Senseonics

A Post Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System

Protocol Number CTP-0034, Version 10

Statistical Analysis Plan

Version 1.0, 08NOV2023

Version History

Version	Version Date	Author/Title	Summary of Key Changes
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Document Approval

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Table of Contents

1 Introduction

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 CTP-0034. This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol Version 10, 20 March 2023. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Study Objectives

2.1 Primary Objective

The primary safety objective of the study is to demonstrate the long-term safety of the Eversense CGM System.

The primary effectiveness objective of the study to demonstrate the long-term effectiveness of the Eversense CGM System.

2.2 Study Endpoints

The primary safety endpoint is incidence of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity.

The primary effectiveness endpoint is time in range, defined as glucose values between 70 mg/dL and 180 mg/dL, at 12 months compared to the first month post-first Sensor insertion.

3 Study Design

Prospective, multi-center study at up to 30 sites in the U.S. enrolling up to 400 adult subjects with diabetes (to insert 273 subjects) including at least 40 subjects ≥65 years to achieve at least 1400 Sensor cycles. The subjects will have one Sensor inserted by trained health care professionals approximately every 3 to 6 months dependent upon the Sensor used (90-day Eversense Sensor or 180-day Eversense E3 Sensor).

3.1 Blinding

There is no blinding in this study.

4 Sample Size Determination

At least 273 enrolled subjects will be inserted with Sensors to achieve at least 1400 Sensor cycles. Subjects will be encouraged to remain in the study up to 27 months of follow-up or after at least 1400 Sensor cycles are completed study wide.

Based on data from the PRECISE (n=81 subjects), PRECISE II (n=90 subjects), PRECISION (n=35 subjects) and PMCF (n=1686 subjects) studies, a total of 31 events occurred that would meet the definition of the primary safety endpoint in this study. With a total of 1892 subjects, this equates to an observed rate of approximately 1.6% with an associated 95% confidence interval of 1.1% to 2.3%. As there is variability associated with this sample, as evidenced by the confidence interval, a conservative expected rate of events for this study is 2.3%. The planned sample size of 1400 total cycles) with this expected rate should provide greater than 95% power for the test of the performance goal of 4%.

Meeting the performance goal of 4% for the planned sample size would require a worst-case observation of a rate of approximately 3% or less (i.e., 41 or fewer events among 1400 cycles). This result will be clinically acceptable and similar to results observed in past studies.

5 Statistical Analyses

5.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required.

5.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

5.1.2 Study Day

Study day 0 is the date of the index procedure. Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = End Date – Start Date

5.1.3 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.

5.2 Analysis Populations

Primary Analysis population: The primary safety and effectiveness analyses will be based on data from all enrolled subjects in this post approval study (ITT, Intention-to-treat).

Per-Protocol Safety Analysis Population: A per-protocol (PP) population will be identified based on those subjects who met the original inclusion and exclusion criteria, have demonstrated substantial compliance with the protocol and no significant protocol deviations affecting the primary endpoints. Supportive analyses for the primary effectiveness endpoint and all secondary and exploratory analyses will be performed in the PP population.

5.3 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.

5.4 Subject Disposition

The number of subjects in each analysis population 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.

5.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables.

5.6 Analysis of Study Endpoints

5.6.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity.

5.6.1.1 Primary Analysis

The primary safety composite endpoint will be evaluated in the following hypothesis, against a Performance Goal of 4%:

H0: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is greater than or equal to 4%.

$H0: p \geq 4\%$

H1: The rate of the composite of infection, secondary procedures to remove the Sensor, or procedure-related adverse events of at least moderate severity (p) is less than 4%.

$H1: p < 4\%$

The rate will be tested against the Performance Goal of 4%, using an exact, binomial test, with a one-sided p-value of 0.05 considered evidence of statistical significance. For the primary analysis, data will be analyzed on a per cycle basis, with each cycle contributing an independent observation.

The endpoint will be evaluated using the ITT analysis set.

5.6.1.2 Sensitivity Analysis

Sensitivity analyses for the primary safety endpoint will be performed including:

- Analysis using the PP safety analysis population.
- As an additional analysis, analysis will be performed using a logistic regression model fit via generalized estimating equations and a working compound symmetric covariance structure; this allows for the modeling of potential within-subject correlation. The model will consist of only an intercept term; estimates will be transformed to the proportion scale to facilitate comparisons to the primary analysis of the performance goal.
- An additional analysis will be performed based on only the first cycle for each subject. This will be based on an exact binomial method.

For each sensitivity analysis, the estimated endpoint rate and the associated one-sided 95% confidence interval will be calculated.

5.6.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is Time in range, defined as glucose values between 70 mg/dL and 180 mg/dL, at 12 months compared to the first month post-first sensor insertion.

5.6.2.1 Primary Analysis

Effectiveness will be measured as percentage change in the percent time in range (based on hours) at one month post-first sensor insertion compared to 12 months post-first sensor insertion using a time in range definition of glucose values between 70 mg/dL and 180 mg/dL. The Time in Range will be summarized as the mean of the subject percentages, together with the median, standard deviation, minimum, maximum, and 25th / 75th percentiles.

Summary statistics will also be provided for the change in HbA1c levels from baseline, and average hours of use per day.

5.6.2.2 Sensitivity Analysis

Sensitivity analyses for the primary safety endpoint will be performed including:

- Analysis using the PP safety analysis population

5.6.3 Additional Safety Endpoints

There are no formal hypotheses or tests for statistical significance associated with additional safety endpoints. Analyses will be based on the general methods outlined in this SAP. The following additional endpoints will be summarized with descriptive statistics, overall, and by subgroups as defined in Section 6.9:

- Rate of all device-related and insertion and removal procedure-related adverse events
- Rate of device breakage
- Rate of device-related and insertion and removal procedure related
- Serious adverse events up to 27 months post-first sensor insertion

5.6.4 Additional Effectiveness Endpoints

There are no formal hypotheses or tests for statistical significance associated with additional effectiveness endpoints. Analyses will be based on the general methods outlined in this SAP. The following additional endpoints will be summarized with descriptive statistics.

- Average hours of use per day
- Change in HbA1c levels at each 6-month interval from baseline

5.6.5 Secondary/Other Endpoints

There are no formal hypotheses or tests for statistical significance associated with secondary endpoints. Analyses will be based on the general methods outlined in this SAP. The following additional endpoints will be summarized with descriptive statistics:

- Patient satisfaction with CGM system use (CGM-SAT scale) including total score and 2 subscale scores (Benefits and Lack of Hassles)
- Patient reported Diabetes Distress Scale (DDS) including the total and 4 subscale scores (Emotional Burden, Physician Distress, Regimen Distress, and Interpersonal Distress)
- Success rate of insertion and removal procedures, overall and by HCP experience (learning curve by number of cases), to evaluate the training program
- Rate of serious adverse events based on HCP experience with the insertion and removal of Sensors (learning curve by number of cases)
- HCP feedback questionnaire regarding insertion/removal
- Residual dexamethasone level in explanted sensors

5.7 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational sites will be evaluated using a regression model for site. If the p-value for the site effect is <0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site. Assessment of poolability by <geography (US vs. OUS) will be performed as described for site.

5.8 Safety Analyses

Adverse events (AE) will be reported for the ITT primary analysis population. AEs 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. The rate of all AEs and SAEs reported in the study will be reported.

All AEs and SAEs will also be summarized by relatedness as described above. Adverse events leading to death or study discontinuation will be provided in listing format.

All device deficiencies will be reported in listing format.

5.9 Subgroup Analyses

Subgroup analysis of the primary safety, primary effectiveness, and additional safety endpoints will be performed for the following subgroups: sex, age (Age<median , Age≥median), race (Caucasian vs. non-Caucasian), diabetes type (I vs. II), and sensor life (90-day vs. 180-day). In addition, the rate of procedure-related adverse events will be performed for the subgroup defined by subjects receiving care from a healthcare provide with vs. without an MD degree). These analyses are intended to demonstrate consistency of results across subgroups.

Subgroup analyses will be performed using the primary analysis set. For each subgroup, a regression model will be fit that includes a fixed effect for subgroup. If the p-value for the subgroup term is less than 0.15, additional exploratory analysis may be performed to understand any variations in outcomes by subgroup.

For each subgroup analysis, the summary statistics for each subgroup level will be presented.

5.10 Interim Analyses

Statistical analysis with interim reports will be initiated per FDA PAS guidelines of every 6 months for the first 2 years and annually thereafter. Study hypotheses will be evaluated at end of study.

5.11 Protocol Deviations

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

6 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.

7 Subject Listings

Subject listings of individual subject values (or summary values, as appropriate) will be provided for the primary endpoints.