Cover Page

Title: PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days

NCT Number: 03808376

Document Type: Statistical Analysis Plan

Document Date: August 11, 2020

Signature Manifest

Document Number: EXT-0755 **Revision:** 03
Title: PROMISE Study Statistical Analysis Plan (SAP)
Effective Date: 13 Aug 2020

All dates and times are in Eastern Standard Time.

PROMISE Study Statistical Analysis Plan (SAP)

Approval

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Sponsor	Study	Version
Senseonics, Incorporated	PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days	3.0

Senseonics, Incorporated

PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days

Protocol Number: CTP-0036
Version 7

Statistical Analysis Plan

Version 3.0, 11 August 2020

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	20 December 2019	Chris Mullin	Initial Release.
2.0	23 March 2020	Chris Mullin	Updated section 6.2 to be consistent with section 4.3.9.1 of the study protocol regarding blood sampling
3.0	11 August 2020	Chris Mullin	Clarified section 6.2 use of exclusion, defined primary sensor and SBA sensors. Added Section 6.10 to define analyses to be performed on the SBA subgroup

Sponsor	Study	Version
Senseonics, Incorporated	**PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days**	**3.0**

Document Approval

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1 Introduction

PROMISE is a prospective multi-center study for comparing the accuracy of glucose concentrations measured by the Eversense® Continuous Glucose Monitoring (CGM) System (referred to as the "Sensors" in the rest of this document) with laboratory blood glucose concentrations (YSI model 2300) as the reference standard in adults with Type 1 or Type 2 diabetes mellitus. Sensors will be inserted into study participant's arm and remained in-situ for 180 days. Follow-up visits will take place up to 10 days after Sensors removal and data on safety of the Sensors will also be collected.

Participants will receive standard diabetic care from their own physicians. Diabetes management decisions will be based on standard self-monitoring blood glucose (SMBG) values from a study provided glucose meter, not results from the Sensors.

The Eversense® 180 CGM System is designed to monitor the concentration of glucose in interstitial fluids continuously. Its intended purposes are:

- To provide real-time glucose readings directly to the user.
- To provide glucose trend information.
- To provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol "PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days". This SAP should be read in conjunction with the study clinical investigation plan and case report forms. This version of the SAP has been developed with respect to the Clinical Investigation Protocol CTP-0036 Version 7. Any revisions to the protocol or case report forms that impact the planned analyses may require updates to the SAP.

Applicable Documents:

Document Number, Version	*Document Title*

2 Abbreviations

Abbreviation/Term	*Definition*
AD	absolute difference
ARD	absolute relative difference
CGM	continuous glucose monitoring
MARD	mean absolute relative difference
PCV	percent coefficient of variation
RD	relative difference

3 Study Objectives

3.1.1 Effectiveness

To determine accuracy of the Eversense® 180 CGM System measurements through approximately 180 days post-insertion.

3.1.2 Safety

To demonstrate safety of the Eversense® 180 CGM System through 180 days post-insertion or removal and follow-up by measuring the incidence of device-related and Sensor insertion / removal procedure-related serious adverse events during the investigation.

3.2 Study Endpoints

3.2.1 Effectiveness measure

The effectiveness measure is the mean absolute relative difference (MARD) for paired Sensor and reference measurements up to 180 days post-insertion for reference glucose values from 40-400 mg/dL. Effectiveness measures are evaluated descriptively. Neither inferential analysis nor hypothesis testing will be performed.

3.2.2 Main safety endpoint

Incidence of device-related or sensor insertion/removal procedure-related serious adverse events up to 180 days post-Sensor insertion or removal and follow-up.

3.2.3 Other safety endpoints

1. Incidence of all device-related or sensor insertion/removal procedure-related adverse events in the clinic and during home use.
2. Incidence of all adverse events in the clinic and during home use.
3. Incidence of hospitalizations due to hypoglycemia, hyperglycemia or ketoacidosis occurring during home use.
4. Incidence of reported hypoglycemic and hyperglycemic events occurring during home use.

4 Study Design

This is a prospective study involving around 210 participants across 15 study sites in the United States. Approximately 180 participants will have a Sensor inserted into their arm, of which, at least 80 will have two Sensors inserted (one in each arm).

Participants need to attend 12 visits over a period of about eight months. At each clinic visit, the accuracy of the Eversense® 180 CGM System is evaluated by comparing glucose concentrations recorded by the Sensor with blood glucose concentrations from a bedside glucose analyzer. Most participants also undergo supervised hypoglycemia and hyperglycemia challenges during a visit.

Care decisions are based on self-monitoring blood glucose (fingerstick) tests and usual standard medical practice, and not on Eversense® 180 CGM System results.

The study population includes adults with Type 1 or Type 2 diabetes mellitus. This study takes approximately 12 months to complete, inclusive of the enrollment period.

A subgroup of subjects received a modified indicator hydrogel which includes the addition of a new monomer, 4-vinylphenylboronic acid. The VPBA monomer serves as a sacrificial boronic acid that reacts with reactive oxygen species (ROS) generated during the body's normal healing response to Sensor insertion without affecting the glucose recognition element, thereby increasing the longevity of the Sensor in vivo. Internally, the modified hydrogel indicator is referred to as the "sacrificial

boronic acid – SBA" hydrogel, hence the modified Sensor is referred to as the "SBA Sensor" in this document.

4.1 Randomization

Patients are considered enrolled in this study after providing informed consent. Participants failing to meet one of more of the eligibility criteria are deemed to have failed the screening stage. Every study participant passing the screening stage will receive the study device (Eversense® 180 CGM System) and at least 80 participants receive a primary and secondary CGM System– one sensor in each arm.

Each participant attends 12 follow-up visits and is randomly allocated, to each follow-up schedule.

- One of three groups for visit 3 (day 1 after implant): early shift, middle shift or late shift.
- One of two groups for visit 4: to take place on day 7 or day 14.

4.2 Blinding

Every participant will receive a CGM device (Eversense® 180 CGM System) and at least 80 participants receive a primary CGM System and secondary CGM System – one in each arm. The secondary CGM system will not calculate or display glucose information. The system will not require calibration and will have the ability to only collect and log raw sensor data.

Some of the primary Sensors may enter a "blinded mode" (known as "Clinical Mode") during sensor life in which the Eversense® 180 CGM System does no longer provides any sensor glucose information or glucose related alerts. When this happens, participants continue to wear the Sensor, enter calibrations (as prompted) and glucose concentrations from fingerstick tests, and attend follow-up visits.

4.3 Study Assessments

1. Screening (45 days before Sensor insertion)
    - Determine eligibility for Sensor insertion.
    - Medical history and physical examination, electrocardiogram, urine pregnancy test.
    - Diabetes Distress Scale questionnaire, laboratory assessments, HbA1c level.
    - Random allocation to a visit schedule.

2. Day 0 (Sensor insertion)
    - Sensor insertion: at least 80 participants have two Sensors inserted for investigating the effect of placing the Sensor in dominant or non-dominant limb and for calculating percent absolute relative difference.
    - Training of participants on study and devices.
    - Fingerstick test for capillary blood glucose concentration and ketone assessment. Urine pregnancy test.

The following visits (Day 1 visit to Day 180 visit) are for:

- Comparing Sensor records with those from a bedside glucose analyzer.
- Sensor calibration with self-monitoring blood glucose (fingerstick) meters.
- Urine pregnancy test, venous blood glucose, blood ketones concentration. Blood is sampled every 5-15 minutes for glucose depending on each participant's glucose level. Ketones are assayed hourly when blood glucose reaches 300 mg/dL, when ketone levels are ≥0.6 mmol/L, or if the subject is displaying symptoms of hyperglycemia regardless of glucose level.
- Assess: change in medications, adverse events (including episodes of hypoglycemia, diabetic ketoacidosis), Sensor site.
- Hypoglycemic or hyperglycemic challenge at investigators' discretion.

3. Day 1 – participants will be randomly allocated to one of:
    - Visit 3A to take place at hours 1-8 (early shift).
      Participants in this group have their CGM system calibrated by staff at this visit as prompted by the system.
    - Visit 3B to take place at hours 9-16 (middle shift).
      Participants in this group calibrate their CGM system at home and as prompted while in clinic.

- Visit 3C to take place at hours 17-24 (late shift).
  Participants in this group calibrate their CGM system at home and as prompted while in clinic

4. Day 7 or Day 14 – study sites will be randomly allocated to one of Visit 4A or 4B. This random allocation will be independent of the allocation to Visit 3A, 3B or 3C.
   - Visit 4A to take place on day 6-8 for participants allocated to "day 7 group".
   - Visit 4B to take place on day 13-15 for participants allocated to "day 14 group".
5. Day 22±1
6. Day 30 (day 27-37)
7. Day 60 (day 53-67)
8. Day 90 (day 83-97)
   - Assessments as in other visits.
   - Glycated hemoglobin HbA1c.
   - Questionnaires: Diabetes Distress Scale.
9. Day 120 (day 113-127)
10. Day 150 (day 143-157)
11. Day 180 (day 177-182)
    - The Sensors are removed at the end of or within seven days of this visit.
    - Glycated hemoglobin HbA1c.
    - Questionnaires: Diabetes Distress Scale and CGM satisfaction questionnaire.
12. Final follow-up (7-17 days after Sensor removal)
    - Assessment of wound healing.

- If any concerns about the wound, participants are followed up every ten days until resolution.

During day-to-day home use, each participant is requested to complete approximately seven fingersitck tests for glucose concentration each day for diabetes care decisions:

- 3 pre-prandial fingersticks before meals
- 3 post-prandial fingersticks approximately two hours after meals
- 1 fingerstick before bed

Subjects will be trained to enter all fingerstick values into the Eversence app as glucose events or calibrations as applicable. Study sites will monitor and remind participants to complete a minimum of four tests (at least one pre-prandial and one before bed) per day and enter those values in the Eversense app (2 calibrations and 2 glucose events). Insulin injections/boluses are also to be entered into the app.

Study participation is complete after Visit 12. Participants exiting the study prematurely may not re-enter the study and will not be replaced.

5 Sample Size Determination

Only descriptive analyses have been planned and no inferential analysis or hypothesis testing will be carried out. The size of this investigation is thus not based on a study power calculation but on the intention to ensure a minimum of 120 participants are followed up to the end (that is 180 days after insertion of the Sensor).

An enrollment target of 20 participants per subgroup of interest (see Section 6.9) should provide sufficient data to characterize these subgroups. The probability of detecting one or more events in a group of 20 participants is 80%, when such event occurs with a probability of 8%.

For the SBA sensor configuration, a total of 43 sensors are planned.

6 Statistical Analyses

6.1 General Considerations

The statistical analysis is focused on assessing performance of the Eversense® 180 CGM System in measuring glucose concentration under various clinical situations (day-to-day normal use, hypoglycemia and hyperglycemia). The accuracy of Eversense® 180 CGM System is assessed by comparing with measurements from:

1. Capillary blood glucose concentration from Self-Monitoring Blood Glucose Meter
2. Yellow Springs Instrument (YSI model 2300 blood glucose analyzer) reference glucose test

All statistical analysis will be conducted using SAS version 9.3 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

6.1.1 Descriptive Statistics

Participants' demographic and baseline data and their outcome data collected during the course of this study are summarized as descriptively in Tables, Figures and Listings.

Continuous data will be summarized as means, standard deviations, medians, minimums, maximums, and number of evaluable observations. Categorical variables will be summarized as frequency counts and percentages. Confidence intervals may be presented where appropriate.

6.1.2 Study Day

Day 0 (Visit 2 in the study schedule) is the date of insertion of the Sensor. Day in study will be calculated as Study Day = Visit Date – Date of insertion of the Sensor.

Duration in study will be based on last study contact date, which is the latest date of all follow-up visits or assessments, adverse event onset or resolution, or study exit including date of death. It will be calculated as Duration Days = Study Exit – Date of insertion of the Sensor.

6.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

6.2 Analysis Populations

The following analysis populations are defined for analysis:

1. Per-protocol effectiveness analysis population: This is based on laboratory reference values which are equilibrated with capillary blood glucose values[1], obtained at 15 minutes intervals with matching CGM pairs from measurements, and which are free from protocol deviations, which include:
    a. Protocol deviations that were not identified at intake (e.g. hematocrit out of window, visit out of window, recent use of tetracycline/sorbitol/mannitol, DKA or Severe hypoglycemia during the past 30 days)
    b. Flagged reference measurement as indicated in source documentation (e.g., expired membrane, expired calibration, dilute sample)
2. Evaluable analysis population: This is based on data from participants with a minimum of three paired glucose readings since a smaller number of data points from a subject would not be considered representative of intended clinical use. A measurement from the reference test is paired with a reading from the Sensor that took place within a 5-minute period after sample acquisition.
3. Safety analysis population: This is based on data from participants who have undergone the Sensor insertion procedure at day 90 and day 180 visits.

The Per-protocol effectiveness analysis population will be considered the primary analysis set for effectiveness evaluations for the primary sensor configuration described in G180235. The Safety analysis population will be considered the primary analysis set for safety evaluations. Analysis of additional populations will be considered supportive in nature, in particular for the SBA sensor configuration, as described in G180235 S006.

[1] Liu D, et al, "Aterial, arterialized venous, venous and capillary blood glucose measurements in normal man during hyperinsulinaemic euglycaemia and hypoglycaemia", Diabetologia, 1992, 35:287-290.

6.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed.

6.4 Subject Disposition

The number of subjects in each analysis population at each stage of the study, from informed consent to the end of study, will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

6.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic (for example: age, sex, ethnicity), medical history (body mass index, diabetes type, insulin therapy, history of hypoglycemia or diabetic ketoacidosis), and participant characteristics.

6.6 Analysis of Study Endpoints

6.6.1 Safety Endpoints

The primary safety endpoint is defined as the incidence rate of device-related or procedure-related (from insertion or removal of the Sensor) serious adverse events occurring up to 180 days after the insertion procedure. The assessment of seriousness and relatedness will be made by the Medical Monitor. An adverse event is classified as “related” if its relatedness is assessed to be “possibly related” or “related”.

The number (and percentages) of serious adverse events and participants affected for each type of adverse event will be tabulated. No hypothesis testing will be carried out.

Apart from serious adverse events, other safety endpoints include:

- Incidence rates of device-related or procedure-related (from insertion or removal of the Sensor) adverse events that occurred at home or during clinic visits.
- Incidence rates of any adverse events, serious or not serious, that occurred at home or during clinic visits.
- Incidence rate of hospitalizations due to hypoglycemia, hyperglycemia or ketoacidosis that occurred at home.
- Incidence rate of self-reported episodes of hypoglycemia or hyperglycemia that occurred at home.

For each of the above endpoint, the number (and percentage) of events and participants affected, stratified by age, will be presented as a table. A list of patients affected with information on date of onset, severity, seriousness, relatedness, classification as anticipated or unanticipated, corrective actions and resolution status will be prepared.

6.6.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as the mean absolute relative difference, estimated from all paired measurements from the Eversense® 180 CGM System and reference measurements up to 180 days after Sensor insertion.

For each participant, the mean absolute relative difference is

$$Mean\ ARD = \left(\sum_{i=1}^{n} \frac{|glucose(sensor)_i - glucose(reference)_i|}{glucose(reference)_i} \right) / n \times 100\%$$

where n is the total number of pairs of the Eversense® 180 CGM System and reference measurements during the evaluation period.

Only descriptive analysis will be carried out. No hypothesis will be tested.

6.6.3 Secondary Effectiveness Endpoints

In each of the following endpoints, the subscript “i” identifies each pair of the Eversense® 180 CGM System and reference measurements during the evaluation period for each participant and n is the total number of such pairs.

Mean absolute difference

$$Mean\ AD = \left(\sum_{i=1}^{n} |glucose(sensor)_i - glucose(reference)_i|\right) / n \times 100\%$$

Mean relative difference

$$Mean\ RD = \left(\sum_{i=1}^{n} \frac{glucose(sensor)_i - glucose(reference)_i}{glucose(reference)_i}\right) / n \times 100\%$$

Median absolute relative difference

$$Median\ ARD = median\left(\frac{|glucose(sensor)_i - glucose(reference)_i|}{glucose\ (reference)_i}\right) \times 100\%$$

for i = 1, 2, …, n.

Median absolute difference

$$Median\ AD = median(|glucose(sensor)_i - glucose(reference)_i|) \times 100\%$$

Median relative difference

$$Median\ RD = median\left(\frac{glucose(sensor)_i - glucose(reference)_i}{glucose\ (reference)_i}\right) \times 100\%$$

Agreement between the Sensor and the reference measurements will be assessed by examining

$$\left(\frac{|glucose(sensor)_i - glucose(reference)_i|}{glucose\ (reference)_i}\right) \times 100\%$$

6.6.4 Other Effectiveness Endpoints

The means and medians of absolute relative difference, absolute difference and relative difference when the reference measurements (Yellow Springs Instrument analyzer) will be presented.

The agreement between the Sensor and the reference measurements at different ranges of reference measurements and of Sensor measurements will also be presented.

Concurrence of the Sensor and the reference standard (Yellow Springs Instrument analyzer) will be presented as Tables. Performance of the Eversense® 180 CGM System over the study period will be assessed by visit.

6.6.5 Device Precision

The means of the following two measures will be tabulated.

Paired absolute relative difference

$$Paired\ ARD = \left(\sum_{i=1}^{n} \frac{|glucose(sensor\ 1)_i - glucose(sensor\ 2)_i|}{\frac{1}{2} \times (glucose(sensor\ 1)_i + glucose(sensor\ 2)_i)} \right) / n \times 100\%$$

Percent Coefficient of Variation

$$\text{PCV} = \sum_{i=1}^{n} (100 \times \frac{\text{SD of } (glucose(sensor\ 1)_i \text{ and } glucose(sensor\ 2)_i)}{\text{Mean of } (glucose(sensor\ 1)_i \text{ and } glucose(sensor\ 2)_i)}) / n$$

6.7 Poolability Analyses

All investigational sites follow the requirements of a common protocol and standardized data collection procedures and forms.

Data from different study sites will be pooled for analyzing the primary effectiveness measure. Study site effects will only be examined descriptively. Sites enrolling fewer than five participants will be combined as one group.

6.8 Safety Analyses

Adverse events (AE) will be reported for the safety analysis population. Adverse events will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Serious adverse events will also be tabulated.

Adverse events leading to death or study discontinuation will be provided as Listings.

All device deficiencies for the Sensor and the transmitter will be reported as Tables and Listings.

6.9 Additional Analyses

Descriptive analysis will be carried out on data from all participants, and separately for each of the following groups. No hypothesis testing on the difference between groups will be carried out.

- Type 1 versus Type 2 diabetes mellitus.
- Age (18-20, 21-44, 45-65, and over 65 years)
- Baseline HBA1c level below 8% versus 8% or over
- Glucose range strata (e.g. <40, 40-60, 61-80, 81-180, 181-300, 301-350, 351-400, > 400 mg/dL) to include all samples, i.e. more frequent than 15-minute sampling

6.10 Sensor Design Change Analysis

The SBA sensor configuration is of key interest. The following analyses will be performed for the SBA sensor configuration, separately and within subject as appropriate for:

- Primary, secondary and other effectiveness endpoints
- Sensor longevity

Further analysis on an expanded set of sensors that have slower indicator degradation rates will pool data from SBA sensors along with subjects with only primary sensors whose sensors have a degradation that falls within the distribution of degradation for the SBA sensors.

6.11 Interim Analyses

There are no planned formal interim analyses for the purposes of early stopping or sample size adjustment.
This does not preclude reporting of accruing data to the FDA.

6.12 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on case report forms. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

6.13 Other Analyses

6.13.1 Calibration frequency

The effectiveness of an alternative scheme in which device calibration took place twice daily in the first 21 days after insertion and then once daily afterwards may be carried out.

Alternative calibration methodologies that modify durations between calibration point entry may be analyzed. These calibration schemes will be pre-specified in compiled transmitter software which will be used for the analysis.

This part is separate to the clinical raw data collected by the Eversense® 180 CGM System. This part is the subject of a separate SAP.

7 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

8 Appendices

Appendix A. Table Templates

Examples of Tables and Listings to be generated after descriptive analyses described in this SAP.

A.1 Participant accountability

109 subjects consented	
	13 subjects (01-001, 04-002, 05-001, 06-001, 05-012, 04-011, 02-007, 02-008, 07-002, 07-006, 05-021, 07-008, and 07-009) had screen failure **15** subjects (01-005, 01-006, 01-007, 01-009, 01-010, 01-012, 01-013, 01-014, 04-003, 04-004, 05-003, 03-002, 05-015, 02-011, and 07-003) withdrew consent due to exceeding screening window

81 subjects completed sensor insertion

- **10** subjects (02-001, 03-001, 04-001, 05-002, 06-004, 01-002, 01-003, 01-004, 01-008, and 01-011) are the training subjects

71 subjects are included in the effectiveness and safety endpoints

71 subjects completed Day 30 Visit

- **2** subject (01-017 and 04-009) withdrew consent
- **1** subject (03-010) withdrew consent due to AE

68 subjects completed Day 90 Visit

- **2** subjects (04-008 and 06-017) completed study with sensor retirement alert

66 subjects completed Day 180 Visit

A.2 Investigational Transmitter Deficiencies (Sample Data)

Type of Transmitter Deficiency	Number Reported	% of Total
Package Label	0	0%
Product Defect	21	87.5%
Damaged Package	0	0%
Product Safety	0	0%
Product Performance	1	4.2%
Other	2	8.3%

A.3 Investigational Sensor Deficiencies (Sample Data)

Type of Sensor Deficiency	Number Reported	% of Total
Package Label	0	0%

Product Defect	21	87.5%
Broken Sterile Seal	0	0%
Damaged Package	0	0%
Product Safety	0	0%
Product Performance	1	4.2%
Other	2	8.3%

A.4 Summary of Serious Adverse Events (Sample Data)

SAEs by Relationship to Study	Number of SAEs	Number of Patients with SAEs (%; 95% Confidence Interval)
All SAEs	1	1 (1.4%; 0.0%-7.6%)
Device Related SAEs	0	0 (0.0%; 0.0%-5.1%)
Sensor Insertion/Removal Procedure Related SAEs	0	0 (0.0%; 0.0%-5.1%)
Unrelated to Study SAEs	1	1 (1.4%; 0.0%-7.6%)

A.5 Other Safety Endpoint (Sample Data)

This Table is generated for all participants combined and each of the following subgroups: 18-20 year-olds, 21-44 year-olds, 45-65 year-olds and over 65 year-olds.

Type of Incidence	Number of Incidents	Number (%) of Subjects with Incidents
Incidence of device-related or insertion/removal procedure-related serious adverse events over the operating life of the Sensor	0	0 (0.0%)
Incidence of insertion/removal procedure or	12	11 (15.5%)

device-related adverse events in the clinic and during home use		
Incidence of all adverse events in the clinic and during home use	35	24 (26.6%)
Incidence of hospitalizations due to hypoglycemia, hyperglycemia, or ketoacidosis occurring during home use	0	0 (0.0%)
Incidence of reported hypoglycemic and hyperglycemic events occurring during home use	2	2 (2.8%

A.6 List of Adverse Events (Sample Data)

Descriptions

	ID	AE Description
1	1-16	Depressive period
2	1-22	Hypoglycaemic episode during the night, patient had to be assisted to drink glucose to regain full conciousness.
3	1-22	Reduced vision due to ocular ischaemia
4	1-23	Contact dermatitis at the precise location of the transmittersticker. left arm - Dermatitis has healed
5	2-02	Cold and runny nose - allergies? ?hayfever

Characteristics

	ID	AE Category	AE Physiologic System	Implant Date	Date AE Onset	Resolution Date	Status	Seriousness	Severity	Device Related	Procedure Implant/Removal Related
1	1-16	Psychological disorder	Other	04-DEC-2014	22-DEC-2014	31-DEC-2014	Resolved	Not SAE	Moderate	Possibly Related	Not Related
2	1-22	Hypoglycemic Event	Endocrine	20-JAN-2015	29-JAN-2015	29-JAN-2015	Resolved	Not SAE	Moderate	Not Related	Not Related
3	1-22	Ocular ischemia	HEENT	20-JAN-2015	24-DEC-2014	.	Ongoing	Not SAE	Moderate	Not Related	Not Related
4	1-23	Dermatitis	Dermatological	20-JAN-2015	28-FEB-2015	18-MAR-2015	Resolved	Not SAE	Moderate	Definitely Related	Not Related
5	2-02	Allergy - Seasonal	HEENT	19-JAN-2015	01-FEB-2015	16-FEB-2015	Resolved	Not SAE	Mild	Not Related	Not Related

A.7 CGM System Difference to YSI

A.7.1 CGM System Difference to YSI within YSI Glucose Range (Sample Table)

YSI Glucose Ranges (mg/dL)	Number of Paired CGM-YSI	Mean Relative Difference (%)	Median Relative Difference (%)	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall					
<40*					
40-60*					
61-80*					
81-180					
181-300					
301-350					
351-400					
>400					

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

A.7.2 CGM System Difference to YSI within CGM System Glucose Range (Sample Table)

CGM System Glucose Ranges (mg/dL)	Number of Paired CGM-YSI	Mean Relative Difference (%)	Median Relative Difference (%)	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)
Overall					
40-60*					
61-80*					
81-180					
181-300					
301-350					
351-400					

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

A.7.3 CGM System Agreement to Reference within YSI Glucose Ranges (Sample Table)

YSI Glucose Range (mg/dL)	Number of Paired Eversense® CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall						
< 40						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						
351 - 400						
> 400						

A.7.4 CGM System Agreement to Reference within CGM System Glucose Ranges (Sample Table)

CGM System Glucose Range (mg/dL)	Number of Paired Eversense® CGM and YSI Reference	Percent of CGM System Readings Within				
		Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Overall						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						
351 - 400						

A.8 Concurrence of CGM System Readings and YSI Values (Sample Table)

A.8.1 Concurrence of CGM System Readings and YSI Values within YSI Glucose Ranges (Sample Table)

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										
40-60										
61-80										
81-120										
121-160										
161-200										
201-250										
251-300										
301-350										
351-400										

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
>400										

A.8.2 Concurrence of CGM System Readings and YSI Values within CGM System Ranges (Sample Table)

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Percent of Matched Pairs in Each YSI Glucose Range for Each CGM Glucose Range YSI (mg/dL)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
40-60												
61-80												
81-120												
121-160												
161-200												
201-250												
251-300												
301-350												
351-400												

A.9 CGM System Accuracy by Visit Number (Sample Table)

Day Number	Number of Paired CGM-YSI	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Day 1								
Day 7								
Day 14								
Day 22								

Day Number	Number of Paired CGM-YSI	Mean Absolute Relative Difference (%)	Median Absolute Relative Difference (%)	Percent of CGM System Readings Within				
				Percent 15/15% of Reference	Percent 20/20% of Reference	Percent 30/30% of Reference	Percent 40/40% of Reference	Percent Greater than 40/40% of Reference
Day 30								
Day 60								
Day 90								
Day 120								
Day 150								
Day 180								

A.10 CGM System between System Precision

Level of Mean Glucose	Mean Difference (Sensor 1 - Sensor 2) (mg/dL)	SD of Difference (mg/dL)	N Pairs
<= 70			
71-180			
> 180			
All			
PARD			
PCV			