People with Type II diabetes typically perform fewer SMBG measurements per day.

CGMs provide a "continuous" series of glucose readings (typically a new glucose reading is determined every few minutes). Though CGMs have lower point accuracy than SMBG, CGMs have other features which provide additional information to the user. Real-time glucose results may be displayed along with a trend line graph for recent past glucose level readings. Trend information provides the direction of the current glucose trend and approximate rate of change (see Figure 1 below depicting the Eversense Continuous Glucose Monitoring System mobile app display).

Figure 1 *- Eversense CGM display. The status bar reports the current, real-time glucose value as well as a trend arrow, whose direction informs the user about the glucose trend direction and rate (i.e., glucose is 109 mg/dL and dropping in this example). The glucose information window provides the glucose trace graph (tracking information) for the previous several hours.*

In addition to the tracking and trending information described above, CGMs typically provide users with real-time alerts and alarms (e.g., alarms that sound when current glucose values exceed pre-set glucose thresholds, or are predicted to exceed them). For example, when a user's glucose values go below a pre-set low glucose threshold (e.g. below 70 mg/dL), an alarm will notify the user of this event. Thresholds for high glucose can typically also be set (e.g., when glucose values rise above 250 mg/dL).

CGMs also allow users and their healthcare providers to evaluate historical glucose trends to help adjust disease management strategies. For example, users can view daily glucose peaks and troughs, glucose trends while sleeping, glucose rates of change, and potentially correlate those features to diabetes management activities.

The first CGM (Medtronic MiniMed) was approved for the U.S. market in 1999. In the years following, other device manufacturers received FDA approval for their CGMs. These sensors, and all CGM sensors since, use an enzymatic reaction between glucose and glucose oxidase to measure glucose levels electrochemically. Early devices were prone to interferences from ascorbic acid, uric acid, and acetaminophen, and had significantly inferior accuracy performance compared to current CGMs.

In all previously approved CGMs, continuous monitoring is accomplished by a sensor that is temporarily inserted under the skin that measures the glucose concentration in interstitial

fluid (ISF) rather than blood (see Figure 2 below). Sensors in all previous CGMs use a similar design: they consist of a thin wire-like substrate, several current-carrying electrodes attached to the substrate, and an electrochemistry region towards the distal end of the sensor that resides in the interstitial fluid.

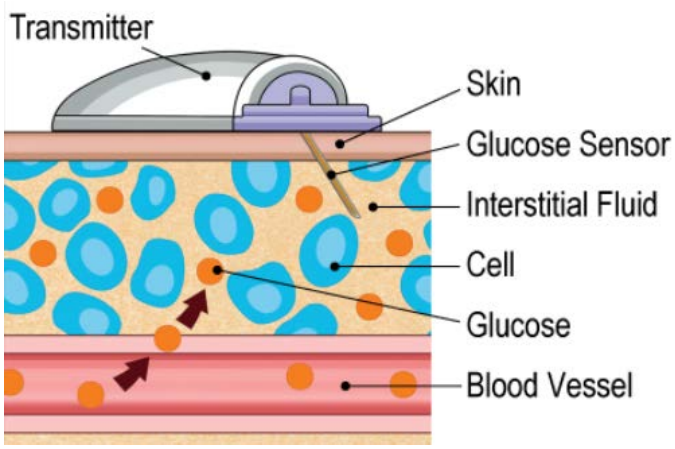


Figure 2 - *Example of sensor placement for previously approved CGM systems*

The insertion for all previously approved CGMs is carried out by the end user at home with the aid of an insertion tool. These insertion tools use a small gauge needle to insert a portion of the sensor wire under the skin. After insertion, one end of such a sensor is located under the skin, and the other end of the sensor is located above the skin so that the sensor can be connected to the electrical device (typically referred to as a transmitter) that provides electrical power to the sensor and measures sensor output (via amperometry) before transmitting the data the CGM system display device. For some CGM systems, the transmitter is responsible for converting the raw sensor data into estimated glucose values; in other systems, this step takes place in the receiver/user interface device.

Currently marketed CGMs fall into three categories based on device design:

- **"Conventional" CGM:** These devices provide updated glucose values every one to five minutes, and typically include options for low and high glucose alerts to notify users when their glucose value approaches hypoglycemic or hyperglycemic ranges. Glucose values and alerts are provided to the user via a user interface, which is either a standalone hardware device or a mobile app running on a smartphone or similar device.

- **Professional CGM:** These devices record CGM glucose measurements but do not display them to users. Data from the device is downloaded at the end of the wear period (1-2 weeks for current devices) by a healthcare professional who can review trends in the data and determine if adjustments to therapy may be needed. A professional CGM provides more frequent measurements than an SMBG would provide (including overnight periods), but it does not provide any real-time information to the user.

- **"Flash" CGM:** There is currently one device, the Abbott FreeStyle Libre CGM System, which does not fit into either of the above two classes of CGM. This device is similar to a tracking and trending CGM in how it is generally designed to detect glucose in interstitial fluid, however it does not automatically send these measurements to a display device and it cannot provide automated alerts like a "conventional" CGM. Instead, a user must bring the display device in very close proximity to the sensor (e.g., "scan" the sensor) when they wish to see their current CGM glucose measurement. With each "scan", the prior eight hours of retrospective CGM data, collected every 15 minutes, can also be retrieved and viewed for glucose trends.

The Eversense CGM system has some important differences compared to currently approved CGMs that are described below. However, the Eversense CGM is most similar in data output to a "conventional" CGM as described above.

Currently marketed CGMs can also be distinguished based on their intended use. There are two classes of intended use that current CGMs fall into:

- **Adjunctive Use:** The information provided by these devices is not intended to be used to make therapy decisions. For example, the CGM value should not be used to calculate an insulin dose. For a user of an adjunctive CGM, an SMBG measurement should be used to confirm the blood glucose value prior to any therapy decisions.

- **Non-Adjunctive Use:** The information provided by these devices may be used for without confirmation by SMBG measurements. A non-adjunctive claim carries a higher risk because inaccurate CGM values can lead directly to incorrect therapy decisions which can have serious and immediate health consequences.

Senseonics is requesting approval for an adjunctive use claim for the Eversense CGM system. This should be considered when evaluating the risk profile of the system.

IV. Senseonics Eversense Continuous Glucose Monitoring System

i. Indications for Use

Senseonics has proposed the following Indications for Use for the Eversense CGM system:

> The Eversense Continuous Glucose Monitoring System is indicated for continually measuring interstitial fluid glucose levels in adults (age 18 and older) with diabetes for the operating life of the sensor.
>
> The system is intended to:
> - Provide real-time glucose readings.
> - Provide glucose trend information.
> - Provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

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

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

ii. System Components

The Eversense CGM (see Figure 3 below) consists of:

- a subcutaneously implanted glucose sensor (for detecting interstitial fluid glucose)
- a transmitter that converts sensor glucose signals to glucose concentrations and transmits the calculated values to display devices
- sensor insertion tools for use by a physician (See Figure 8 below)
- and a software application (mobile medical app) installed on a mobile device (e.g. smartphone or tablet) that displays the glucose concentration received from the transmitter and serves as the user interface.

Figure 3 *- Eversense CGM system components*

The Eversense system must be calibrated twice per day with measurements from an SMBG meter (provided by the user – not included as part of the system).

The Eversense CGM system provides glucose measurements over a 40-400 mg/dL range. New values are generated and displayed to the user every five minutes. The system calculates glucose, provides trend information, and provides alerts for measured and (optionally) predicted high and low glucose. Information display, system interaction and control are accomplished using a Mobile Medical Application (MMA) installed on a compatible mobile device. Table 1 below describes some general similarities and differences between the Eversense CGM and other approved home use CGM devices.

Table 1 *- Similarities and Differences Between the Eversense CGM and Other CGM devices*

	Previously FDA Approved	**Eversense CGM System**

	Home Use CGMs	
Intended Use	Some are intended for tracking and trending glucose values adjunctive to SMBG, others are intended for replacement of SMBG readings in making treatment decisions	Intended for tracking and trending glucose values adjunctive to SMBG
Wear time	3-10 days	90 days
Glucose sensing technology	Enzymatic, electrochemical	Fluorescence
Transmitter Design	Direct electrical connection to the sensor	Wireless connection to the sensor
Insertion Procedure	Inserted at home by device user	Inserted by a physician during a minor office based surgical procedure using local anesthesia
Physical location of the sensor	Abdomen, upper buttock, and/or back of the upper arm	Outer side of the upper arm
Drug component(s)	None	Dexamethasone Acetate
Type of data receiver/display device	Standalone receiver device, or mobile medical application (app)	Mobile medical application (app) only
Need for SMBG Calibration	Most require calibration at least 2x per day, one is factory calibrated and does not require user calibration	Yes, 2x per day
Type of information provided	All CGMs provide point estimates of blood glucose concentration, most also provide high/low threshold alarms and high/low predictive alarms	Provides point estimates of glucose, high/low threshold alerts, and high/low predictive alarms

Sensor Component

The sensor of the Eversense system is responsible for measuring glucose levels and reporting those measurements to the system. The sensor is inserted under the skin of the upper arm, where it resides for up to 90 days.

The sensor uses a fluorescence-based sensing mechanism to detect interstitial fluid glucose. The sensor is powered by the transmitter using a wireless magnetic link, and the same magnetic link is used to send raw sensor measurements to the transmitter. The transmitter calculates, stores, and transmits the glucose data via Bluetooth Low Energy (BLE) to the MMA.

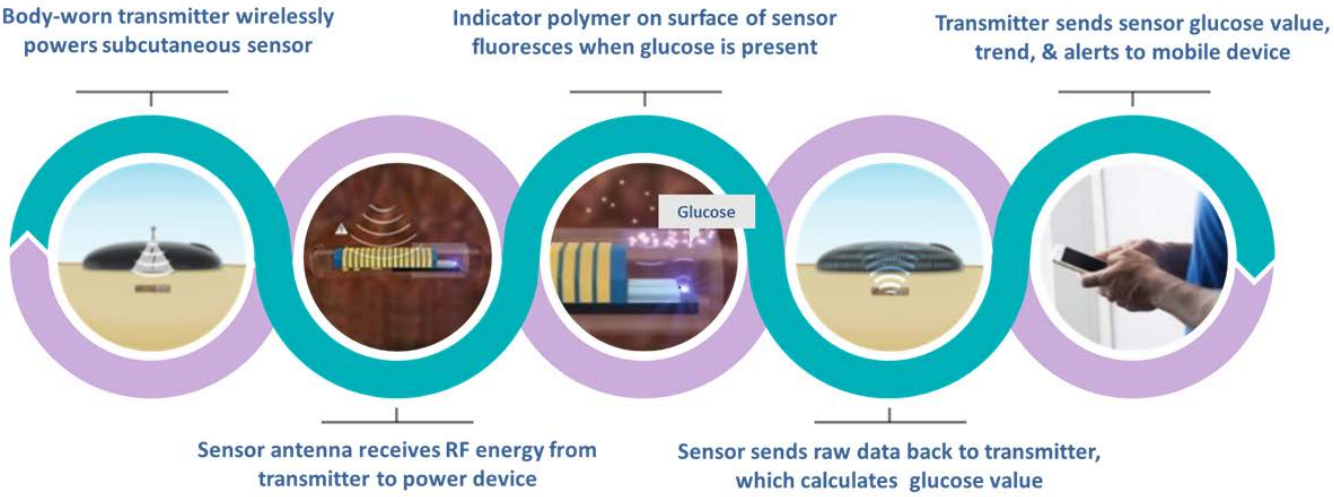


Figure 4 – *Interaction of the various Eversense CGM system components*

The Sensor's optical system functions as a two-channel fluorimeter designed to measure light intensity from the indicator hydrogel. The optical system is comprised of a light-emitting diode (LED), which serves as the excitation source for the fluorescent indicator hydrogel, and two spectrally filtered photodiodes. One photodiode measures the fluorescence intensity in a specific wavelength range; the second photodiode measures LED intensity. Reversible binding of interstitial glucose to the indicator hydrogel modulates the fluorescence of the indicator in a predictable fashion. See the executive summary provided by Senseonics for a detailed description of the sensor chemistry.

The optical and electrical components are potted in epoxy within a rigid, translucent and biocompatible polymethylmethacrylate (PMMA) encasement onto which the indicator hydrogel is grafted. A thin layer of platinum covers the entire surface of the Sensor.

The sensor is 18.3mm long and 3.5mm in diameter.

Unlike all previous CGM sensors, the Eversense sensor includes a drug component. The sensor has a dexamethasone acetate (DXA) eluting silicone collar attached at one end of the sensor. Senseonics determined that reactive oxygen species, which are part of the inflammation signaling pathway, accelerate the degradation of the glucose recognition element. The DXA collar was added to the sensor to reduce the degree of inflammation around the sensor after the insertion process. The collar contains 1.75 mg of DXA.

As part of their clinical studies (see PRECISION study section below) Senseonics assessed subjects' systemic exposure to DXA by measuring DXA concentrations in blood samples for several days after sensor insertion.

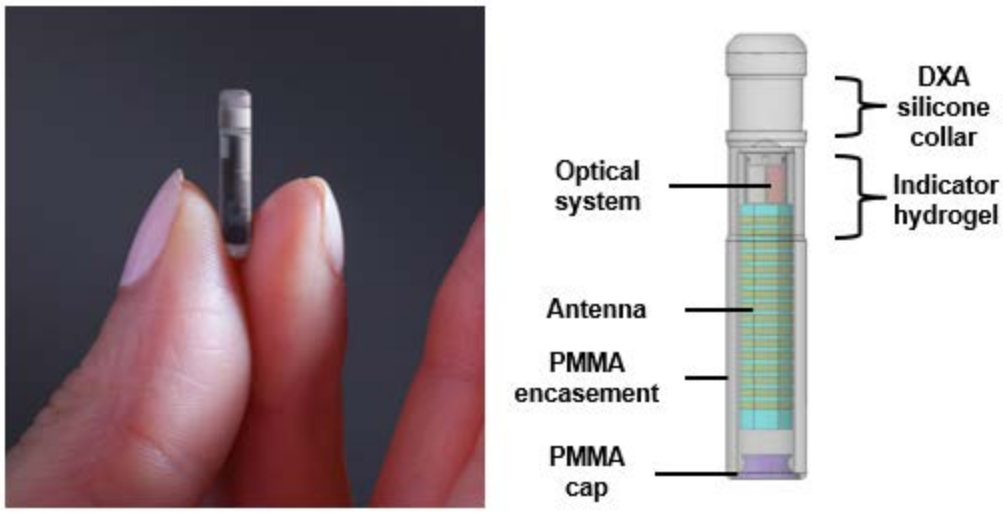


Figure 5 *- Senseonics Eversense CGM Sensor*

CGMs in general (including the Eversense system) are contraindicated for use during magnetic resonance imaging (MRI), computed tomography (CT) scans, or diathermy treatment.

Transmitter Component

The Transmitter contains a rechargeable battery that powers, communicates, and captures information from the Sensor, calculates glucose values and trends using a proprietary algorithm (see System Algorithm, below), 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-backed adhesive patch. 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.

Figure 6 *- Eversense Transmitter in position on the upper arm*

System Algorithm

The CGM system algorithm is responsible for converting between the fluorescence measurements from the sensor (which are measured in units of light intensity) to glucose concentration (in units of mg/dL typically being used in the US). These algorithms are a component of all CGM systems and they are unique to each system.

In the Eversense system (and in most other CGM systems), the algorithm uses SMBG measurements provided by the user to calibrate itself. Like many other CGM systems, the Eversense algorithm requires calibration twice per day.

In the Eversense system, the algorithm resides in the transmitter component. The transmitter receives and stores the raw fluorescence measurements from the sensor and then uses the system algorithm to calculate glucose values.

Mobile Medical Application

The MMA, often called an "app," 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.

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.

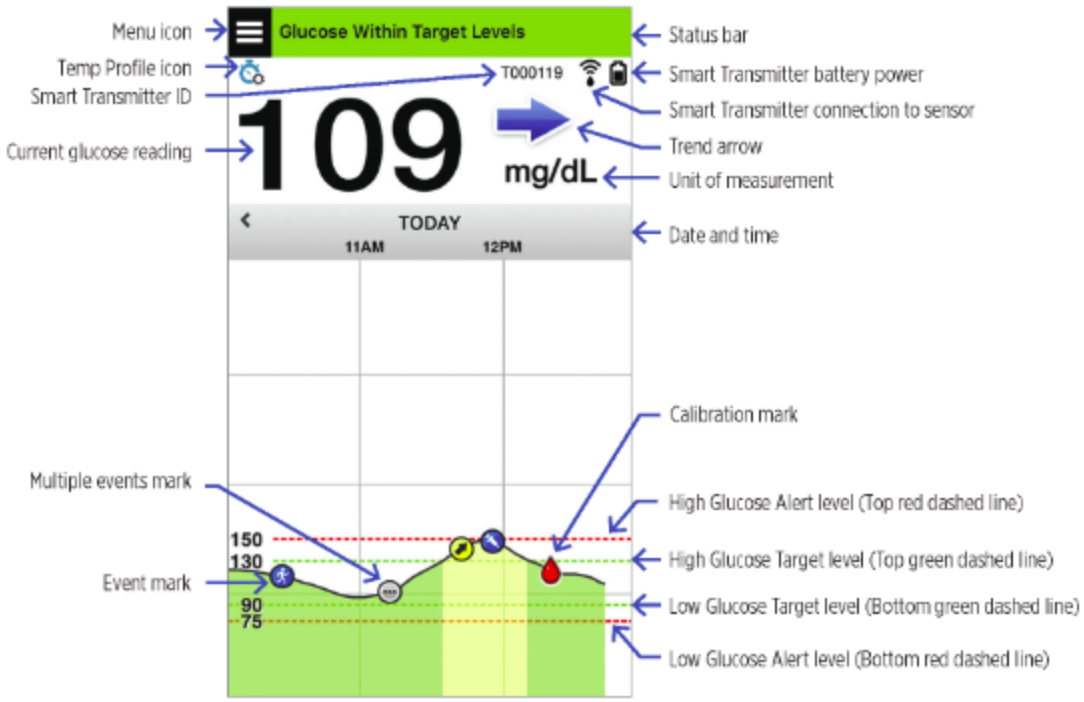


Figure 7 *- Eversense Mobile Medical App display*

Sensor Insertion Tools

In the Eversense CGM system, the sensor is implanted by a physician during a minor office-based surgery (see Figure 9 and Figure 10 below), and it remains implanted for up to 90 days. The Eversense CGM sensor is fully subcutaneous after implantation (no portion remains above the skin), and electrical power is provided wirelessly by the transmitter which is placed on the skin directly over the sensor and held in place with double-sided adhesive patch (see Figure 4 above).

Insertion Tools are provided for Sensor implantation (Figure 8, below). The Blunt Dissector is used to create the subcutaneous space in which the Sensor is placed. This tool has two guide marks and depth guards to assist in determining the correct pocket depth and length. The Sensor Holder in which the Sensor is stored during transport and sterilization is used to transfer the Sensor to the Insertion Tool. The Insertion Tool is used to place the Sensor into the subcutaneous space. The Insertion Tool also has two guide marks on the cannula to assist in proper placement.

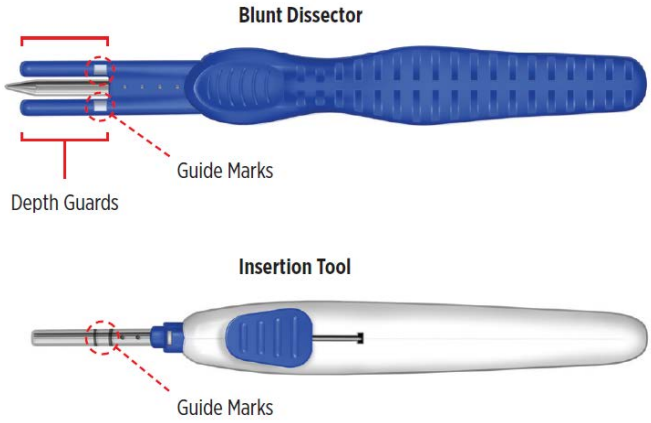


Figure 8 *- Insertion tools provided with the Eversense system, for use by a physician*

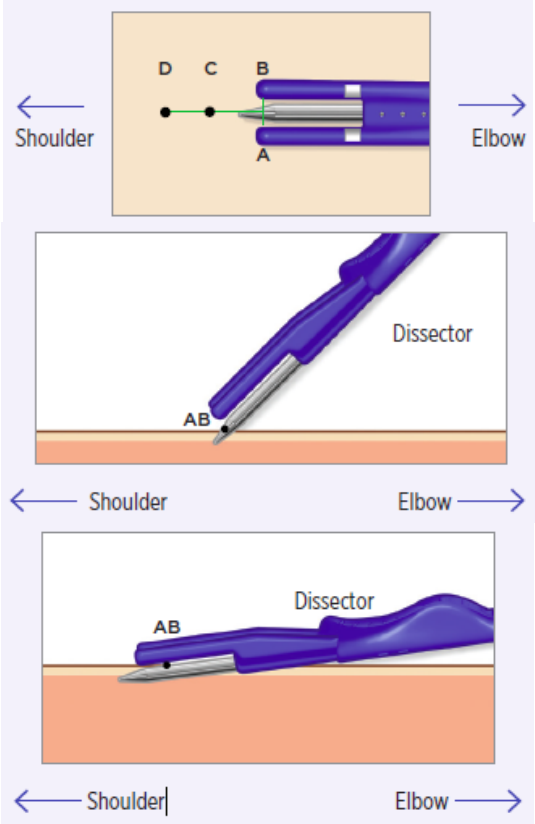


Figure 9 – *Process of creating the subcutaneous sensor pocket using the blunt dissector tool. A 5mm long incision is first made by the physician (on the line AB in the top image) at the sensor insertion site on the upper arm using a scalpel. The blunt dissector is inserted into this incision at an angle of approximately 45º to a depth of 3-5mm below the skin surface. The dissector is then pivoted down so that it is parallel to the skin surface, and pushed forward (along the line CD in the figure above) until the incision is aligned with the guide marks on the tool (Figure 8 above).*

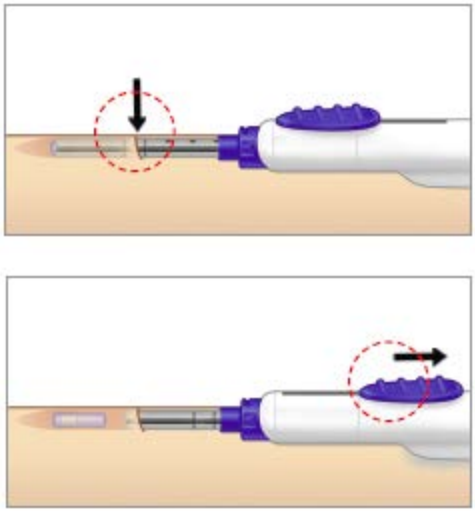


Figure 10 *- Sensor placement using the sensor insertion tool. The sensor is loaded into the insertion tool with the button in the forwards position. Then the tool is inserted into the subcutaneous pocket until the incision is aligned with the guide marks (dotted circle in the top image), and the button is pulled backwards to release the sensor (dotted circle in bottom image).*

The wound channel created during implantation of the Eversense sensor (referred to as the subcutaneous sensor pocket) is much larger than that of other CGMs. Other CGMs use a small gage needle (<1mm diameter) to insert their thin wire sensor. The Eversense sensor has a diameter of 3.5mm and is about 18mm long. The blunt dissector used to create the sensor pocket is approximately 4mm in diameter.

The Eversense system is intended to be used indefinitely, resulting in repeated sensor insertion/removal cycles up to four times per year, potentially for decades. The comparatively large wound channel, combined with the relatively small area in which the Eversense sensor can be inserted (limited to the outer surface of the two upper arms, see Figure 11 below) suggests that over time sensors may need to be inserted in the same area where they had been previously inserted.

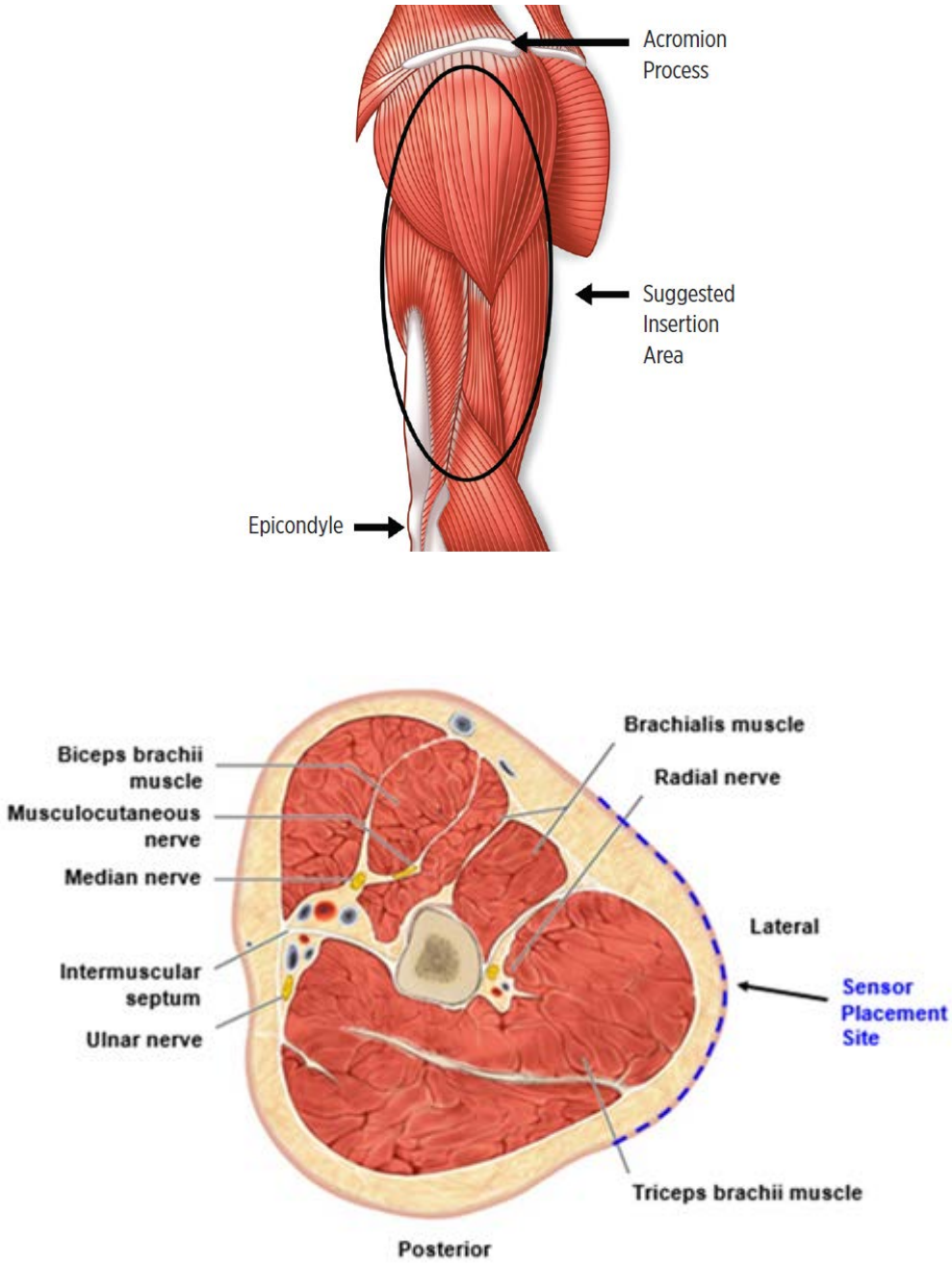


Figure 11 *- Suggested insertion area for the Eversense sensor, as presented in the proposed device labeling.*

V. Bench Testing

Interference in the Eversense CGM system was assessed using *in vitro* testing. During *in vitro* testing, sensors were placed into glucose solutions to which potentially interfering substances were then added. Concentrations of potential interferents were either based on recommendations from interference testing standards/guidelines (e.g. Clinical & Laboratory Standards Institute (CLSI) EP7A2), FDA guidance documents for other glucose

measurement devices (e.g. "Self-Monitoring blood glucose test systems for over-the-counter use" issued October, 2016), or based on information available in literature. In some cases, information on ISF concentration of potential interferants was not available. In these situations, plasma concentrations were used to assess interference. This should represent a worst-case scenario, as ISF concentrations should not be higher than plasma concentrations. Most tested substances occur in ISF due to diffusion of the substance into ISF from the bloodstream.

Substances were tested at 2 glucose concentrations – a low concentration of 72 mg/dL and a high concentration of 324 mg/dL. The glucose level measured by the sensors was recorded before and after the addition of the potential interferant, and the degree of bias was calculated.

Senseonics defined significant interference as a bias greater than 10 mg/dL for glucose levels below 100 mg/dL, or greater than 10% for glucose levels above 100 mg/dL. See the table below for test results:

Table 2 *- Substances tested for potential interference with the Senseonics sensor*

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

Of the 41 substances tested, two showed an interfering effect at concentrations associated with therapeutic doses (mannitol and tetracycline). At the concentrations tested (0.09 mg/dL), Sorbitol did not exhibit an interfering effect. However, it was later identified as a potential interferent under certain conditions of use. Senseonics identified the following substances as potential interferents:

- Mannitol, when administered intravenously or in irrigation solution, may afford concentrations that could produce a positive bias in Eversense glucose readings. The magnitude of the positive bias increases as the concentration of mannitol increases. For a glucose concentration of 76 mg/dL, it was found that a concentration of >5.6 mg/dL of mannitol would produce a bias greater than 10 mg/dL (concentrations of mannitol above 5.6 mg/dL would produce positive bias of greater magnitude). For a glucose concentration of 321 mg/dL, a concentration of >23 mg/dL of mannitol was necessary to produce a bias greater than 10% (concentrations of mannitol above 23 mg/dL would produce positive bias of greater magnitude). Plasma concentrations of mannitol for patients undergoing a procedure where irrigation with a mannitol was used were reported to be as high as 32.8 mg/dL (Renner, Schmitz, & Gehring, 1998). This concentration of mannitol would result in a positive bias of approximately 62 mg/dL for a sample with true glucose concentration of 76 mg/dL, and a positive bias of 42 mg/dL for a sample with true glucose concentration of 321 mg/dL, based on the *in vitro* results obtained by Senseonics. A positive bias may have negative clinical consequences if used to influence treatment strategy. The sponsor has proposed 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 be included in the Eversense labeling.

- Sorbitol was tested at 0.09 mg/dL, per the FDA guidance document listed above, and did not demonstrate an interfering effect. Sorbitol was not tested at higher concentrations. Senseonics concluded that given the bias observed with very high concentrations of mannitol, it was likely that sorbitol would have a similar degree of bias at very high concentrations. Based on a review of literature, they concluded that the only way the Eversense Sensor could be exposed to such high concentrations of sorbitol would be through IV administration or the use of sorbitol in an irrigation solution. Based on this assessment, Senseonics has proposed to include a warning against the use of sorbitol in these administration routes while using the Eversense system.

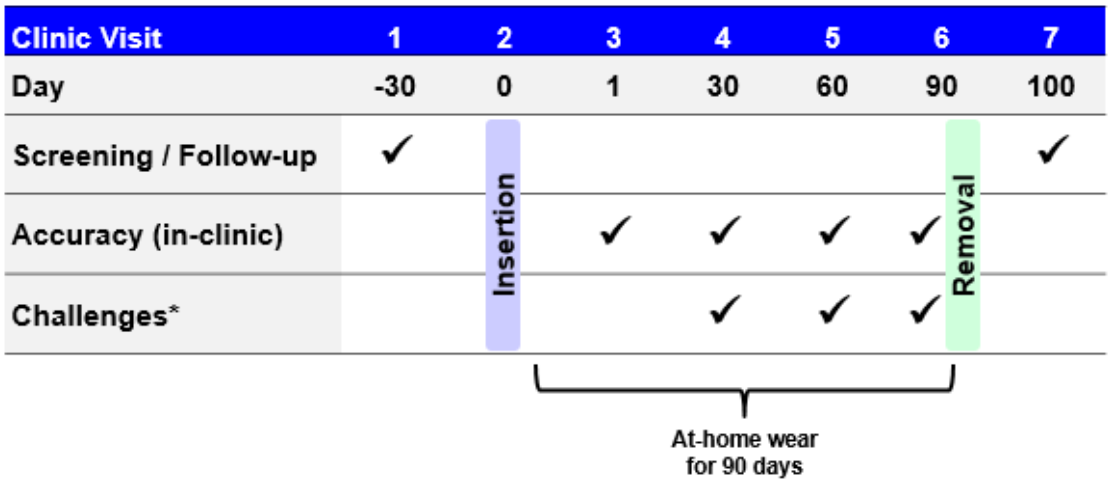
- Tetracycline introduced a negative bias in glucose reading from the Eversense CGM System. At low glucose concentrations, 0.5 mg/dL of tetracycline was shown to produce a bias of -46 mg/dL. At high glucose concentrations, the same amount of tetracycline produced a bias of -31%. A plasma concentration of 0.5 mg/dL was the highest reported for tetracycline based on a literature review conducted by Senseonics. ISF concentration measurements for tetracycline could not be found, so the plasma concentration was assumed to be the worst case. An animal study (minipig) was conducted by Senseonics, and confirmed that plasma concentrations of tetracycline near 0.5 mg/dL could cause a significant negative bias in sensor glucose measurements. A negative bias may have negative clinical consequences if used to influence treatment strategy. The sponsor has proposed that the Eversense labeling inform users that the use of tetracycline may falsely lower Sensor glucose readings and that they should not rely on their CGM system while using tetracycline.

VI. Clinical Data

Senseonics performed two clinical studies to assess safety and effectiveness of the Eversense CGM System: the PRECISE II study consisting of 90 subjects, and the PRECISION study consisting of 35 subjects. These clinical studies were performed in the United States.

i. Eversense CGM Pivotal Clinical Study (PRECISE II study)

The PRECISE II study was a non-randomized, blinded, prospective, single-arm, multi-center study, evaluating 90 adult subjects with diabetes mellitus in the United States at 8 sites. The investigation included both clinic visits and home use of the Senseonics CGM System. The majority of subjects had one sensor inserted in the upper arm by trained investigators. A subset of 15 subjects, at one clinical site, had two Sensors inserted (one in each arm). The accuracy of the Senseonics CGM System was evaluated during clinic visits by comparing sensor values to laboratory plasma glucose value drawn every 5 to 15 minutes. Clinic sessions were performed on days 1, 30, 60 and 90 for a period of approximately 4 ½ to 12 ½ hours. During Sensor accuracy clinic visits, qualifying subjects participated in hyperglycemia and hypoglycemia challenges, as well as upper arm exercise sessions for duration of 30 minutes. For subjects inserted with two Sensors, in addition to glucose challenges, the effects of compression (e.g., caused due to sleeping on the arm with transmitter) were also evaluated.



** Glycemic, exercise, and compression challenges*

Figure 12 *- PRECISE II Study Design*

PRECISE II Safety Results

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 in the study were reviewed and adjudicated by an independent medical monitor.

The adverse events the sponsor reported for this study are summarized in the table below:

Table 3 *- Summary of adverse events during the PRECISE II study*

Patient	Adverse Event (Severity)	Time of Onset	Outcome	Intervention
A	Bruising, Left Arm (mild)	3 days after removal	Resolved	None
	Bruising, RightArm (mild)	3 days after removal	Resolved	None
	Erythema, Left Arm (mild)	3 days after removal	Resolved	Hydrocortisone cream
	Erythema, RightArm (mild)	3 days after removal	Resolved	Hydrocortisone cream
B	Pinpoint tenderness (mild)	2 days after insertion	Resolved	None
C	Device fragment[a] not recovered (mild)	Day of removal	Resolved	None
	Insertion site pain (mild)	Day of removal	Resolved	None
	Discomfort (mild)	18 days after removal	Resolved[b]	None
D	Musculoskeletal pain (mild)	45 days after insertion (patient had performed heavy lifting)	Resolved	None
E	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	Resolved	Removal by general surgeon using general anesthesia and fluoroscopy
	Pain (moderate)	1 day after unsuccessful removal	Resolved	Pain medication
F	Device fragment[a] not recovered (mild)	Day of removal	Resolved	None
G	Syncope (mild)	Day of insertion	Resolved	Lying down with feet elevated

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

There was one 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. The patient was referred to a surgeon, who used general anesthesia and visualized the Sensor using fluoroscopy. The Sensor was removed intact, and the patient recovered.

PRECISE II Accuracy Results

The accuracy results from the PRECISE II in-clinic sessions are summarized in the tables below.

There are multiple ways to look at accuracy of a CGM system. Each approach relies on comparing CGM values to measurements taken concurrently with another instrument that is known to be sufficiently accurate, referred to as the comparator method. Senseonics chose to use a laboratory device, the Yellow Springs Instruments (YSI) model 2300 (referred to as 'YSI' in the tables below).

The following four tables show a representation of system accuracy on individual days of sensor wear. See Appendix 1 for additional representations of system accuracy from the PRECISE II study.

Note that table cells with dashes indicate that zero percent of data falls within these ranges, when rounded to exclude fractional percent results.

Table 4 – *Concurrence between CGM readings and comparator method (YSI) on* ***day 1*** *of sensor wear during the* ***PRECISE II*** *clinical study. The table is arranged by each YSI glucose range (first column) and tabulates, for each range of YSI glucose readings, the percentage of paired CGM values that were in the identical glucose range (shaded diagonal), as well as those reference values that were in glucose ranges above and below the paired YSI readings.*

Day 1	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	20	--	40%	55%	5%	--	--	--	--	--	--	--
61-80	76	--	24%	47%	29%	--	--	--	--	--	--	--
81-120	385	--	2%	10%	69%	19%	--	--	--	--	--	--
121-160	460	--	1%	2%	23%	59%	14%	--	--	--	--	--
161-200	372	--	--	--	2%	23%	57%	16%	1%	--	--	--
201-250	231	--	--	--	--	1%	21%	65%	11%	1%	--	--
251-300	86	--	--	--	--	--	2%	42%	52%	3%	--	--
301-350	16	--	--	--	--	--	--	6%	50%	44%	--	--
351-400	0	--	--	--	--	--	--	--	--	--	--	--
> 400	0	--	--	--	--	--	--	--	--	--	--	--

Table 5 *- CGM concurrence to YSI on* ***Day 30*** *of the PRECISE II study*

Day 30	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	4	100%	--	--	--	--	--	--	--	--	--	--
40-60	180	--	61%	38%	1%	--	--	--	--	--	--	--
61-80	512	--	17%	67%	16%	1%	--	--	--	--	--	--
81-120	1169	--	1%	9%	79%	11%	--	--	--	--	--	--
121-160	1165	--	--	--	14%	77%	9%	--	--	--	--	--
161-200	804	--	--	--	--	16%	75%	9%	--	--	--	--
201-250	704	--	--	--	--	1%	20%	73%	7%	--	--	--
251-300	343	--	--	--	--	--	--	23%	67%	9%	--	--
301-350	141	--	--	--	--	--	--	1%	41%	46%	11%	--
351-400	60	--	--	--	--	--	--	--	5%	32%	63%	--
> 400	4	--	--	--	--	--	--	--	--	--	100%	--

Table 6 *- CGM concurrence to YSI on* ***Day 60*** *of the PRECISE II study*

Day 60	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
<40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	139	--	62%	33%	5%	--	--	--	--	--	--	--
61-80	291	--	21%	56%	22%	--	--	--	--	--	--	--
81-120	797	--	--	8%	82%	10%	--	--	--	--	--	--
121-160	826	--	--	--	13%	72%	15%	--	--	--	--	--
161-200	759	--	--	--	--	18%	65%	17%	--	--	--	--
201-250	889	--	--	--	--	--	16%	72%	12%	1%	--	--
251-300	514	--	--	--	--	--	1%	28%	62%	9%	--	--
301-350	348	--	--	--	--	--	--	1%	42%	53%	4%	--
351-400	139	--	--	--	--	--	--	--	11%	50%	40%	--
> 400	9	--	--	--	--	--	--	--	--	--	100%	--

***Table 7** – CGM concurrence to YSI on **Day 90** of the PRECISE II study*

Day 90	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	98	--	37%	52%	11%	--	--	--	--	--	--	--
61-80	274	--	9%	59%	32%	--	--	--	--	--	--	--
81-120	606	--	--	7%	75%	16%	1%	--	--	--	--	--
121-160	776	--	--	--	11%	73%	14%	1%	--	--	--	--
161-200	720	--	--	--	1%	24%	65%	10%	1%	--	--	--
201-250	779	--	--	--	--	1%	30%	61%	7%	1%	--	--
251-300	537	--	--	--	--	--	1%	43%	45%	12%	--	--
301-350	323	--	--	--	--	--	--	2%	45%	44%	9%	--
351-400	130	--	--	--	--	--	--	--	2%	48%	50%	--
> 400	18	--	--	--	--	--	--	--	--	--	100%	--

(See Appendix 1 for additional representations of the accuracy data from the PRECISE II study.)

During the PRECISE II study, nine sensors failed prior to the intended 90-day sensor life out of a total of 106 sensors inserted during the study. Of these nine sensor failures, three failures occurred in the first two months post-insertion and the remaining six occurred between days 60 and 90. Overall, 99% of Sensors were functional through 30 days, 97% functioned through 60 days, and 92% functioned through 90 days.

The Agency has made the following observations about the in-clinic data collected during the PRECISE II study:

- The in-clinic accuracy session for day 1 of sensor wear lasted 4.5 hours and did not include glycemic challenges. As a result, there was little data outside of the euglycemic range on Day 1 of sensor wear. Subsequent in-clinic sessions on days 30, 60, and 90 were >8 hours in duration, and included hypo- and hyperglycemic challenges which resulted in more data being collected across a wider range of CGM values.

- The available data indicates that the Eversense system is less accurate on day 1 than on day 30, 60, and 90, particularly in the hypoglycemic range.

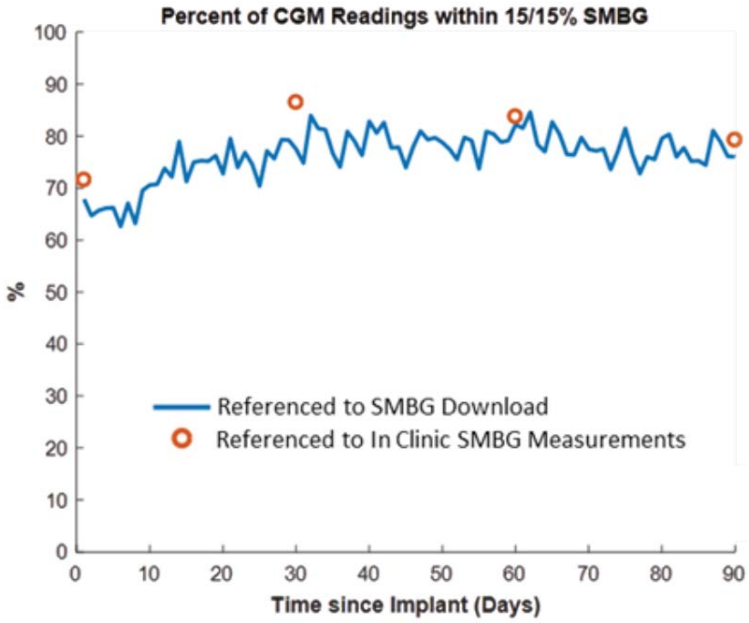
- As a percent of the total sensor wear time, the amount of accuracy data available is significantly less than what has been available for other approved sensors

Because of the long delay between successive in-clinic accuracy sessions (30 days), it was not clear when the system performance improved from the level of accuracy observed on day one to that observed on day 30. For example, it was not clear whether the performance improved by day 2, or by day 20.

To contrast this situation with accuracy studies conducted to support approval of other CGM systems, previously approved sensors with a 6 or 7 day wear period had 3 to 4 sensor accuracy visit days within those 7 days, with durations of 8 hours or greater.

Further, this data does not address whether system accuracy might deteriorate after day 1 before improving ahead of day 30. Senseonics had previously described how the body's inflammatory response to the sensor implantation procedure was a known source of degradation (which lead to the addition of the DXA containing collar on the sensor). This inflammatory response would be changing significantly over the first few weeks after sensor implantation as the wound site attempted to heal itself. There was therefore a particular interest to see what the system accuracy looked like during the course of this wound healing process. Senseonics provided the following plot of system performance when compared to measurements taken by study participants using SMBG devices during the at-home portions of the study.

Table 8 *- The rate that CGM measurements agreed with subject-collected SMBG measurements, as observed during the PRECISE II study, within a range of 15 mg/dL for SMBG measurements below 80 mg/dL, and within 15% for measurements above 80 mg/dL.*



While not a very detailed analysis, this plot seemed to indicate that sensor accuracy may remain low for several days before improving. To resolve these questions, Senseonics proposed to provide additional accuracy data during the early sensor wear period in order to provide a better picture of what true system performance would be. Senseonics conducted a supplementary clinical study, referred to as the PRECISION study, which is described in the following section.

ii. Eversense CGM Supplementary Clinical Study (PRECISION study)

Senseonics initiated this study to provide additional precision data and to more thoroughly assess sensor performance on day 1 and within the first month of sensor wear. PRECISION is a non-randomized, prospective, single-arm, unblinded, multi-center study enrolling adult subjects with diabetes mellitus in the United States at up to 4 sites. The investigation includes both clinic visits and home use of the Senseonics CGM System. Subjects have one or two sensors inserted in the upper arms by trained Investigators. Accuracy is assessed by comparing CGM glucose with laboratory comparator values. For qualifying subjects during the clinic visits, there were planned hyperglycemia and hypoglycemia challenges. Accuracy was also assessed during compression in overnight sleep challenges.

The study was also used to assess systemic exposure to DXA. To address this question, a subset of 8 subjects with one Sensor inserted into the left arm had blood samples drawn at 30 minutes, 1 hour, 2 hours and 4 hours post-insertion and then daily for at least the first 8 days of Sensor wear for additional DXA evaluation and to determine blood draw time points during the first week of Sensor wear for the remaining subjects. The remaining 27 subjects had 2 Sensors inserted, one in each arm, and underwent blood draws for DXA evaluation 2 hours post-insertion. All subjects had blood samples drawn for DXA evaluation at each visit and during each calendar day at the visits that spanned two days (i.e., days 1, 7 and 14).

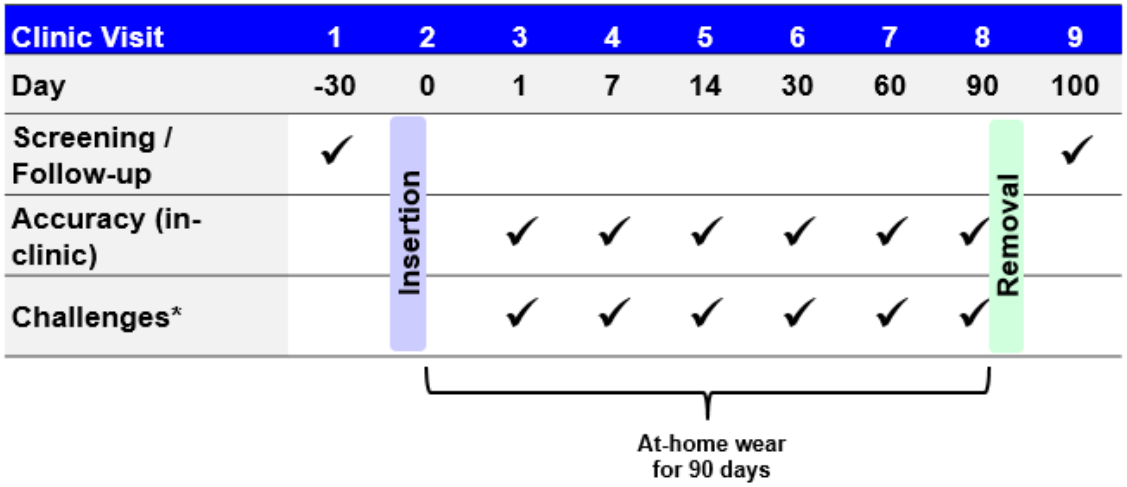


Figure 13 *- PRECISION Study Design*

PRECISION Study Results

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 Grade 4 infection in a patient's foot.

A total of 8 device or procedure-related AEs were reported in 5 (14.3%) patients in the PRECISION study. Note that 27 patients had 2 Sensors inserted in this study.

Table 9 *- Adverse events observed during the PRECISION clinical studies*

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

Regarding the adverse event "Unsuccessful removal of sensor," there was one similar event in the PRECISE II study, as described in that section above. In that case, the sensor was successfully removed on a subsequent attempt by a surgeon. That case was determined to be an SAE because general anesthesia was used. The two similar cases that occurred in the PRECISION study were determined to be AEs as only local anesthesia was required.

The following tables summarize the PRECISION study accuracy results.

Table 10 *– Concurrence between CGM readings and comparator method (YSI) on* ***day 1*** *of sensor wear during the PRECISION clinical study. The table is arranged by each YSI glucose range (first column) and tabulates, for each range of YSI glucose readings, the percentage of paired CGM values that were in the identical glucose range (shaded diagonal), as well as those reference values that were in glucose ranges above and below the paired YSI readings.*

Day 1	Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)											
YSI (mg/dL)	Number of Paired CGM-YSI	<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
< 40	4	--	75%	25%	--	--	--	--	--	--	--	--
40-60	222	--	73%	24%	3%	--	--	--	--	--	--	--
61-80	469	--	21%	52%	26%	--	--	--	--	--	--	--
81-120	470	--	2%	16%	70%	12%	--	--	--	--	--	--
121-160	361	--	--	1%	17%	64%	15%	3%	--	--	--	--
161-200	242	--	--	--	--	17%	54%	27%	2%	--	--	--
201-250	254	--	--	--	--	1%	15%	58%	20%	4%	1%	--
251-300	245	--	--	--	--	--	--	17%	48%	27%	8%	--
301-350	234	--	--	--	--	--	--	--	12%	45%	42%	--
351-400	154	--	--	--	--	--	--	--	1%	42%	56%	--
> 400	10	--	--	--	--	--	--	--	--	20%	80%	--

Table 11 *- CGM concurrence to YSI on* ***day 7*** *of the PRECISION study*

Day 7	Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	7	--	100%	--	--	--	--	--	--	--	--	--
40-60	213	--	56%	35%	9%	--	--	--	--	--	--	--
61-80	472	--	18%	61%	18%	2%	--	--	--	--	--	--
81-120	472	--	--	8%	79%	12%	--	--	--	--	--	--
121-160	391	--	--	--	14%	67%	18%	1%	--	--	--	--
161-200	253	--	--	--	--	13%	66%	19%	1%	--	--	--
201-250	281	--	--	--	--	--	19%	57%	23%	1%	--	--
251-300	194	--	--	--	--	--	--	12%	66%	21%	2%	--
301-350	369	--	--	--	--	--	--	--	17%	66%	16%	--
351-400	272	--	--	--	--	--	--	--	--	36%	64%	--
> 400	2	--	--	--	--	--	--	--	--	--	100%	--

Table 12 *- CGM concurrence to YSI on* ***day 14*** *of the PRECISION study*

Day 14	Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	4	--	50%	50%	--	--	--	--	--	--	--	--
40-60	273	--	61%	36%	3%	--	--	--	--	--	--	--
61-80	423	--	22%	62%	16%	--	--	--	--	--	--	--
81-120	416	--	2%	10%	73%	13%	1%	--	--	--	--	--
121-160	434	--	--	--	10%	75%	15%	--	--	--	--	--
161-200	262	--	--	--	--	17%	68%	15%	--	--	--	--
201-250	290	--	--	--	--	--	17%	72%	10%	--	--	--
251-300	199	--	--	--	--	--	1%	21%	67%	11%	--	--
301-350	371	--	--	--	--	--	--	--	16%	69%	15%	--
351-400	307	--	--	--	--	--	--	--	--	34%	66%	--
> 400	18	--	--	--	--	--	--	--	--	--	100%	--

Table 13 *- CGM concurrence to YSI on* ***day 30*** *of the PRECISION study*

Day 30	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	262	--	57%	42%	--	--	--	--	--	--	--	--
61-80	405	--	15%	69%	17%	--	--	--	--	--	--	--
81-120	437	--	--	6%	74%	20%	--	--	--	--	--	--
121-160	326	--	--	--	8%	78%	14%	1%	--	--	--	--
161-200	272	--	--	--	--	19%	61%	19%	--	--	--	--
201-250	192	--	--	--	--	--	16%	71%	13%	--	--	--
251-300	117	--	--	--	--	--	--	20%	75%	5%	--	--
301-350	156	--	--	--	--	--	--	--	31%	68%	1%	--
351-400	113	--	--	--	--	--	--	--	--	63%	37%	--
> 400	4	--	--	--	--	--	--	--	--	--	100%	--

Table 14 *- CGM concurrence to YSI on* ***day 60*** *of the PRECISION study*

Day 60	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI/Unique Subjects**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	167	--	69%	28%	2%	--	--	--	--	--	--	--
61-80	186	--	26%	62%	12%	--	--	--	--	--	--	--
81-120	317	--	--	4%	76%	20%	--	--	--	--	--	--
121-160	413	--	--	--	10%	67%	22%	1%	--	--	--	--
161-200	271	--	--	--	--	14%	73%	13%	--	--	--	--
201-250	219	--	--	--	--	--	27%	63%	10%	--	--	--
251-300	151	--	--	--	--	--	1%	22%	66%	11%	--	--
301-350	217	--	--	--	--	--	--	2%	30%	60%	7%	--
351-400	180	--	--	--	--	--	--	--	18%	49%	32%	--
> 400	12	--	--	--	--	--	--	--	25%	17%	58%	--

Table 15 *- CGM concurrence to YSI on* ***day 90*** *of the PRECISION study*

Day 90	**Percent of Matched Pairs in Each CGM Glucose Range for Each YSI Range CGM (mg/dL)**											
YSI (mg/dL)	**Number of Paired CGM-YSI/Unique Subjects**	**<40**	**40-60**	**61-80**	**81-120**	**121-160**	**161-200**	**201-250**	**251-300**	**301-350**	**351-400**	**>400**
< 40	0	--	--	--	--	--	--	--	--	--	--	--
40-60	130	--	51%	45%	4%	--	--	--	--	--	--	--
61-80	257	--	15%	58%	26%	--	--	--	--	--	--	--
81-120	328	--	--	4%	67%	29%	1%	--	--	--	--	--
121-160	433	--	--	--	6%	71%	23%	--	--	--	--	--
161-200	277	--	--	--	1%	18%	64%	18%	--	--	--	--
201-250	260	--	--	--	--	1%	17%	72%	10%	--	--	--
251-300	118	--	--	--	--	--	--	36%	60%	3%	--	--
301-350	180	--	--	--	--	--	--	1%	44%	49%	6%	--
351-400	148	--	--	--	--	--	--	--	5%	59%	36%	--
> 400	34	--	--	--	--	--	--	--	--	24%	76%	--

During the PRECISION study, 100% of Sensors were functional through 90 days.

DXA Exposure Results

A subset of 8 subjects with one Sensor inserted into the left arm had blood samples drawn at 30 minutes, 2 hours and 4 hours post-insertion and then daily for at least the first 8 days of Sensor wear for additional DXA evaluation and to determine blood draw time points during the first week of Sensor wear for the remaining subjects. The assay used to measure DXA in plasma had a detection limit of 50 pg/mL. The analysis showed that DXA greater than 50 pg/ml was not detected in any subject during the first 8 days nor at subsequent visits through 90 days in this group.

The remaining subjects had 2 Sensors inserted, one in each arm, and underwent blood draws for DXA evaluation 2 hours after insertion and at every clinic visit including 2 draws on clinic visits that spanned two calendar days. There were 18 of 27 (66%) subjects with two Sensors that had detectable levels above 50 pg/ml in the first 8 days. In all cases in these 18 subjects, the plasma DXA was below the detectable limit of 50 pg/mL by day 8 post-insertion. The maximum level detected was 114 pg/ml at day 2 in one subject which fell below the detection limit by day 7. DXA greater than 50 pg/ml was not detected at subsequent visits through 90 days in this group.

The results from the DXA measurements taken throughout this study are provided below in Table 16 below.

Table 16 *- Plasma DXA measurements in subjects during the PRECISION clinical study. Subjects with 1 sensor implanted had serial measurements collected on the day of sensor insertion, all of which showed DXA values below the cutoff of 0.050 ng/mL.*

Time After Insertion	Subjects with 1 Sensor (n=8)	Subjects with 2 Sensors (n=27)
	Detections >0.050 ng/mL	Detections >0.050 ng/mL
Day 0 (Immediate Post Insertion)	0	0
Day 1	0	18
Day 2*	0	10
Day 3	0	0
Day 4	0	0
Day 5	0	0
Day 6	0	0
Day 7	0	1
Day 8	0	1
Day 9	0	0
Day 14	0	0
Day 15	0	0
Day 30	0	0

* Highest detected amount was 114 pg/mL on Day 2

Sensors removed from patients in clinical studies were returned to Senseonics for evaluation of residual DXA content. Explanted Sensors retained approximately 80-90% of their original DXA content at 90 days. This corresponds to approximately 0.18 - 0.35 mg of DXA being released into the body from a single Sensor over the course of 90 days.

VII. Design Changes after US Clinical Studies

The device Senseonics has proposed for approval is not identical to the device studied in the two pivotal clinical studies. After conducting the clinical studies, Senseonics made several design changes to the Eversense CGM system. The changes are presented below, along with a summary of the supporting information Senseonics has provided to support approval of these changes.

i. New System Algorithm

Senseonics has proposed to implement a modified software algorithm that is used to calculate sensor glucose values. Senseonics states that the purpose of this algorithm is to improve system accuracy, particularly in the early sensor wear period and in the hypoglycemic range.

One key element of the system that is responsible for Sensor performance and accuracy is the glucose determination algorithm (which includes the finger-stick calibration algorithm). The glucose determination algorithm is pre-programmed in the transmitter firmware, and it converts the raw data collected by the Sensor into glucose readings.

The version of this algorithm that was used during the US clinical studies is referred to as the "study software" and is abbreviated "study SW." The proposed new version of this algorithm is referred to as "software version 602" and is abbreviated "SW 602."

The algorithm changes within the SW 602 algorithm version targeted accuracy improvement in: 1) the early Sensor life, and 2) the hypoglycemic range throughout the Sensor life. The clinical accuracy data from a 71-subject European pivotal study, PRECISE (Kropff, Choudhary, Neupane, & Barnard, 2017), was used for as a training set for this new algorithm. Data from the PRECISE II study and PRECISION study were not used to develop the new algorithm (SW 602).

Senseonics has not studied this new algorithm (SW 602) in real-time in a clinical trial. Rather, they have *post hoc* processed the raw sensor data from the PRECISE II and PRECISION studies using the new algorithm. Senseonics stated that the raw sensor data is independent of this algorithm, so performing this processing post-hoc should yield the same final glucose values as if the algorithm had been used during the study.

This type of *post hoc* processing of raw sensor data has been used previously by CGM companies to validate new system algorithms. The Agency has accepted this approach in the past when the algorithm has been validated using valid clinical datasets which are independent of the dataset(s) used to develop and train the algorithm.

Tables 17-20 provide examples of the performance changes due to the change to SW 602. Tables 17 and 18 are the day 1 data from PRECISE II with study SW and SW 602, respectively. Tables 19 and 20 are the day 1 data from PRECISION with study SW and SW 602, respectively.

Table 17 *- PRECISE II study results for day 1 of sensors wear, as measured during the study using the original algorithm* ***(Study-SW)***

YSI Glucose Range (mg/dL)	Number of Paired Senseonics CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall (40-400)	1646	74.7%	84.9%	94.4%	97.9%	2.1%
<40	0	0%	0%	0%	0%	0%
40 - 60	20	60.0%	85.0%	95.0%	95.0%	5.0%
61 - 80	76	69.7%	78.9%	94.7%	100.0%	0%
81 - 180	1048	71.6%	82.7%	92.8%	97.2%	2.8%
181 - 300	486	82.3%	90.1%	97.5%	99.0%	1.0%
301 - 350	16	93.8%	100.0%	100.0%	100.0%	0%
351 - 400	0	0%	0%	0%	0%	0%
> 400	0	0%	0%	0%	0%	0%

Table 18 - *PRECISE II study results for day 1 of sensor wear, obtained after re-analyzing the raw sensor data using the new algorithm* ***(SW-602)***

YSI Glucose Range (mg/dL)	Number of Paired Senseonics CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall (40-400)	1708	76.8%	87.1%	96.3%	98.5%	1.5%
< 40	0	0%	0%	0%	0%	0%
40 - 60	39	59.0%	76.9%	87.2%	94.9%	5.1%
61 - 80	107	59.8%	67.3%	83.2%	91.6%	8.4%
81 - 180	1024	77.1%	88.5%	97.4%	99.0%	1.0%
181 - 300	519	80.9%	88.8%	97.3%	99.0%	1.0%
301 - 350	19	84.2%	100.0%	100.0%	100.0%	0%
351 - 400	0	0%	0%	0%	0%	0%
> 400	0	0%	0%	0%	0%	0%

Table 19 - *In-clinic accuracy results from day 1 of the PRECISION study, as measured during the study using the original algorithm* ***(Study-SW)***

YSI Glucose Range (mg/dL)	Number of Paired CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall	2450	65.8%	78.9%	91.3%	95.9%	4.1%
< 40	4	0%	0%	50.0%	75.0%	25.0%
40 - 60	196	48.0%	71.9%	92.9%	98.0%	2.0%
61 - 80	426	57.5%	75.1%	92.7%	96.0%	4.0%
81 - 180	898	60.2%	72.0%	85.7%	92.9%	7.1%
181 - 300	527	70.0%	82.4%	93.0%	97.2%	2.8%
301 - 350	222	83.8%	96.4%	100.0%	100.0%	0%
351 - 400	170	100.0%	100.0%	100.0%	100.0%	0%
> 400	7	100.0%	100.0%	100.0%	100.0%	0%

Table 20 *– In-clinic accuracy results from day 1 of the PRECISION study, obtained after re-analyzing the raw sensor data using the new algorithm* ***(SW-602)***

YSI Glucose Range (mg/dL)	Number of Paired CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall	2665	79.1%	88.9%	95.8%	98.5%	1.5%
< 40	4	50.0%	75.0%	75.0%	100.0%	0.0%
40 - 60	222	86.5%	92.8%	96.8%	100.0%	0.0%
61 - 80	469	81.9%	90.0%	97.4%	98.9%	1.1%
81 - 180	974	74.3%	84.6%	93.4%	96.9%	3.1%
181 - 300	598	77.6%	89.0%	95.5%	99.3%	0.7%
301 - 350	234	82.9%	93.6%	100.0%	100.0%	0.0%
351 - 400	154	90.3%	100.0%	100.0%	100.0%	0.0%
> 400	10	100.0%	100.0%	100.0%	100.0%	0.0%

Senseonics has proposed to use the clinical accuracy results obtained with the SW 602 algorithm to support the safety and efficacy of the Eversense CGM system. If approved, they propose to use this algorithm in the marketed device. The following tables provide a representation of system accuracy results during the PRECISE II and PRECISION studies on each day of sensor wear using the SW 602 algorithm.

Table 21 *– CGM System agreement to YSI comparator method, with YSI glucose ranges;* ***PRECISE II*** *study data analyzed using SW-602 algorithm, data pooled from all four in-clinic accuracy visits* ***(days 1, 30, 60, and 90)***

YSI Glucose Range (mg/dL)	Number of Paired CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall	18310	86.4	93.7	98.3	99.5	0.5
< 40	8	62.5	62.5	87.5	87.5	12.5
40 - 60	532	86.5	92.5	97.6	99.8	0.2
61 - 80	1291	83.0	90.4	96.6	98.7	1.3
81 - 180	9168	85.3	92.6	97.9	99.3	0.7
181 - 300	5982	88.2	95.5	99.1	99.8	0.2
301 - 350	923	88.8	97.3	99.8	100.0	0.0
351 - 400	371	87.9	96.8	98.7	100.0	0.0
> 400	35	91.4	100.0	100.0	100.0	0.0

Table 22 *– CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISE II*** *study data from* ***day 1****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	1	100%	--	--	--	--	--	--	--	--
40-60	27	63%	37%	--	--	--	--	--	--	--
61-80	91	21%	59%	20%	--	--	--	--	--	--
81-120	451	1%	9%	71%	19%	--	--	--	--	--
121-160	567	--	2%	20%	60%	17%	1%	--	--	--
161-200	471	--	--	1%	18%	61%	19%	1%	--	--
201-250	259	--	--	--	--	17%	68%	15%	--	--
251-300	87	--	--	--	--	1%	28%	62%	9%	--
301-350	16	--	--	--	--	--	--	31%	69%	--
351-400	0	--	--	--	--	--	--	--	--	--
>400	0	--	--	--	--	--	--	--	--	--

Table 23 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISE II*** *study data from* ***day 30****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	5	60%	20%	20%	--	--	--	--	--	--
40-60	222	56%	42%	2%	--	--	--	--	--	--
61-80	571	11%	66%	22%	2%	--	--	--	--	--
81-120	1439	--	7%	81%	12%	--	--	--	--	--
121-160	1372	--	--	13%	77%	10%	--	--	--	--
161-200	913	--	--	--	17%	73%	9%	--	--	--
201-250	793	--	--	--	--	21%	73%	5%	--	--
251-300	370	--	--	--	--	--	22%	69%	9%	--
301-350	161	--	--	--	--	--	3%	34%	53%	9%
351-400	84	--	--	--	--	--	--	5%	30%	65%
>400	4	--	--	--	--	--	--	--	--	100%

Table 24 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISE II*** *study data from* ***day 60****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	0	--	--	--	--	--	--	--	--	--
40-60	157	77%	20%	3%	--	--	--	--	--	--
61-80	317	21%	54%	26%	--	--	--	--	--	--
81-120	1053	--	8%	82%	10%	--	--	--	--	--
121-160	1023	--	--	11%	74%	15%	--	--	--	--
161-200	897	--	--	--	18%	65%	16%	--	--	--
201-250	969	--	--	--	1%	18%	68%	13%	--	--
251-300	555	--	--	--	--	1%	28%	61%	10%	--
301-350	395	--	--	--	--	--	2%	41%	54%	3%
351-400	143	--	--	--	--	--	1%	10%	49%	40%
>400	10	--	--	--	--	--	--	--	20%	80%

Table 25 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISE II*** *study data from* ***day 90****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	2	100%	--	--	--	--	--	--	--	--
40-60	126	39%	51%	10%	--	--	--	--	--	--
61-80	312	10%	55%	35%	--	--	--	--	--	--
81-120	730	--	7%	76%	16%	1%	--	--	--	--
121-160	908	--	--	11%	75%	13%	--	--	--	--
161-200	839	--	--	1%	21%	68%	10%	1%	--	--
201-250	884	--	--	--	3%	27%	62%	7%	--	--
251-300	570	--	--	--	--	1%	41%	49%	10%	--
301-350	351	--	--	--	--	--	1%	42%	46%	10%
351-400	144	--	--	--	--	--	--	1%	44%	55%
>400	21	--	--	--	--	--	--	--	5%	95%

Table 26 *- CGM System agreement to YSI comparator method, with YSI glucose ranges;* ***PRECISION*** *study data analyzed using SW-602 algorithm, data pooled from all six in-clinic accuracy visits (****days 1, 7, 14, 30, 60, and 90****)*

YSI Glucose Range (mg/dL)	Number of Paired CGM and YSI	Percent of CGM System Readings Within				
		Percent 15/15% of YSI	Percent 20/20% of YSI	Percent 30/30% of YSI	Percent 40/40% of YSI	Percent Greater than 40/40% of YSI
Overall	15170	85.4%	92.8%	98.1%	99.3%	0.7%
< 40	15	60.0%	73.3%	86.7%	100.0%	0.0%
40 - 60	1267	86.8%	92.6%	98.1%	99.1%	0.9%
61 - 80	2212	85.8%	93.0%	98.5%	99.3%	0.7%
81 - 180	5685	80.6%	89.4%	96.7%	98.8%	1.2%
181 - 300	3210	87.4%	94.9%	98.6%	99.8%	0.2%
301 - 350	1527	91.4%	97.8%	100.0%	100.0%	0.0%
351 - 400	1174	93.4%	97.5%	99.7%	100.0%	0.0%
> 400	80	81.3%	93.8%	97.5%	100.0%	0.0%

Table 27 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 1****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	4	75%	25%	--	--	--	--	--	--	--
40-60	222	73%	24%	3%	--	--	--	--	--	--
61-80	469	21%	52%	26%	--	--	--	--	--	--
81-120	470	2%	16%	70%	12%	--	--	--	--	--
121-160	361	--	1%	17%	64%	15%	3%	--	--	--
161-200	242	--	--	--	17%	54%	27%	2%	--	--
201-250	254	--	--	--	1%	15%	58%	20%	4%	1%
251-300	245	--	--	--	--	--	17%	48%	27%	8%
301-350	234	--	--	--	--	--	--	12%	45%	42%
351-400	154	--	--	--	--	--	--	1%	42%	56%
>400	10	--	--	--	--	--	--	--	20%	80%

Table 28 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 7****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	7	100%	--	--	--	--	--	--	--	--
40-60	213	56%	35%	9%	--	--	--	--	--	--
61-80	472	18%	61%	18%	2%	--	--	--	--	--
81-120	472	--	8%	79%	12%	--	--	--	--	--
121-160	391	--	--	14%	67%	18%	1%	--	--	--
161-200	253	--	--	--	13%	66%	19%	1%	--	--
201-250	281	--	--	--	--	19%	57%	23%	1%	--
251-300	194	--	--	--	--	--	12%	66%	21%	2%
301-350	369	--	--	--	--	--	--	17%	66%	16%
351-400	272	--	--	--	--	--	--	--	36%	64%
>400	2	--	--	--	--	--	--	--	--	100%

Table 29 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 14****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	4	50%	50%	--	--	--	--	--	--	--
40-60	273	61%	36%	3%	--	--	--	--	--	--
61-80	423	22%	62%	16%	--	--	--	--	--	--
81-120	416	2%	10%	73%	13%	1%	--	--	--	--
121-160	434	--	--	10%	75%	15%	--	--	--	--
161-200	262	--	--	--	17%	68%	15%	--	--	--
201-250	290	--	--	--	--	17%	72%	10%	--	--
251-300	199	--	--	--	--	1%	21%	67%	11%	--
301-350	371	--	--	--	--	--	--	16%	69%	15%
351-400	307	--	--	--	--	--	--	--	34%	66%
>400	18	--	--	--	--	--	--	--	--	100%

Table 30 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 30****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	0	--	--	--	--	--	--	--	--	--
40-60	262	57%	42%	--	--	--	--	--	--	--
61-80	405	15%	69%	17%	--	--	--	--	--	--
81-120	437	--	6%	74%	20%	--	--	--	--	--
121-160	326	--	--	8%	78%	14%	1%	--	--	--
161-200	272	--	--	--	19%	61%	19%	--	--	--
201-250	192	--	--	--	--	16%	71%	13%	--	--
251-300	117	--	--	--	--	--	20%	75%	5%	--
301-350	156	--	--	--	--	--	--	31%	68%	1%
351-400	113	--	--	--	--	--	--	--	63%	37%
>400	4	--	--	--	--	--	--	--	--	100%

Table 31 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 60****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	0	--	--	--	--	--	--	--	--	--
40-60	167	69%	28%	2%	--	--	--	--	--	--
61-80	186	26%	62%	12%	--	--	--	--	--	--
81-120	317	--	4%	76%	20%	--	--	--	--	--
121-160	413	--	--	10%	67%	22%	1%	--	--	--
161-200	271	--	--	--	14%	73%	13%	--	--	--
201-250	219	--	--	--	--	27%	63%	10%	--	--
251-300	151	--	--	--	--	1%	22%	66%	11%	--
301-350	217	--	--	--	--	--	2%	30%	60%	7%
351-400	180	--	--	--	--	--	--	18%	49%	32%
>400	12	--	--	--	--	--	--	25%	17%	58%

Table 32 *- CGM System concurrence to YSI organized by YSI glucose ranges;* ***PRECISION*** *study data from* ***day 90****, analyzed using SW-602 algorithm*

YSI (mg/dL)	Number of Paired CGM-YSI	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	0	--	--	--	--	--	--	--	--	--
40-60	130	51%	45%	4%	--	--	--	--	--	--
61-80	257	15%	58%	26%	--	--	--	--	--	--
81-120	328	--	4%	67%	29%	1%	--	--	--	--
121-160	433	--	--	6%	71%	23%	--	--	--	--
161-200	277	--	--	1%	18%	64%	18%	--	--	--
201-250	260	--	--	--	1%	17%	72%	10%	--	--
251-300	118	--	--	--	--	--	36%	60%	3%	--
301-350	180	--	--	--	--	--	1%	44%	49%	6%
351-400	148	--	--	--	--	--	--	5%	59%	36%
>400	34	--	--	--	--	--	--	--	24%	76%

Use of at-home SMBG data to supplement in-clinic accuracy data

During the two US clinical studies, in-clinic accuracy data was collected with up to 30 days between successive in-clinic sessions. To help understand how the system performs between in-clinic sessions, Senseonics provided accuracy assessments using subjects' SMBG measurements collected during the at-home portion of the PRECISE II and PRECISION studies. This data is provided in appendix 5 (PRECISE II data) and appendix 6 (PRECISION data). A selection of this data is provided below.

While reviewing the data below it should be noted that SMBG devices are less accurate and precise than the laboratory comparator method used during the in-clinic accuracy sessions. It is recommended that this data be used to look at general trends in CGM system performance; it may not be as useful to assess point accuracy.

Table 33 *– CGM accuracy observed during the PRECISE II study, as compared to SMBG measurements obtained by study subjects during the at-home portions of the sudy. For each SMBG range, this table shows the percent of CGM measurements that were within 15 mg/dL of paired SMBG measurements for values below 80 mg/dL, or within 15% for values above 80 mg/dL. Data is grouped by sensor wear day ranges.*

		Percent of CGM System Readings within 15/15% of SMBG Day Ranges						
SMBG Range	**N**	**1-7**	**8-14**	**15-29**	**30-44**	**45-59**	**60-74**	**75-90**
<40	73	50.0%	75.0%	69.2%	50.0%	78.6%	38.5%	63.6%
40-60	1224	74.7%	82.5%	89.4%	87.4%	82.7%	80.5%	82.8%
61-80	2275	72.8%	71.3%	81.0%	83.4%	79.8%	74.8%	75.9%
81-180	18879	66.9%	71.1%	76.1%	79.5%	79.4%	79.0%	78.8%
181-300	10504	75.6%	78.1%	82.5%	85.2%	86.7%	88.5%	83.8%
301-350	1105	82.3%	83.9%	78.3%	84.1%	81.7%	89.7%	83.4%
351-400	432	75.8%	73.2%	71.4%	72.1%	73.8%	79.8%	73.7%
>400	168	53.3%	44.4%	43.8%	46.2%	46.7%	33.3%	67.7%

Table 34 *- The rate at which CGM bias was greater than 40 mg/dl for values below 80 mg/dL, or 40% for values above 80 mg/dL, as assessed by paired SMBG measurements obtained by study subjects during the PRECISION study. Data is grouped by sensor wear day ranges.*

		Percent of CGM System Readings beyond 40/40% of CM Day Ranges						
SMBG Range	**N**	**1-7**	**8-14**	**15-29**	**30-44**	**45-59**	**60-74**	**75-90**
<40	73	7.1%	25.0%	0.0%	25.0%	7.1%	15.4%	36.4%
40-60	1224	4.2%	3.9%	2.7%	2.0%	5.3%	5.6%	0.5%
61-80	2275	3.0%	1.9%	2.0%	1.0%	0.5%	1.9%	2.5%
81-180	18879	3.2%	2.7%	1.3%	1.1%	1.2%	1.3%	1.1%
181-300	10504	2.1%	0.6%	0.6%	0.3%	0.3%	0.4%	0.5%
301-350	1105	0.0%	0.0%	0.6%	0.0%	0.0%	2.1%	0.6%
351-400	432	3.0%	2.4%	4.3%	1.5%	0.0%	2.2%	1.8%
>400	168	20.0%	0.0%	6.3%	3.8%	0.0%	6.7%	3.2%

Table 35 – *CGM accuracy observed during the PRECISION study, as compared to SMBG measurements obtained by study subjects during the at-home portions of the sudy. For each SMBG range, this table shows the percent of CGM measurements that were within 15 mg/dL of paired SMBG measurements for values below 80 mg/dL, or within 15% for values above 80 mg/dL. Data is grouped by sensor wear day ranges.*

		Percent of CGM System Readings within 15/15% of CM Day Ranges						
SMBG Range	**N**	**1-7**	**8-14**	**15-29**	**30-44**	**45-59**	**60-74**	**75-90**
<40	5	0.0%	--	--	--	100.0%	100.0%	100.0%
40-60	433	77.2%	92.5%	83.3%	77.3%	77.9%	89.8%	79.2%
61-80	1128	78.7%	78.6%	84.8%	76.2%	72.8%	71.6%	73.4%
81-180	9586	62.9%	72.3%	72.7%	75.8%	77.8%	77.9%	72.2%
181-300	5868	73.1%	77.8%	78.0%	79.8%	83.0%	80.9%	74.1%
301-350	868	82.5%	82.1%	78.7%	82.0%	68.8%	76.2%	76.3%
351-400	390	90.8%	89.8%	79.7%	76.9%	79.4%	58.8%	79.5%
>400	91	60.0%	80.0%	35.7%	37.5%	60.0%	44.4%	57.1%

Table 36 – *The rate at which CGM bias was greater than 40 mg/dl for values below 80 mg/dL, or 40% for values above 80 mg/dL, as assessed by paired SMBG measurements obtained by study subjects during the PRECISION study. Data is grouped by sensor wear day ranges.*

		Percent of CGM System Readings beyond 40/40% of CM Day Ranges						
SMBG Range	**N**	**1-7**	**8-14**	**15-29**	**30-44**	**45-59**	**60-74**	**75-90**
<40	5	0.0%	--	--	--	0.0%	0.0%	0.0%
40-60	433	7.0%	0.0%	1.3%	1.5%	2.9%	2.0%	7.5%
61-80	1128	1.1%	1.7%	0.5%	0.0%	0.6%	2.1%	7.1%
81-180	9586	3.9%	2.4%	1.5%	1.5%	1.0%	1.4%	3.5%
181-300	5868	1.2%	1.7%	0.9%	0.8%	0.2%	0.5%	3.7%
301-350	868	0.0%	0.0%	1.2%	0.0%	0.9%	0.0%	5.3%
351-400	390	0.0%	0.0%	0.0%	2.6%	0.0%	2.0%	0.0%
>400	91	0.0%	0.0%	7.1%	25.0%	13.3%	7.4%	0.0%

Hypoglycemia Alert Performance (with SW-602):

Since CGMs evaluate users' glucose levels continuously, and in real time, they allow for configurable alerts.

- The hypoglycemia confirmed event detection rate (see Table 37 below) is the rate that the device alerted when it should have alerted. It is the ratio of the number of times an alert was sounded when blood glucose was below the threshold to the total number of times blood glucose went below the threshold.
- The Missed Event Detection Rate is the rate at which the device did not alert when it should have (i.e., the rate at which blood glucose, as measured by comparator method, was below the low glucose alert threshold and the device did not sound an alert – this is the complement of the confirmed event detection rate). Missed detection rates are important in hypoglycemic conditions because it is important that users be notified when their blood sugar is low so that they can correct the low blood sugar. A low missed detection rate indicates that users can have confidence that they will be notified by the device if their blood sugar is low.
- The true alert rate is the ratio of the number of times an alert was sounded while blood glucose was below the alert threshold to the total number of times an alert was sounded (i.e. if 100 alerts were given saying "your glucose level is below 70," and for 90 of those alerts it was verified that blood glucose was indeed below 70, then the true alert rate would be 90%).
- The false alert rate is the complement of the true alert rate (i.e. if the true alert rate is 90%, the false alert rate would be 10%).

Table 37 - *The Hypoglycemia alert performance for various alert thresholds as observed in the PRECISE II study, using the new SW-602 algorithm, with data pooled for all four in-clinic accuracy visits (days 1, 30, 60, and 90)*

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

Table 38 *- The Hypoglycemia alert performance for various alert thresholds as observed in the PRECISION study, using the new SW-602 algorithm, with data pooled for all six in-clinic accuracy visits (days 1, 7, 14 30, 60, and 90)*

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60	89%	11%	77%	23%
70	95%	5%	92%	8%
80	97%	3%	93%	7%
90	98%	2%	93%	7%

For additional assessment of hypoglycemia alert performance using the SW-602 algorithm, see appendix 3 (PRECISE II study) and appendix 4 (PRECISION study). These appendices include alert accuracy by day. In general, these data show that the alert accuracy during the early sensor wear period (e.g. day 1) is worse than subsequent in-clinic assessment days.

Hyperglycemia Alert Performance with New Algorithm:
Likewise, users can set Eversense CGM alerts to indicate when blood glucose rises to high set thresholds (hyperglycemia alerts).

- The hyperglycemia confirmed event detection rate (see Table 39 below) is the rate that the device alerted when it should have alerted. It is the ratio of the number of times an alert was sounded when blood glucose was above the threshold to the total number of times blood glucose went above the threshold.
- The Missed Event Detection Rate is the rate at which the device did not alert when it should have (i.e., the rate at which blood glucose, as measured by comparator method, was above the high glucose alert threshold and the device did not sound an alert – this is the complement of the confirmed event detection rate).
- The true alert rate is the ratio of the number of times an alert was sounded while blood glucose was above the alert threshold to the total number of times an alert was sounded (i.e. if 100 alerts were given saying “your glucose level is above 300,” and for 90 of those alerts it was verified that blood glucose was indeed above 300, then the true alert rate would be 90%).
- The False Alert Rate (see Table 40 below) is the ratio of the number of times that the alarm incorrectly alerted when the users’ glucose was actually below the high threshold to the total number of times it alerted. False alert rates are important in hyperglycemic conditions because if a user is falsely notified that their blood sugar is high, they might treat themselves based on this false high result inappropriately. A

low false alert rate gives a user confidence that the glucose values in the hyperglycemic range are likely to be accurate most of the time.

Table 39 *- The Hyperglycemia alert performance for various alert thresholds as observed during the PRECISE II study with the SW-602 algorithm; data is pooled across all in-clinic study days.*

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120	98%	2%	96%	4%
140	99%	1%	95%	5%
180	97%	3%	94%	6%
200	95%	5%	93%	7%
220	94%	6%	91%	9%
240	93%	7%	90%	10%
300	84%	16%	86%	14%

Table 40 *- The Hyperglycemia alert performance for various alert thresholds as observed during the PRECISION study with the SW-602 algorithm; data is pooled across all in-clinic study days.*

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

For additional assessment of hyperglycemia alert performance using the SW-602 algorithm, see appendix 3 (PRECISE II study) and appendix 4 (PRECISION study). These appendices include alert accuracy by day. In general, these data show that the alert accuracy during the early sensor wear period (e.g. day 1) is worse than subsequent in-clinic assessment days.

Please refer to appendix 3 (PRECISE II study) and appendix 4 (PRECISION study) for additional representation of in-clinic system accuracy using the SW-602 algorithm in both studies.

The Agency would like feedback from the panel on whether the information provided by Senseonics is sufficient to allow for the conclusion that the Eversense CGM system will be reasonably safe and effective when used with this new algorithm.

ii. Sensor Insertion Tools

The insertion tools, as pictured below, were used during the Eversense CGM clinical studies.

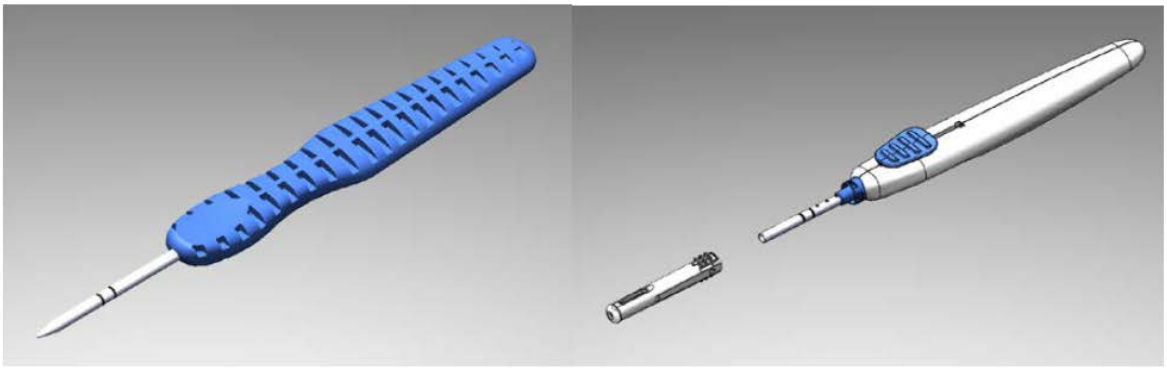


Figure 14 *- Sensor Insertion tools that were used for the PRECISE II and PRECISION clinical studies*

During review of this PMA, Senseonics has developed a new version of the Blunt Dissector tool (Figure 15 below). Senseonics states that this re-design is being made to mitigate the risk of physicians inserting sensors too deeply. This was observed once during the PRECISE II study, and the result was that exploratory surgery with the patient under general anesthesia was required to remove the sensor; this was categorized as a serious adverse event. This event happened three times during the PRECISION study, and a surgeon was able to remove the sensor in each case using local anesthesia.

The new blunt dissector design has not been used in clinical studies. Senseonics is seeking approval for this modified version of the blunt dissector in this PMA. The design of the blunt dissector has been updated to add two guides (indicated by an orange arrow in figure 15 below). Also, the metal dissector portion is now shorter, and the user inserts it fully into the subdermal space. Previously, there were two lines etched onto the metal portion of the dissector to indicate how deep it should be inserted (see Figure 14 above).

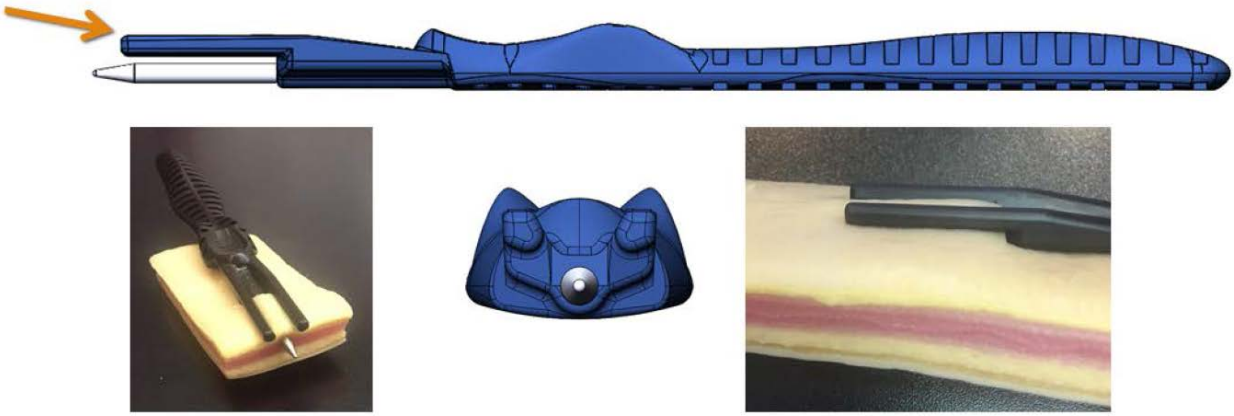


Figure 15 *- Updated design of the Blunt Dissector tool*

To validate the new blunt dissector tool, Senseonics performed a human factors study. The human factors study participants included 16 healthcare providers who treat patients with diabetes. Participants completed sessions that included a system overview, watching a training video, a discussion of the package insert, and product training using simulated skin and the insertion tools. The synthetic tissue used for this process was a commercially available product sold by Syndaver. This was followed by a decay period of at least one hour before participants completed a usability testing scenario. This usability test involved participants performing a complete sensor insertion procedure on simulated skin installed in a model human arm (to mimic realistic arm position). Participants had an assistant available to assist with ancillary tasks (i.e. handling materials so sterility could be maintained). Successful use of the blunt dissector was judged based on the final insertion depth of the sensor in the simulated skin. Correct sensor depth was judged based on whether the sensor could be palpated after implantation. A selection of these synthetic tissue specimens (four of the fifteen) were dissected later and the actual sensor depth was measured and found to be within the intended insertion depth of 3-5mm (actual depths ranged from 3.3 to 3.9 mm).

Senseonics concluded that all participants were able to use the tool successfully to create a satisfactory sensor pocket in synthetic tissue. The one error scenario reported was when a participant failed to load a sensor into the insertion tool before inserting the tool into the sensor pocket in the artificial tissue.

The Agency would like feedback from the panel on whether the approach taken by Senseonics to validate this change in insertion tool design (i.e. the use of non-clinical Human Factors testing) is sufficient to allow for the conclusion that the Eversense CGM system will be reasonably safe and effective when used with this new insertion tool.

As described above, during the PRECISE II and PRECISION clinical studies, there were a total of three adverse events where the Eversense sensor could not be removed at the first attempt. In all three cases the device was removed by a surgeon. In the one instance in the PRECISE II study, general anesthesia was used during the procedure. In the two instanced that occurred during the PRECISION study, the sensor was removed using local anesthesia.

To mitigate the risk of unsuccessful removal requiring additional interventions, Senseonics has updated the physician training so that it now emphasizes proper depth of placement to facilitate removal and includes instructions for management of difficult to remove Sensors.

The Agency would like feedback from the Panel on whether the information provided about the validation and use of the new blunt dissector design is adequate to demonstrate safe and effective use as part of the Eversense CGM system.

iii. Sensor End Cap

The Eversense sensor includes a plastic end cap that is attached using epoxy after the electronics assembly is installed. The function of the cap is to seal the end of the sensor and to provide a smooth, uniform surface.

During sensor removal procedures in the clinical studies, there were several instances where the end cap of the sensor was broken off or missing after sensor removal. In some cases, the broken end caps were located, and in other cases the end caps were not located. A root-cause analysis into this failure concluded that the cause was most likely physicians grasping the end cap with the forceps during removal, instead of grabbing the sensor body. To reduce the potential for this failure, Senseonics is proposing a redesigned sensor end cap (see Figure 16 below) which would be flush with the end of the sensor.

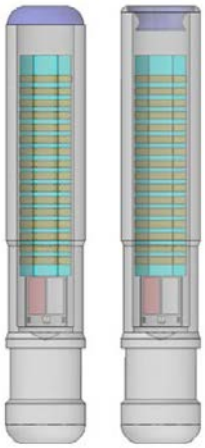


Figure 16 *- (A) Sensor design used in PRECISE II and PRECISION studies, and (B) the proposed new sensor design with modified end cap. This design has not been used in any clinical studies to date.*

This updated sensor design has not been studied in any clinical study. Senseonics has provided the results of manufacturing validation studies to demonstrate that the new sensors are being manufactured to the correct specifications. Part of this testing includes simulating the forces involved during sensor removal to demonstrate that the new end cap design can withstand greater forces than the previous design.

The Agency would like feedback from the panel on whether the approach taken by Senseonics to validate this change (i.e. the use of non-clinical testing) is sufficient to allow for the conclusion that the Eversense CGM system will be reasonably safe and effective when used with this new sensor design.

iv. New Transmitter

After the PRECISE-II study was concluded and prior to the start of the PRECISION study, Senseonics finished development of a new version of their Eversense system transmitter. The purpose of the new transmitter was to provide a thinner, lighter, and less obtrusive design. Figure 17 below provides a side-by-side visual comparison of the two transmitters.

Generation 1 Transmitter Design

Generation 2 Transmitter Design

Figure 17 *- Visual comparison between the Generation 1 and Generation 2 transmiters*

Senseonics explained to the Agency that they would prefer to obtain approval for the new Generation 2 (Gen-2) transmitter design. Senseonics included the Gen-2 transmitter as part of the PRECISION study. During the PRECISION study, 27 subjects had two sensors inserted (one in each arm). Each of these subjects wore one Gen-1 transmitter and one Gen-2 transmitter. Accuracy of each system was evaluated as part of the study. The results are presented below.

Table 41 *– Concurrence of CGM measurements collected using* ***Generation 1 transmitter*** *with paired YSI blood glucose measurements within YSI glucose ranges*

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	15	80%	20%	--	--	--	--	--	--	--
40-60	1267	62%	35%	3%	--	--	--	--	--	--
61-80	2212	19%	61%	20%	--	--	--	--	--	--
81-120	2440	1%	9%	73%	17%	--	--	--	--	--
121-160	2358	--	--	11%	70%	18%	1%	--	--	--
161-200	1577	--	--	--	16%	64%	18%	1%	--	--
201-250	1496	--	--	--	--	18%	65%	15%	1%	--
251-300	1024	--	--	--	--	--	20%	62%	15%	2%
301-350	1527	--	--	--	--	--	1%	23%	61%	16%
351-400	1174	--	--	--	--	--	--	4%	44%	53%
>400	80	--	--	--	--	--	--	4%	15%	81%

Table 42 - *Concurrence of CGM measurements collected using* ***Generation 2 transmitter*** *with paired YSI blood glucose measurements within YSI glucose ranges*

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each CGM System Glucose Range for Each YSI Glucose Range CGM (mg/dL)								
		40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400
<40	15	73%	20%	7%	--	--	--	--	--	--
40-60	938	63%	35%	2%	--	--	--	--	--	--
61-80	1631	16%	64%	19%	--	--	--	--	--	--
81-120	1733	1%	8%	74%	16%	1%	--	--	--	--
121-160	1527	--	--	11%	70%	17%	1%	--	--	--
161-200	1031	--	--	--	16%	65%	18%	1%	--	--
201-250	974	--	--	--	1%	18%	63%	16%	2%	--
251-300	729	--	--	--	--	2%	18%	54%	21%	5%
301-350	1154	--	--	--	--	--	2%	18%	57%	23%
351-400	946	--	--	--	--	--	--	2%	35%	63%
>400	37	--	--	--	--	--	--	--	8%	92%

Senseonics also assessed system availability to demonstrate that the new transmitter had a similar degree of reliability. System availability is assessed as the percentage of time the system provides glucose values, compared to the total time the sensor is inserted and active. For example, if the sensor is inserted for 24 hours, with a new glucose value being presented every 5 minutes this would be a total of 288 CGM values. If there were 270 CGM values recorded during that period, this would be an availability of 94%.

System availability in the PRECISE II study (which used Gen-1 transmitters only), and the PRECISION study (with both Gen-1 and Gen-2 transmitters) is presented below.

Table 43 *- System availability observed during the PRECISE II study over time, which includes only* ***Gen-1 transmitters***

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

Table 44 - *System availability for the* ***Gen-2 transmitter*** *observed during the PRECISION study*

	Days 1-7	Days 8-14	Days 15-30	Days 31-60	Days 61-90	All Days
Mean	97%	97%	96%	95%	95%	96%
Median	99%	98%	98%	96%	97%	97%
STD	4%	5%	4%	4%	4%	4%

In addition to this clinical data, Senseonics has provided the results of bench testing to show that the new transmitter design meets requirements related to functionality and durability. These requirements are similar to the requirements established for the previous transmitter, and are related to such features as battery life, functionality after drop/vibration, functionality during and after exposure to electromagnetic fields and static discharge, as well as other similar assessments.

The Agency would like feedback from the panel on whether the clinical data presented here is sufficient to allow for the conclusion that the Eversense CGM system will be reasonably safe and effective when used with this new transmitter design.

VIII. Data available from the European market

A previous version of the Eversense CGM system became commercially available in Europe in June, 2016 and has been modified since initial approval. The currently-approved version of the device in Europe uses the same sensor that was studied in the PRECISE II and PRECISION studies in the US, it uses the Gen-2 transmitter, and it uses the original software algorithm.

As part of the CE mark authorization, Senseonics agreed to conduct a Post Market Clinical Follow-up (PMCF) registry to collect safety data on long term use of the Eversense CGM System, specifically repeat Sensor insertions. Fourteen (14) countries with 350 centers are currently enrolling patients into the registry. For simplicity, this study is referred to as the European Patient Registry.

In these countries, every patient who receives an Eversense CGM System is enrolled. The European Patient Registry as of February 2, 2018 remains open and is enrolling all inserted patients. The registry will remain open and continue to follow all patients until 100 patients have completed 4 insertion/removal cycles. As a prospective study, follow-up visits are scheduled according to standard medical practice every 3 to 6 months, when the Sensor requires replacement.

The Eversense sensor initially approved in Europe had a different design (see Figure 18 below). The sensor design was later updated before the start of the PRECISE II study in the US.

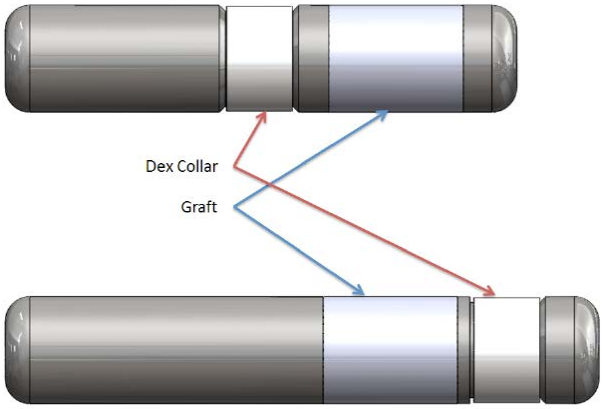


Figure 18 *- Sensor design used during the PRECISE study in Europe (top) compared to the sensor design used during the PRECISE II and PRECISION studies in the US. The design was changed before the PRECISE II study in order to make it easier to install the DXA-containing collar ("Dex Collar" in this figure). The "Graft" is the hydrogel that contains the glucose-sensitive fluorescent material.*

The table below summarizes how much of the European registry data is from the previous sensor design, and how much is with the newer sensor design.

The design of the transmitter system component that is on the market in Europe has also changed since the original approval. This is described in detail above in section VII – Design Changes after US Clinical Studies. The original transmitter marketed in Europe, referred to as Generation 1, was also used in both US clinical studies. The new transmitter design, referred to as Generation 2, has been released in Europe and was also used during the PRECISION study in the US.

Table 45 *- Summary of Sensor and Transmitter configurations used (as of February 2, 2018) in the European market, and included in the associated safety data. The "US Pilot" configuration of the sensor refers to the version used in the US clinical studies.*

Device Component	**Configuration**	**Numbers Used**
Sensor (2,386 total)	EU Pilot	756
	US Pilot	1,630
Transmitter (1,999 total)	Generation 1	148
	Generation 2	1,851

Senseonics recently received approval in Europe for a 180-day version of their device, which is referred to as "Eversense XL." The Eversense XL system has the same components as the Eversense system (i.e. there are no differences between the two systems), but it carries a longer approved sensor use period. To date, 10 subjects have been inserted with the Eversense XL sensor. Senseonics expects that by April – May of 2018 all subjects in Europe will be receiving the Eversense XL device, so all safety data past that point would be for a 180-day insertion/removal cycle.

The system approved for use in Europe uses a different version of the blunt dissector than what Senseonics is seeking approval for in the US. This difference is explained above in section VII – Design Changes after US Clinical Studies. The insertion tools used in Europe are the same ones used during the US clinical studies.

As of February 2, 2018, 1,686 patients have enrolled in the registry. These patients have received 2,386 insertions under real-world use conditions. One-hundred and fifty-one (151) patients have discontinued use of the system. The sponsor states that eighty-five (85) of these patients discontinued use after the first insertion cycle due to reimbursement issues. Table 46 provides a summary of the current enrollment status.

Table 46 - *European Patient Registry enrollment summary*

Number of Patients	**1st Insertion Cycle**	**2nd Insertion Cycle**	**3rd Insertion Cycle**	**4th Insertion Cycle**	**5th Insertion Cycle**	**6th Insertion Cycle**	**7th Insertion Cycle**
Total inserted	1686	443	143	58	39	14	3
Currently wearing	1114	285	78	19	25	11	3
Continued to next insertion	443	143	58	39	14	3	0
Discontinued	129	15	7	0	0	0	0

Sixty-six (66) adverse events have been reported as of February 2, 2018. There have been no serious adverse events related to the device or the insertion/removal procedure and no unanticipated adverse events. Table 47 provides a summary of the adverse events considered potentially related to the device and/or insertion/removal procedure.

Table 47 - *Summary of AEs from European Registry data related or probably/possibly related to device and/or procedure*

Device and/or procedure related (or probably/possibly related) AEs	**Number of Events**	**Percentage of Occurrence (N=1686)**	**AE Rate per 100 Patient-Years**
SAEs	0	0	0
Sensor location site infection	14	0.8	2.9
Skin atrophy over sensor	1	0.1	0.2
Skin atrophy over sensor with discoloration	3	0.2	0.6
Skin discoloration	3	0.2	0.6
Adhesive patch location site irritation	7	0.4	1.5
Prolonged wound healing after procedure	3	0.2	0.6
Sensor location site pain/discomfort	1	0.1	0.2
Unable to remove sensor at first attempt	9	0.5	1.9
Bruising	3	0.2	0.6
Sensor site redness/reaction to dressing	3	0.2	0.6
Other – sensor broke during removal	3	0.2	0.6
Other – patient fainted during procedure	1	0.1	0.2
Other - Hematoma	1	0.1	0.2

Senseonics has provided additional details on the observed Adverse Events for the available safety data from the European patient registry. Please refer to the Senseonics executive summary (section 7 – Clinical Safety) for this information.

IX. Postmarket Data and Proposed Post-Approval Study

Understanding the potential risks of the Eversense CGM, including the sensor insertion and removal process, can be informed by an analysis of post-market signals, including adverse event surveillance and device recalls, related to Senseonics CGM devices.

Analysis of Medical Device Reports (MDRs) submitted to FDA for adverse events associated with CGMs (product code MDS) is presented below. MDRs are submitted by device manufacturers, user facilities (e.g., hospitals), healthcare providers, and consumers. The MDR volume for CGMs is among the highest volume of MDRs submitted to the agency for any device. This may be due to the large population of people with diabetes in the US, the significant risks people with diabetes face every day, and the widespread use of these devices in diabetes management and care. The large volume of adverse event reports associated with these devices is also consistent with the criticality of the information they provide and the extent to which people with diabetes depend on these devices on a routine basis.

***Table 48** – MDR Summary for CGM devices*

Year	MDRs (total)	Malfunctions	Serious Injuries	Deaths	Other/No Value
2017	42587	41825	738	24	0
2016	96006	93956	1925	100	25
2015	43920	42580	1262	77	1
2014	27329	26329	985	12	3
2013	13355	12802	540	1	12

Proposed Post-Approval Study

Senseonics has proposed to conduct a post-approval study (PAS) to obtain a better understanding of the safety and effectiveness of the Eversense system under real-world conditions. Senseonics proposed a 2-year, prospective, multi-center study 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 receive up to 8 consecutive Sensors.

FDA is requesting panel input, provided the device is approved, on information that would be valuable to assess as part of a post-approval study.

X. Summary

FDA seeks the Panel's input on whether the information submitted by Senseonics, including the sensor accuracy studies, are adequate to support the safety and effectiveness of the Eversense CGM for the intended use period of 90 days. This includes the panel's input on the accuracy in the early wear period (i.e. <14 days), as well as the amount of accuracy data available as a fraction of total sensor lifetime. In addition, FDA seeks the panel's input on whether the design changes made to the device following the clinical studies have been adequately validated.

XI. Questions for the Panel

Ballot Questions

1. Is there reasonable assurance that the Senseonics Eversense Continuous Glucose Monitoring System is safe for the proposed indications for use?

2. Is there reasonable assurance that the Senseonics Eversense Continuous Glucose Monitoring System is effective for the proposed indications for use?

3. Do the benefits of the Senseonics Eversense Continuous Glucose Monitoring System for the proposed indications for use outweigh the risks of the Senseonics Eversense Continuous Glucose Monitoring System for the proposed indications for use?

XII. Appendices:

i. Appendix 1: PRECISE II Study accuracy results using the original glucose determination algorithm ("Study-SW" algorithm) with laboratory comparator method

ii. Appendix 2: PRECISION Study accuracy results using the original glucose determination algorithm ("Study-SW" algorithm) with laboratory comparator method

iii. Appendix 3: PRECISE II Study accuracy results using the new glucose determination algorithm ("SW-602" algorithm) with laboratory comparator method

iv. Appendix 4: PRECISION Study accuracy results using the new glucose determination algorithm ("SW-602" algorithm) with laboratory comparator method

v. Appendix 5: PRECISE II Study accuracy results using the new glucose determination algorithm ("SW-602" algorithm) with SMBG comparator method

vi. Appendix 6: PRECISION Study accuracy results using the new glucose determination algorithm ("SW-602" algorithm) with SMBG comparator method

XIII. References

Kropff, J., Choudhary, P., Neupane, S., & Barnard, K. (2017). Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial. *Diabetes Care*, *40*(1), 63-68.

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