PRECISION Study Statistical Analysis Plan (SAP)

PRECISION Study: A Prospective, Multicenter Evaluation of Precision, Compression, Accuracy and Updated Algorithm of a Novel Continuous Implanted Glucose Sensor

SAP Version: 2.0
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Version 2.0

November 8, 2017

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List of Abbreviations and Acronyms

BG	Blood Glucose
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CRC	Clinical Research Center
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
MARD	Mean absolute relative difference
PARD	Percent absolute relative difference
PCV	Percent coefficient of variation
SMBG	Self-Monitoring Blood Glucose
YSI	Yellow Springs International

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1 OVERVIEW

This document outlines the statistical analysis plan (SAP) for the PRECISION evaluation study. It is intended to outline the statistical procedures and methods used to design the study and to analyze the resulting clinical data, in conformance with the recommended practices contained in *ICH E9 Statistical Principles for Clinical Trials*. The statistical procedures that are described in this document are consistent with those contained in the associated *Protocol Number CTP-0031* but contain additional details on their implementation. Senseonics data processing procedure will follow PLN-0079.

Changes to the original released version of this SAP will be documented in its document history. Deviations from the applicable SAP version will be documented and described in any reporting of study statistical results.

2 DEVICE OVERVIEW

The **Senseonics Continuous Glucose Monitoring (CGM) System** is a glucose monitoring device indicated for continually measuring interstitial fluid glucose levels in adults with diabetes for the operating life of the Sensor. The Senseonics Continuous Glucose Monitoring System is intended to be used:

- 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).

3 STUDY DESIGN

This is a non-randomized, prospective, single-arm, multi-center study, whereby approximately 44 subjects will be enrolled and 36 subjects will be inserted in the United States at up to 4 sites. The investigation will include both clinic visits and home use of the Senseonics CGM System. The subjects will have one or two Sensors inserted by trained Investigators. The Sensors will be inserted in the upper arms of the subjects. The accuracy of the Senseonics CGM System will be evaluated during clinic visits comparing Sensor glucose values and plasma glucose values measured on a bedside glucose analyzer. For qualifying subjects, during the clinic visits, there will be planned hyperglycemia and hypoglycemia challenges. Effects of compression/sensor dropout will be evaluated during the designated overnight periods.

In this study, including the clinic and home settings, all diabetes care decisions will be based on SMBG blood glucose values and clinical standard of care, rather than Senseonics CGM System results.

This study will not be randomized. Subjects will be selected consecutively (i.e., selecting every subject in the order they present at the site) among those who meet the

inclusion/exclusion criteria.

The Subject visit schedule includes 9 visits over a period of approximately 4.5 months (inclusive of visit windows from screening visit through follow-up visit). A subset of a minimum of 6 and a maximum of 9 subjects will have blood samples drawn daily for the first 7 days of sensor wear for additional dexamethasone screening and to determine blood draw time points during the first week of sensor wear for the remaining subjects. These subjects will only have one sensor inserted in the left arm, which will be linked to the Gen 1 transmitter. Remaining subjects will have 2 sensors inserted, one in each arm, with the left sensor linked to a Gen 1 transmitter, and the right sensor linked to the Gen 2 transmitter. These subjects may be required to make additional visits for dexamethasone screening between visits 3 and 4.

The study is anticipated to take approximately 6 months, including the enrollment period.

4.1 Study Objectives

4.1.1 Effectiveness

The effectiveness objective is to determine the accuracy of the Senseonics CGM System through 90 days post-insertion for reference glucose values from 40-400 mg/dL. The exploratory objectives are to determine other relevant Senseonics CGM System performance measures during the period of Sensor use and are detailed further in Section 6, along with plans and analysis details on the effectiveness endpoint. An interim analysis will be performed and data submission will be made based on the sensor performance data accrued through the day 30 visit (Visit 6).

4.1.2 Safety

The safety objective is to demonstrate safety of the Senseonics CGM System through 90 days post-insertion by measuring the incidence of device-related or sensor insertion/removal procedure-related serious adverse events (SAEs) during the investigation. The other safety objectives are to evaluate the incidence of all procedure-related or device-related adverse events (AEs) in clinic and home use, and to evaluate the incidence of all adverse events, regardless of relatedness, in clinic and home use. The safety endpoints and their respective analysis are detailed further in Section 6.

4.2 Endpoints

4.2.1 Effectiveness Endpoint

The effectiveness objective is to descriptively document the distribution of absolute relative difference across all subjects and to estimate the MARD. The MARD will be estimated initially when all the subjects complete 30 days of Sensor use for the interim analysis, followed by the MARD based on all the follow-up data through 90 days of Sensor use.

The effectiveness endpoint will be calculated for three different combinations of 2 generations of hardware and 2 generations of firmware. The three configurations are Generation 1 (Gen 1)

transmitter plus study firmware, Generation 2 (Gen 2) transmitter plus study firmware and Gen 2 transmitter plus updated firmware.

Descriptive statistics will be provided for the MARD and other exploratory effectiveness endpoints. There is no hypothesis to be tested. No inferential statistical analysis will be performed.

The effectiveness endpoint is the mean absolute relative difference (MARD), defined as the average of absolute difference of paired Senseonics CGM System and reference glucose readings divided by the reference glucose reading (reference) for all reference glucose values, that is:

$$\mathbf{MARD} = \left(\left(\sum \frac{|\ (\mathbf{Glucose})_{\mathbf{SENSOR}} - (\mathbf{Glucose})_{\mathbf{REFERENCE}}\ |}{(\mathbf{Glucose})_{\mathbf{REFERENCE}}}\right) / \mathbf{n}\right) \times \mathbf{100}\%$$

Where, n is the total number of CGM and reference glucose pairs during the evaluation period, that is, after 30 days of Sensor use for the interim analysis, and after 90 days of use.

4.2.1.1 Reference Glucose Measurements for Endpoint

The primary instrument for plasma glucose measurements is a YSI glucose analyzer (2300 Stat Plus Glucose & Lactate Analyzer, Yellow Springs Instruments, Yellow Springs, OH, USA). Glucose measurements may be re-run on blood samples (replicate measurements). In the event of loss of IV access or loss of functional YSI and need for continued subject monitoring, glucose measurements will be made on capillary whole blood using the Subject SMBG meter as needed.

4.2.2 Safety Endpoint

The safety endpoint is the incidence of device -related or insertion/removal procedure related serious adverse events (SAEs) in the clinic and during home use through 90 days post insertion.

An Adverse Event is considered ‘related’ if the relatedness is categorized as ‘possibly related’ or ‘related’. The assessment of seriousness and relatedness made by the Medical Monitor will be used for analysis. Only descriptive analysis will be performed for safety endpoints. There is no safety hypothesis.

Other safety endpoints include:

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

4.2.2.1 Safety Assessments

Safety will be evaluated by examination of the insertion site at each in-clinic visit and documentation of adverse events occurring in the clinic and during home use.

At each visit, adverse events that occur during the visit and that occurred during home use since the previous visit will be recorded and reported. Subjects will be asked to provide information on any hospitalizations that may have occurred due to hypoglycemia or hyperglycemia events. Information from the self-monitoring blood glucose meter will be downloaded at each in-clinic visit and used to document episodes of hypoglycemia and hyperglycemia.

4.2.3 Exploratory Effectiveness Endpoints

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The exploratory effectiveness endpoints will also be calculated under the same three different configurations of hardware and firmware as noted for the effectiveness endpoint in section 4.2.1. The other effectiveness endpoints include the following.

- System agreement with reference
- Effectiveness measures in full glucose range and different glycemic regions
- Concurrence of System Readings and YSI values
- Stability of the system throughout sensor life
- Sensor precision analysis
- Effect of compression on sensor performance during sleep challenges
- Mean Absolute Difference (MAD) between sensor and reference measurements
- Mean Relative Difference (RD) between sensor and reference measurements
- Median Absolute Relative Difference (ARD) between sensor and reference measurements
- Median Absolute Difference between sensor and reference measurements
- Median Relative Difference between sensor and reference measurements
- Clarke Error Grid Analysis
- Consensus Error Grid Analysis
- Detection and True Alert Analysis
- Deming Regression
- Bland Altman Analysis
- Sensor Survival
- CGM Satisfaction Scale analysis

- Effect of medications
- Calibration Stability

Details of the exploratory effectiveness endpoints are described in Section 6.10.

4.3 Randomization

Subjects will not be randomized. Subjects will be selected consecutively (i.e., selecting every subject in the order they present at the site) among those who meet the inclusion/exclusion criteria.

4.4 Sample Size Determination

Approximately 44 subjects will be enrolled and 36 subjects will be inserted with either one Sensor (dexamethasone sub-group of 6 to 9 subjects) or two Sensors in the clinical investigation. The sample size is not based on any power analysis but was agreed upon by the FDA to satisfy FDA's request for additional data to assess accuracy at different time points through day 30 and to obtain additional plasma levels of dexamethasone using a limit of detection of 50 pg/ml.

5 PROTOCOL

Additional details on the PRECISION protocol not described above can be found in Protocol CTP-0031.

5.1 Schedule of Events

The Schedule of Events for In-Clinic Visits is included below in **Table 1**.

Table 1: Schedule of Events for In-Clinic Visits

Visit Number	**1**	**2**	**3**	4	**5**	**6**	**7**	**8**	**9**
Visit Type	Screening	Sensor Insertion and Training	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit	Accuracy Visit and Sensor Removal	Follow-up Sensor Site Assessment
Study Day and Window		Day 0 (+0 to 30 Days after Visit 1)	Day 1 (±0 Day)	Day 7 (± 1 Days)	Day 14 (±1 Days)	Day 30 (±7 Days)	Day 60 (±7 Days)	Day 90 (-3/+7 days)	10 Days Following Sensor Removal (-3/+7 days)
Anticipated Length of Visit	2 Hours	2 to 6 Hours	19 Hours	18 Hours	18 Hours	14 hours	14 hours	15 hours	30 Minutes
Informed Consent Process	X								
Screening history, exam, labs to assess Inclusion/Exclusion	X								
Sensor Insertion		X							
Device Training		X							
Urine pregnancy	X	X	X	X	X	X	X	X	
IV Catheter			X	X	X	X	X	X	
Approximate length of time to collect blood Samples			16 Hours	16 Hours	16 Hours	12.5 Hours	12.5 Hours	12.5 Hours	
Dexamethasone blood draw (4.0 mL)[2]	X	X	X[3]	X[3]	X[3]	X	X	X	
HCT	X		X	X	X	X	X	X	
A1C (2.0 mL)	X					X	X	X	
Fingerstick blood glucose and ketones per protocol			X	X	X	X	X	X	

Visit Number	1	2	3	4	5	6	7	8	9
Download Transmitter and BG Meters			X	X	X	X	X	X	
Assess changes in medications and Adverse Events		X	X	X	X	X	X	X	X
Assess Sensor site			X	X	X	X	X	X	X
Hypoglycemia and Hyperglycemia Challenge			X	X	X	X[1]	X[1]	X[1]	
Sleep Assessment				X	X				
Sensor Removal								X	
Approximate Samples for glucose analysis			89 (13 hrs @4 per, 3 hrs @ 12 per)	89 (13 hrs @4 per), 3 hrs @ 12 per	89 (13 hrs @4 per), 3 hrs @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	59 (11.5 hrs @4 per), 1 hr @ 12 per	
Maximum Estimated Blood Draw Volume[4]	6	12	97	97	97	65	65	65	Total=504

1 Only hypoglycemia challenge or hyperglycemia challenge, depending on glucose level
2 Designated subjects will have 3 samples drawn at visit 2. A subset of subjects will have daily blood samples drawn for the first 7 days of sensor wear for dexamethasone assessment. Remaining subjects may have an additional blood sample drawn during the first 7 days TBD based on the results from the subset.
3 Subjects will have 2 blood samples drawn for dexamethasone assessment, one at the beginning of the visit, and one at the end.

6 STATISTICAL ANALYSIS

This trial will assess the performance of the Senseonics Continuous Glucose Monitoring System (Senseonics CGM System) when compared to the reference standard (YSI glucose analyzer). The trial has a prospective, single-arm and multi-center design. Approximately 44 subjects with diabetes mellitus will be enrolled in the study. Subjects will be followed for 90 + 10 days following Sensor insertion for safety and effectiveness assessments. The accuracy evaluation period will be from the time of the first valid glucose measurement after Sensor insertion until the Sensor end of life or 90 days post-insertion, whichever occurs first.

6.1 General Considerations

Descriptive statistics will be used to summarize all subject Baseline and outcome data collected during the study. Continuous variables will be summarized using mean, standard deviations, and ranges. Categorical variables will be summarized in frequency distributions.

Statistical analyses will be performed by validated software (e.g., MATLAB, SAS® 9.4 Software). Adequate source document verification and/or audit activities will be utilized to assess the validity of investigation conclusions.

Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.

6.2 Accuracy Evaluation Period and End of Life

The Senseonics CGM System performance will be evaluated in the period after insertion. The Transmitter will assess the Sensor's signal sensitivity in real time for any premature failure independent of the expected lifetime based on time from insertion. If the measurement of potential degraded response of the Sensor optical system signal drops below a pre-defined percent of its original value and/or systemic patterns in Sensor accuracy to entered calibration points drops below a pre-defined threshold, then the device has reached it end of life and will no longer provide glucose readings. This end of life determination marks the end of the accuracy evaluation period for this Sensor. The distribution of times between Sensor insertion and end of life or 90 days, whichever occurs first will be summarized.

6.3 Data for Analysis

All data will be used for the study safety and effectiveness analysis.

6.4 Analysis Populations

Effectiveness Analysis population: The effectiveness analysis and exploratory effectiveness endpoints will be based on all data from all subjects in this investigation with at least one paired glucose reading (one Sensor with one reference glucose). The Senseonics CGM System and reference readings are compared by pairing each reference reading with the first Sensor reading that occurred up to 5 minutes after sample acquisition.

Safety Analysis Population: Safety analysis will be based on all subjects that undergo the sensor insertion in this investigation.

Dexamethasone Analysis Population: The approximately 6 to 9 subjects with Sensor's inserted will constitute the dexamethasone analysis population to determine if and when a peak dexamethasone level occurs. Subsequent to determining if and when a peak occurs, all subjects with Sensor's inserted will constitute the complete dexamethasone analysis population.

6.5 Dexamethasone Analysis

The peak dexamethasone and the timing that the peak dexamethasone occurs will be analyzed descriptively in the subset of approximately 6 to 9 subjects. Subsequent analysis of the dexamethasone levels in all subjects will be analyzed descriptively.

6.6 Interim Analysis

A planned interim analysis will be performed after all the subjects have completed Visit 6 (day 30 accuracy visit). Only descriptive statistics will be performed. This interim analysis does not feature any stopping rules and has no impact on the collection of the complete follow-up data through 90 days of Sensor use.

6.7 Tabulation of Investigational Device Deficiencies

6.7.1 Transmitter Deficiencies

A tabulation of all reported transmitter device deficiencies will be presented (Table 1 in APPENDIX 1).

6.7.2 Sensor Deficiencies

A tabulation of all reported sensor device deficiencies will be presented (Table 2 *in* APPENDIX 1).

6.8 Safety Endpoints

The safety endpoint is the incidence of device-related or insertion/removal procedure-related serious adverse events (SAEs) in the clinic and during home use through 90 days post-insertion.

An Adverse Event is considered 'related' if the relatedness is categorized as 'possibly related', 'or 'related'. The assessment of seriousness and relatedness made by the Medical Monitor will be used for analysis. The numbers of SAEs and the percentage of patients with SAEs will be reported for each SAE type that is observed, identified as device-related, procedure-related or unrelated to the study (Table 3 in APPENDIX 1). The count and proportion of patients experiencing at least one device-related or procedure-related SAE will be presented. No inferential statistical analysis will be performed.

<u>Other safety endpoints include:</u>

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

For each of the adverse event (AE or SAE) categories above, the numbers of AEs and the percentage of patients with AEs will be reported for each AE type that is observed and be stratified by the target age enrollment categories (Tables 4A-4E in APPENDIX 1). A listing (Table 5 in APPENDIX 1) will be prepared that identifies each patient with a reported AE or SAE, and relevant information including date of onset, severity level, seriousness, relatedness to the device or procedure, classification as anticipated or unanticipated, corrective action(s) taken, and resolution status (resolved or ongoing).

6.9 Effectiveness Endpoint

Summary

The effectiveness endpoint will be the mean absolute relative difference (MARD), calculated for all paired Sensor and reference measurements through 90 days post-insertion. For the planned interim analysis, MARD will be based on the first 30 days post-insertion data.

6.9.1.1 Effectiveness Endpoint: Criteria

The effectiveness objective is to descriptively document the distribution of absolute relative difference across all evaluable subjects and to estimate the MARD. The MARD will be estimated initially when all the subjects complete 30 days of Sensor use for the interim analysis, followed by the MARD based on all the follow-up data through 90 days of Sensor use. Descriptive statistics will be provided for the MARD. There is no hypothesis to be tested. No inferential statistical analysis will be performed.

The effectiveness endpoint is the mean absolute relative difference (MARD), defined as the average of absolute difference of paired Senseonics CGM System and reference glucose readings divided by the reference glucose reading (reference) for all reference glucose values, that is:

$$\mathbf{MARD} = \left(\left(\sum \frac{|\ (\mathbf{Glucose})_{\mathbf{SENSOR}} - (\mathbf{Glucose})_{\mathbf{REFERENCE}}\ |}{(\mathbf{Glucose})_{\mathbf{REFERENCE}}}\right) \ /\ \mathbf{n}\right) \times \mathbf{100\%},$$

Where, n is the total number of CGM and reference glucose pairs during the evaluation period, that is, after 30 days of Sensor use for the interim analysis, and after 90 days of use for the final analysis.

6.10 Exploratory Effectiveness Endpoint

Exploratory effectiveness measures are discussed in this section. Only descriptive statistics will be provided for these exploratory outcomes. All analyses will be provided as described below and by clinic visit day. SMBG glucose values may also be used as reference for some of these analyses.

6.10.1.2 System agreement with reference

The Agreement of the CGM System to reference measurements will be assessed by looking at proportions of all differences { (Glucose)SENSOR – (Glucose)REFERENCE } in intervals of [0 – 20%],

[0-30%], and [0-40%). For readings less than or equal to 80 mg/dL, the absolute difference in mg/dL between the two glucose results will be calculated. For values greater than 80 mg/dL, the absolute percent difference (%) from the reference values will be calculated.

6.10.1.3 Effectiveness measures in full glucose range and different glycemic regions

Mean/median absolute relative difference, mean/median relative difference, mean/median absolute different when reference YSI≤80 mg/dl, and Agreement between CGM and YSI glucose will be stratified based on YSI glucose ranges. Similar stratification based on CGM glucose will also be performed. (Tables 6A-6F in APPENDIX 1).

6.10.1.4 Concurrence of System Readings and YSI values

Tables for concurrence of system and YSI values will be tabulated (Tables 7A and 7B in APPENDIX 1).

6.10.1.5 Stability of the system throughout sensor life

For the full 90 day duration of the study, performance of the system overtime will be assessed by visit number (Table 8 in APPENDIX 1).

6.10.1.6 Sensor precision analysis

Sensor precision will be evaluated by paired absolute relative difference (PARD) and percent coefficient of variation (PCV). PARD is the absolute value of the Primary Sensor reading minus the paired Secondary Sensor reading divided by the average of the two Sensor readings. PCV is the standard deviation of the two paired Sensor readings divided by the average of the two paired Sensor readings. The mean values of PARD and PCV will be tabulated (Table 9 in APPENDIX 1).

$$\text{PARD} = \left(\left(\sum \frac{|(\text{Glucose})_{\text{SENSOR 1}} - (\text{Glucose})_{\text{SENSOR 2}}|}{(\text{Mean Glucose})_{\text{SENSOR 1 and 2}}}\right) / \text{n}\right) \times 100\%$$

$$\text{PCV} = \left(\left(\sum \frac{\text{SD of (Glucose)}_{\text{SENSOR 1}} \text{ and (Glucose)}_{\text{SENSOR 2}}}{(\text{Mean Glucose})_{\text{SENSOR 1 and 2}}}\right) / \text{n}\right) \times 100\%$$

6.10.1.7 Effect of compression on sensor performance during sleep challenges

For the sleep assessment periods during visits 4 & 5, compression may occur to the sensor site when the subject is sleeping at night. The system's difference and agreement with reference and between system precision will be compared between the night time and the day time (Tables 10A and 10B in APPENDIX 1).

6.10.1.8 Mean Absolute Difference between sensor and reference measurements for reference values less than or equal to 80mg/dL

The mean absolute difference (MAD) for reference glucose values less than or equal to 80 mg/dL is defined as the absolute difference of paired Senseonics CGM System and Reference readings for reference glucose values ≤ 80 mg/dL.

$$\text{MAD} = \left(\sum \left| (\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}} \right|\right) / \text{n}$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.9 Mean Absolute Difference between sensor and reference measurements for system full scale range (40-400mg/dL)

$$\text{MAD} = \left(\sum \left| (\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}} \right|\right) / \text{n}$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.10 Mean Relative Difference (%) for system full scale range (40-400mg/dL)

$$\text{MRD} = \left(\left(\sum \frac{(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}}{(\text{Glucose})_{\text{REFERENCE}}}\right) / \text{n}\right) \times 100\%$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.11 Median Absolute Relative Difference for system full scale range (40-400 mg/dL)

$$\text{Median ARD} = \text{Median}\left(\left(\frac{|\,(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}\,|}{(\text{Glucose})_{\text{REFERENCE}}}\right)_{\text{i}}\right) \text{x } 100\%, \quad \text{i} = 1, 2, \ldots, \text{n}$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.12 Median Absolute Difference between sensor and reference measurements

$$\text{Median AD} = \text{Median}\left(\left|\,(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}\,\right|_i\right), \text{i} = 1,2, \ldots, \text{n}$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.13 Median Relative Difference between sensor and reference measurements

$$\text{Median RD} = \text{Median}\left(\left(\frac{(\text{Glucose})_{\text{SENSOR}} - (\text{Glucose})_{\text{REFERENCE}}}{(\text{Glucose})_{\text{REFERENCE}}}\right)_i\right) \times 100\%, \text{ i = 1, 2, ..., n}$$

This analysis will quantify both cumulative results as well as stability over time in 30 day intervals (Tables 11A and 11B in APPENDIX 1).

6.10.1.14 Clarke Error Grid Analyses

The glucose accuracy will be assessed using the Clarke Error Grid Analysis (EGA; Figure 2 in APPENDIX 1) (Clarke et al.[15]). The EGA takes into account not only the difference between the system-generated and reference blood glucose values but also the clinical significance of this difference. The grid breaks down a scatterplot of a reference glucose meter and an evaluated glucose meter into five regions:

1. Region A contains values within 20% of the reference Sensor,
2. Region B contains values that are outside of 20% but would not lead to inappropriate treatment,
3. Region C contains values leading to unnecessary overcorrection in treatment,
4. Region D contains values indicating a potentially dangerous failure to detect hypoglycemia or hyperglycemia, and
5. Region E contains values that could lead to errors in treatment of hypoglycemia for hyperglycemia and vice-versa.

The Clarke Error Grid Analysis will be provided by reference glucose level (Table 12 in APPENDIX 1). Percent of measures in the clinical accuracy Zone A will be estimated along with 95% confidence interval.

6.10.1.15 Consensus Error Grid Analyses

Accuracy of Senseonics CGM System versus reference glucose measures will also be summarized using the consensus error grid analysis. [12] (Figure 3 and Table 13 in APPENDIX 1). The revised error grid was based on a survey of a large number of experts (100 endocrinologists) and it retains the 5–risk level format of Clarke EGA. The improved grid has slightly altered the definitions of the risk levels so as to decouple them from the specific assumptions of the Clarke Error Grid.

6.10.1.16 Evaluation of glucose alert performance

The glucose alert performance of the Senseonics CGM System will be evaluated retrospectively on Senseonics CGM and reference measurements collected to determine accuracy of hypo- and hyperglycemic states and associated sensitivity and specificity (Tables 14A and 14B in APPENDIX 1). All rates are calculated assuming both threshold and 10-min ahead predictive alerts are turned on. Only performance against YSI is evaluated. For the alert performance evaluation, the following definitions will be used.

Hypoglycemia Alert Rate:

The Alert Rate shows how often the alert was right or wrong. The True Alert Rate is the % of time the device alerted when the blood glucose level was at or below the hypoglycemia alert setting

within 15 minutes before or after the device alerted. The False Alert Rate is the % of time the device alerted when the blood glucose level was above the hypoglycemia alert setting within 15 minutes before or after the device alerted.

Hypoglycemia Detection Rate:
The Detection Rate shows how often the device recognized and alerted that there was an episode of hypoglycemia or how often it missed such an event. The Confirmed Event Detection Rate is the % of time the blood glucose level was at or below the hypoglycemia alert setting and device alerted within 15 minutes before or after the blood glucose was at or below the alert settings. The Missed Event Detection Rate is the % of time the blood glucose was at or below the hypoglycemia alert setting, but the device did not alert within 15 minutes before or after the blood glucose was at or below the alert setting.

Hyperglycemia Alert Rate:
The Alert Rate shows how often the alert was right or wrong. The True Alert Rate is the % of time the device alerted when the blood glucose level was at or above the hyperglycemia alert setting within 15 minutes before or after the device alerted. The False Alert Rate is the % of time the device alerted when the blood glucose level was below the hyperglycemia alert setting within 15 minutes before or after the device alerted.

Hyperglycemia Detection Rate:
The Detection Rate shows how often the device recognized and alerted that there was an episode of hyperglycemia or how often it missed such an event. The Confirmed Event Detection Rate is the % of time the blood glucose level was at or above the hyperglycemia alert setting and the device alerted within 15 minutes before or after the blood glucose was at or above the alert settings. The Missed Event Detection Rate is the % of time the blood glucose was at or above the hyperglycemia alert setting, but the device did not alert within 15 minutes before or after the blood glucose was at or above the alert setting.

6.10.1.17 Deming regression analysis

The glucose readings of Senseonics CGM System versus reference glucose reference will be analyzed using the Deming regression (Figure 4 in APPENDIX 1). Deming regression (Deming18) is an errors-in-variables linear model for a two-dimensional dataset. It differs from the simple linear regression in that it accounts for errors in observations on both variables. Parameter estimates will be provided for the Deming regression coefficients including slope, intercept as well as correlation coefficient.

6.10.1.18 Bland Altman analysis

A Bland Altman plot analysis will compare the difference in readings between the Sensor and reference glucose to the average of the two readings across the accuracy evaluation period (Figure 5 in APPENDIX 1).

6.10.1.19 Kaplan-Meier Analysis of Sensor Survival

The Kaplan-Meier[13] survival analysis will be used for assessing sensor life (Table 15 and Figure 6 in APPENDIX 1). Only sensors with sensor retirement alert triggered will be considered having reached end of life. Sensors with subject withdrawal or transmitter failure will be considered censored[13].

6.10.1.20 Effect of gender on sensor performance

Sensor Agreement will be stratified by gender and examined to determine whether there is any evidence of differences between genders (Table 16 in APPENDIX 1).

6.10.1.21 Effect of age on sensor performance

Sensor Agreement will be stratified by the target age enrollment categories and examined to determine whether there is any evidence of differences between groups (Table 17 in APPENDIX 1).

6.10.1.22 Effect of BMI on sensor performance

Sensor Agreement will be stratified by the target BMI enrollment categories and examined to determine whether there is any evidence of differences between groups (Table 18 in APPENDIX 1).

6.10.1.23 Effect on sensor performance in dominant or non-dominant arm

Sensor Agreement will be stratified by dominant arm and examined to determine whether there is any evidence of differences (Table 19 in APPENDIX 1).

6.10.1.24 Clinical site subgroup comparison

Sensor Agreement for subjects at the various clinical sites in the study will be compared to determine whether there is any evidence of differences (Table 20 in APPENDIX 1).

6.10.1.25 Effect of rate of change on sensor performance

Sensor Agreement for the different categories of rates of change as displayed by the system will be compared to determine whether there is any evidence of differences (Table 21 in APPENDIX 1).

6.10.1.26 Effect of race skin color on sensor performance

Sensor Agreement will be stratified by race and skin color categories and examined to determine whether there is any evidence of differences between groups (Table 22 in APPENDIX 1).

6.10.1.27 CGM satisfaction survey analysis

CGM satisfaction survey results will be tabulated (Table 23 in APPENDIX 1).

6.10.1.28 Effect of medications

The potential effects (interference) of common medications (e.g., insulin, oral hypoglycemic agents) taken by diabetic subjects on Senseonics CGM accuracy will be evaluated by examining the effectiveness endpoint results (MARD) between patients taking these medications throughout the study (i.e., at screening and upon explant) and not taking these medications throughout the study (Table 24 in APPENDIX 1).

6.10.1.29 Calibration stability

To demonstrate performance of the system spanning the duration between calibration points, the Sensor performance will be assessed using Agreement in 4-hour increments over the period from 0 to 12 hours (Table 25 in APPENDIX 1).

The example tables that compare the effectiveness endpoints calculated for the three different combinations of 2 generations of hardware and 2 generations of firmware are shown in Appendix 2.

7 References and Supporting Documentation

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APPENDIX 1: EXAMPLE FIGURES AND TABLES OF STATISTICAL ANALYSIS RESULTS

Figure 1. Subject Accountability (Sample Data) 114 Subjects Consented

17 subjects screen failures (US0116; US0216; US0219; US0306; US0405; US0503; US0509; US0601; US0603; US0604; US0605; US0606; US0609; US0612; US0613; US0614; US0620)
7 subjects withdrawn prior to insertion (US0121; US0206; US0602; US0616; US0617; US0618; US0619)

90 Subjects Completed Sensor Insertion

90 Subjects Completed Day 1 Visit with Glucose Accuracy Data Collection

90 Subjects Completed Day 7 Visit with Glucose Accuracy Data Collection

90 Subjects Completed Day 14 Visit with Glucose Accuracy Data Collection

90 Subjects Completed Day 30 Visit with Glucose Accuracy Data Collection

1 subject (US0202) lost to follow up

89 Subjects Completed Day 60 Visit with Glucose Accuracy Data Collection

1 subject (US0408) with sensor replacement alert, ending glucose data collection
2 subjects (US0221; US0505) withdrew consent

86 Subjects Completed Day 90 Visit with Glucose Accuracy Data Collection

Table 1. 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%

Table 2. 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%

Table 3. 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%)

Table 4A. Other Safety Endpoint (Sample Data)

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 device-related adverse events in the clinic and during home use	12	11 (15.5%)
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%

Table 4B. Other Safety Endpoint for Subjects between 18 and 20 Years Old (Sample Data)

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 device-related adverse events in the clinic and during home use	12	11 (15.5%)
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%

Table 4C. Safety Endpoint for Subjects between 21 and 44 Years Old (Sample Data)

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 device-related adverse events in the clinic and during home use	12	11 (15.5%)
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%

Table 4D. Safety Endpoint for Subjects between 45 and 65 Years Old (Sample Data)

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 device-related adverse events in the clinic and during home use	12	11 (15.5%)
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%

Table 4E. Safety Endpoint for Subjects over 65 Years Old (Sample Data)

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%

Table 5. Full 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

Table 6A. 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 (%).

Table 6B. 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 (%).

Table 6C. CGM System Agreement to Reference within YSI Glucose Ranges (Sample Table)

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						
< 40						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						

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
351 - 400						
> 400						

Table 6D. CGM System Agreement to Reference within CGM System Glucose Ranges (Sample Table)

CGM System 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						
40 - 60						
61 - 80						
81 - 180						
181 - 300						
301 - 350						
351 - 400						

Table 6E. CGM System Difference to YSI within Glycemic Ranges (Sample Table)

YSI Glucose Ranges (mg/dL)	Number of Paired CGM-YSI	Mean Absolute Difference (mg/dL)	Mean Absolute Relative Difference (%)
Overall			
<70			
70-180			
>180			

Table 6F. CGM System Agreement to Reference within Glycemic Ranges (Sample Table)

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						
< 70						
70-180						
>180						

Table 7A. 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										
>400										

Table 7B. 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												

Table 8. 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 30								
Day 60								
Day 90								

Table 9. CGM System between System Precision (Sample Table)

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

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

Table 10A. CGM System Performance during Sleep Challenges (Sample Table)

Night Time (Y/N)	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
Y								
N								

Table 10B. CGM System between System Precision during Sleep Challenges (Sample Table)

Night Time (Y/N)	N Pairs	PARD
Y		
N		

Table 11A. Additional Accuracy Measures in Cumulative Intervals (Sample Table)

	Level	Days 1-30	Days 1-60	Days 1-90
Mean Absolute Difference (mg/dL)	reference ≤ 80 mg/dL			
Mean Absolute Relative Difference (%)	All Results			
Mean Absolute Difference (mg/dL)	All Results			
Mean Relative Difference (%)	All Results			
Median Absolute Relative Difference (%)	All Results			

Table 11B. Additional Accuracy Measures in Successive Intervals (Sample Table)

	Level	Days 1-30	Days 31-60	Days 61-90
Mean Absolute Difference (mg/dL)	reference ≤ 80 mg/dL			
Mean Absolute Relative Difference (%)	All Results			
Mean Absolute Difference (mg/dL)	All Results			
Mean Relative Difference (%)	All Results			
Median Absolute Relative Difference (%)	All Results			

Figure 2. Clarke Error Grid (sample data)

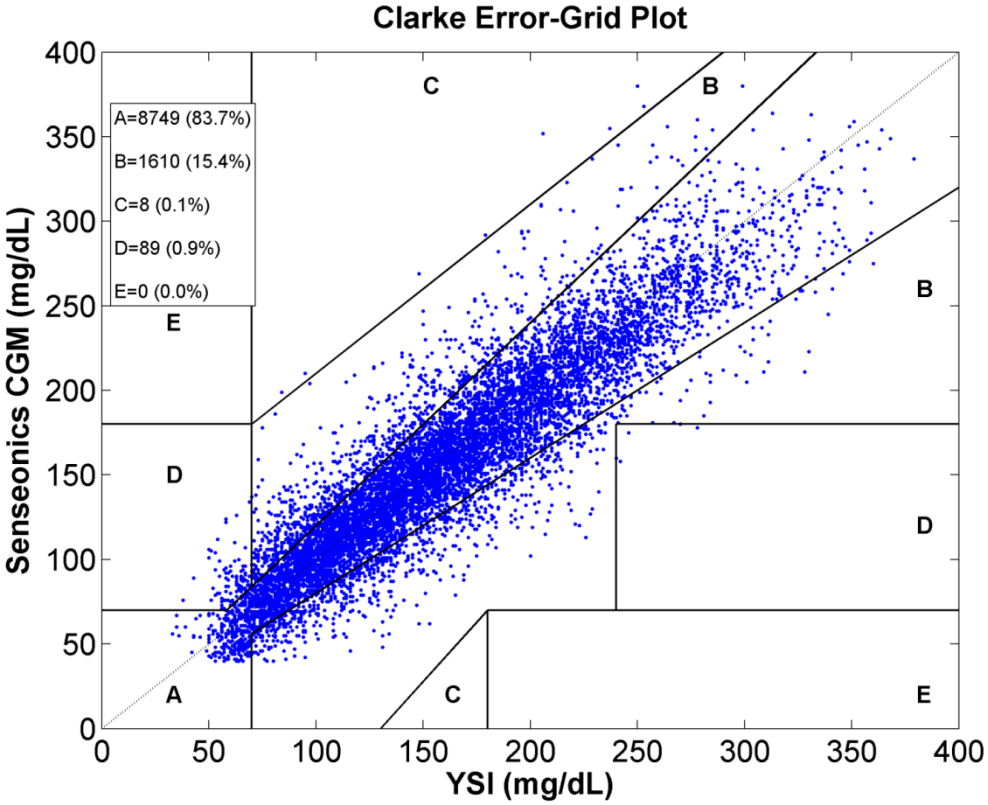

Table 12. Clarke Error Grid Analysis by Reference Glucose Level (Sample Table)

Reference Glucose Range (mg/dL)	Number of Paired System-Reference Readings	A (%; 95% CI)	B (%)	C (%)	D (%)	E (%)
≤70	423					
71-180	6645					
>180	3388					
Overall	10456					

Figure 3. Consensus Error Grid (sample data)

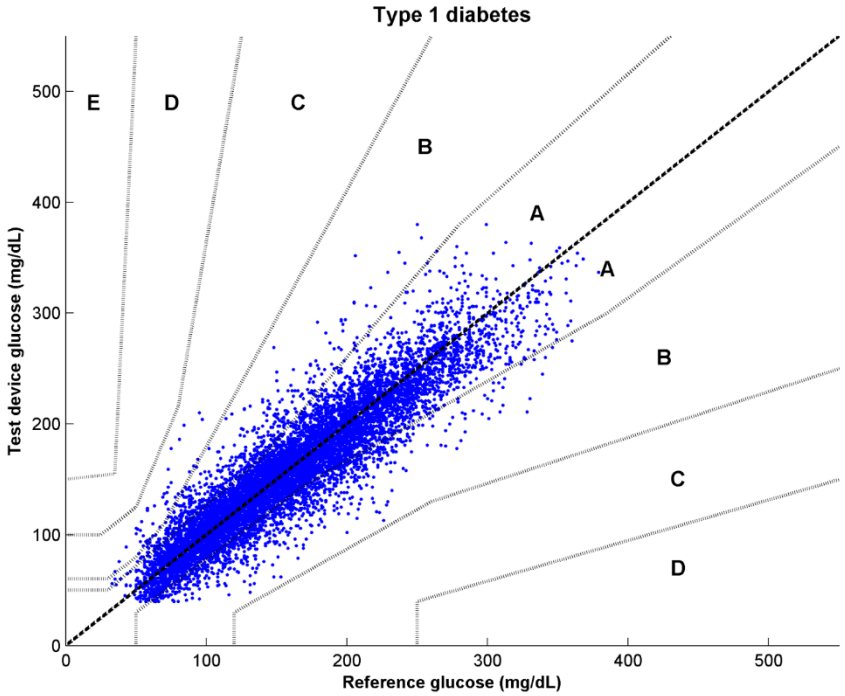

Table 13. Consensus Error Grid Analysis (sample table)

Zone	Frequency	Percent
A		
B		
C		
D		
E		
Total		

Table 14A. In-Clinic Hypoglycemic Event Detection against YSI (sample table)

Low Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
60				
70				
80				
90				

Table 14B. In-Clinic Hyperglycemic Event Detection against YSI (sample table)

High Alert Setting (mg/dL)	Confirmed Event Detection Rate	Missed Event Detection Rate	True Alert Rate	False Alert Rate
120				
140				

180				
200				
220				
240				
300				

Figure 4. Deming Regression Plot (sample data)

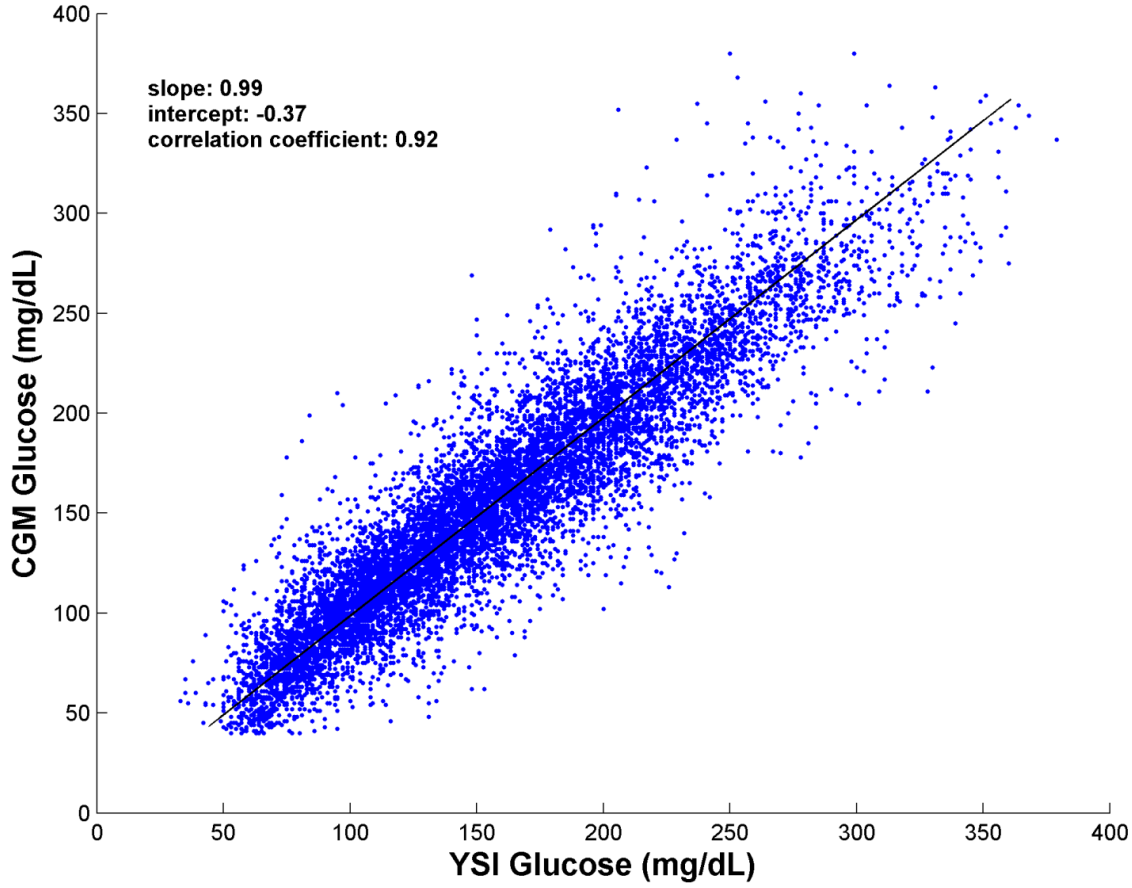

Figure 5. Bland-Altman Plot (sample data)

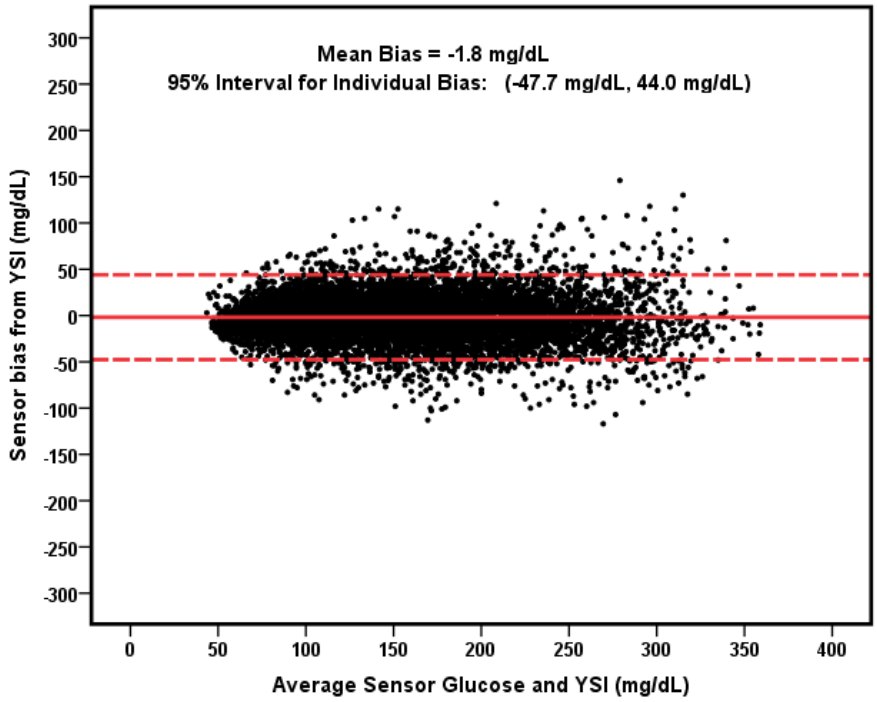

Table 15. Kaplan-Meier Survival Analysis of Sensor Life (sample data)

	Time since Implant (Days)	EOL Reached	Survival Function	SE (Peto)	Cumulative Events	Number Remaining
1	.00	No	1.0000	.0000	0	44
2	1.06	No	1.0000	.0000	0	43
3	32.51	No	1.0000	.0000	0	42
4	50.84	No	1.0000	.0000	0	41
5	65.97	No	1.0000	.0000	0	40
6	68.51	Yes	.9750	.0244	1	39
7	70.40	Yes	.9500	.0340	2	38
8	78.96	Yes	.9250	.0411	3	37
9	79.13	Yes	.9000	.0468	4	36
10	85.60	Yes	.8750	.0516	5	35
11	88.27	No	.8750	.0523	5	34
12	89.27	No	.8750	.0531	5	33
13	89.27	No	.8750	.0539	5	32
14	90.22	No	.8750	.0547	5	31

Figure 6. Kaplan-Meier Survival (sample data)

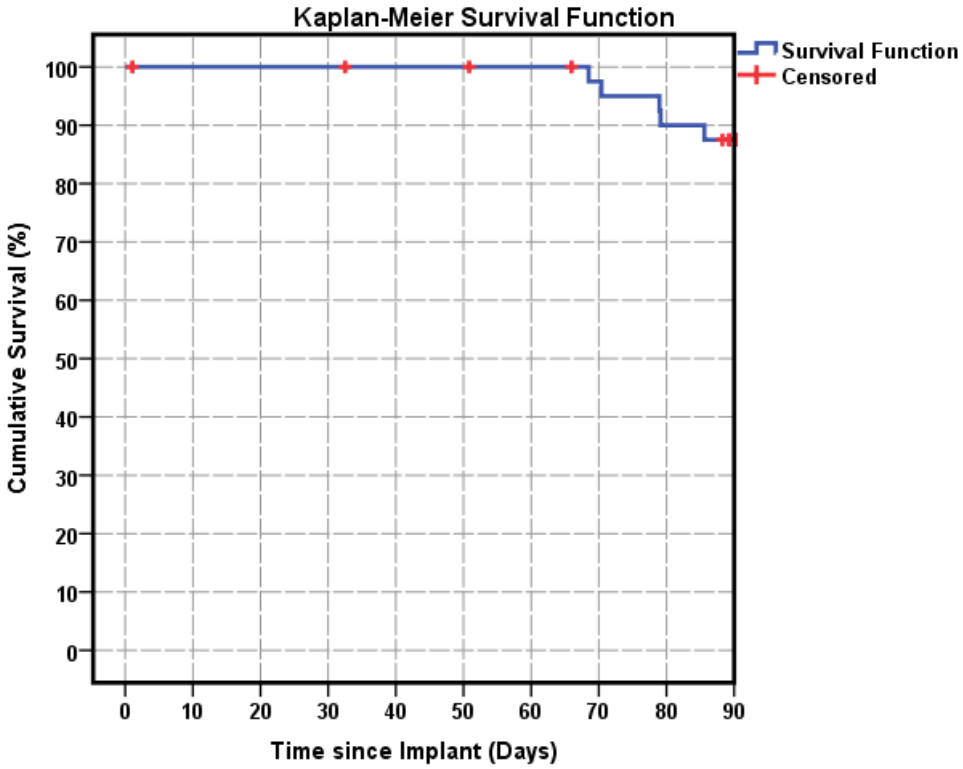

Table 16. Effect of Gender on System and Reference Agreement (sample table)

Gender	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
M				
F				

Table 17. Effect of Age on System and Reference Agreement (sample table)

Age	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
18-20				
21-44				
45-65				
Over 65				

Table 18. Effect of BMI on System and Reference Agreement (sample table)

BMI	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
< 25				
[25, 30)				
≥ 30				

Table 19. Effect of Dominant Hand on System and Reference Agreement (sample table)

Dominant Hand (Y/N)	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
Y				
N				

Table 20. Effect of Clinical Site on System and Reference Agreement (sample table)

Site Number	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
1				
2				
3				

Table 21. Effect of Rate of Change on System and Reference Agreement (sample table)

System Rate of Change	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
<-2				
[-2,-1)				
[-1,1]				
(1,2]				
>2				

Table 22. Effect of Race or Skin Color on System and Reference Agreement (sample table)

Race and Skin Color Category	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
Race and Skin Color Category 1				
Race and Skin Color Category 2				
Race and Skin Color Category 3				

Table 23: CGM Satisfaction Survey Results (sample table)

Survey Questions	Agree Strongly (N/%)	Agree (N/%)	Neutral (N/%)	Disagree (N/%)	Disagree Strongly (N/%)
Question 1					
Question 2					
⋮					
Question N					

Table 24. Effect of Medications (sample table)

Class of Medication	Subjects Taking Medication	MARD with Medication [mean (SD) / n]	MARD with No Medication [mean (SD) / n]	P-value
Diabetes Medication				
Thyroid Medication				
Hypertension Medication				
Cholesterol Medication				

Table 25. Calibration Stability (sample table)

Time from Calibration	Number of Paired Senseonics CGM and Reference	Percent within 20/20% Reference	Percent within 30/30% Reference	Percent within 40/40% Reference
0-4 hours				
4-8 hours				
8-12 hours				

APPENDIX 2: EXAMPLE FIGURES AND TABLES OF STATISTICAL ANALYSIS RESULTS FOR THE DIFFERENT HARDWARE AND FIRMWARE COMBINATIONS

Table 2.1. Investigational Transmitter Deficiencies (Sample Table)

	Gen 1 Tx		Gen 2 Tx	
Type of Transmitter Deficiency	**Number Reported**	**% of Total**	**Number Reported**	**% of Total**
Package Label	TBD	TBD	TBD	TBD
Product Defect	TBD	TBD	TBD	TBD
Damaged Package	TBD	TBD	TBD	TBD
Product Safety	TBD	TBD	TBD	TBD
Product Performance	TBD	TBD	TBD	TBD
Other	TBD	TBD	TBD	TBD

Table 2.2. CGM System Difference to YSI within YSI Glucose Range (Sample Table)

CGM System Difference to YSI within YSI Glucose Range				
YSI Glucose Range (mg/dL)	**Number of Points**	**Hardware Version (Firmware Version)**		
		Gen 1 Tx (Study FW)	**Gen 2 Tx (Study FW)**	**Gen 2 Tx (Updated FW)**
Mean Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
<40*	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Median Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
<40*	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Mean Absolute Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
<40*	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD

CGM System Difference to YSI within YSI Glucose Range				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Median Absolute Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
<40*	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

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

Table 2.3. CGM System Difference to YSI within CGM System Glucose Range (Sample Table)

CGM System Difference to YSI within CGM System Glucose Range				
CGM Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Mean Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
Median Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD

CGM System Difference to YSI within CGM System Glucose Range				
CGM Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Mean Absolute Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
Median Absolute Relative Difference (%)				
Overall	TBD	TBD	TBD	TBD
40-60*	TBD	TBD	TBD	TBD
61-80*	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD

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

Table 2.4. CGM System Agreement to Reference within YSI Glucose Ranges (Sample Table)

Percent of CGM System Readings Agreement By YSI Range				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Within 15/15%				
Overall	TBD	TBD	TBD	TBD
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Within 20/20%				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD

Percent of CGM System Readings Agreement By YSI Range				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Within 30/30%				
Overall	TBD	TBD	TBD	TBD
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Within 40/40%				
Overall	TBD	TBD	TBD	TBD
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

Table 2.5. CGM System Agreement to Reference within CGM System Glucose Ranges (Sample Table)

Percent of CGM System Readings Agreement By CGM Range				
CGM Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Within 15/15%				
Overall	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
Within 20/20%				
Overall	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD

Percent of CGM System Readings Agreement By CGM Range				
CGM Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
Within 30/30%				
Overall	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
Within 40/40%				
Overall	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD

Table 2.6. Concurrence of CGM System Readings and YSI Values within YSI Glucose Ranges (Sample Table)

Table 2.6A

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Gen 1 Tx (Study FW) 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										
>400										

Table 2.6B

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Gen 2 Tx (Study FW) 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										
>400										

Table 2.6C

YSI (mg/dL)	Number of Paired CGM-YSI (n)	Gen 2 Tx (Updated FW) 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										
>400										

Table 2.7. Concurrence of CGM System Readings and YSI Values within CGM System Ranges (Sample Table)

Table 2.7A

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Gen 1 Tx (Study FW) 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												

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Gen 1 Tx (Study FW) 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
161-200												
201-250												
251-300												
301-350												
351-400												

Table 2.7B

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Gen 2 Tx (Study FW) 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												

Table 2.7C

CGM (mg/dL)	Number of Paired CGM-YSI (n)	Gen 2 Tx (Updated FW) 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												

Table 2.8. CGM System Accuracy by Visit Number (Sample Table)

Table 2.8A

Percent of CGM System Readings within 15/15%				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Day 1				

Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 7				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 14				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 30				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

Table 2.8B

Percent of CGM System Readings within 20/20%				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Day 1				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 7				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 14				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 30				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

Table 2.8C

Percent of CGM System Readings within 30/30%				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Day 1				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 7				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 14				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 30				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

Table 2.8D

Percent of CGM System Readings within 40/40%				
YSI Glucose Range (mg/dL)	Number of Points	Hardware Version (Firmware Version)		
		Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Day 1				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 7				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 14				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD
Day 30				
Overall				
<40	TBD	TBD	TBD	TBD
40-60	TBD	TBD	TBD	TBD
61-80	TBD	TBD	TBD	TBD
81-180	TBD	TBD	TBD	TBD
181-300	TBD	TBD	TBD	TBD
301-350	TBD	TBD	TBD	TBD
351-400	TBD	TBD	TBD	TBD
>400	TBD	TBD	TBD	TBD

Table 2.9. System Reliability

System Reliability	Transmitter Version	
	Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)
Matched CGM-YSI Pairs	TBD*	TBD *
Number of Sensors Logging Data with Transmitter	TBD	TBD
Mean Number of Matched Pairs Per Sensor	TBD	TBD

* Does not include data when the Systems displays High or Low Glucose

Table 2.10. CGM System Performance during Sleep Challenges (Sample Table)

During Night	Hardware Version (Firmware Version)		
	Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Mean Absolute Relative Difference (%)	TBD	TBD	TBD
Median Absolute Relative Difference (%)	TBD	TBD	TBD
15/15%			
20/20%			
30/30%			
40/40%			

During Day	Hardware Version (Firmware Version)		
	Gen 1 Tx (Study FW)	Gen 2 Tx (Study FW)	Gen 2 Tx (Updated FW)
Mean Absolute Relative Difference (%)	TBD	TBD	TBD
Median Absolute Relative Difference (%)	TBD	TBD	TBD
15/15%			
20/20%			
30/30%			
40/40%			

Table 2.11. CGM System between System Precision during Sleep Challenges (Sample Table)

Night Time (Y/N)	N Pairs	Gen 1 Tx (Study FW) PARD	Gen 2 Tx (Study FW) PARD	Gen 2 Tx (Updated FW) PARD
Y				
N				