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A Pivotal Study to Evaluate Enlite™ Sensor Performance with iPro™2 in China

Statistical Analysis Plan

V1.0

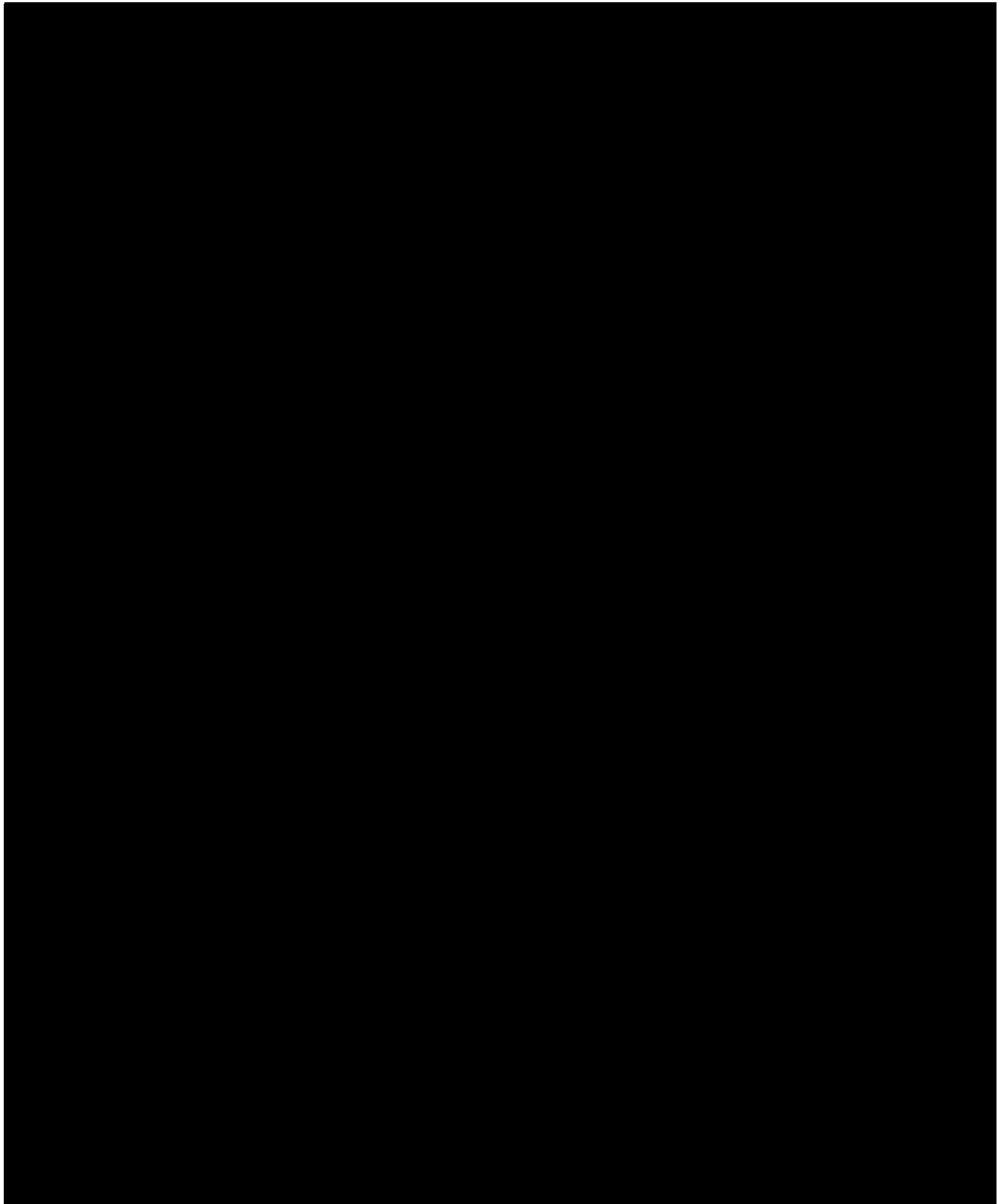
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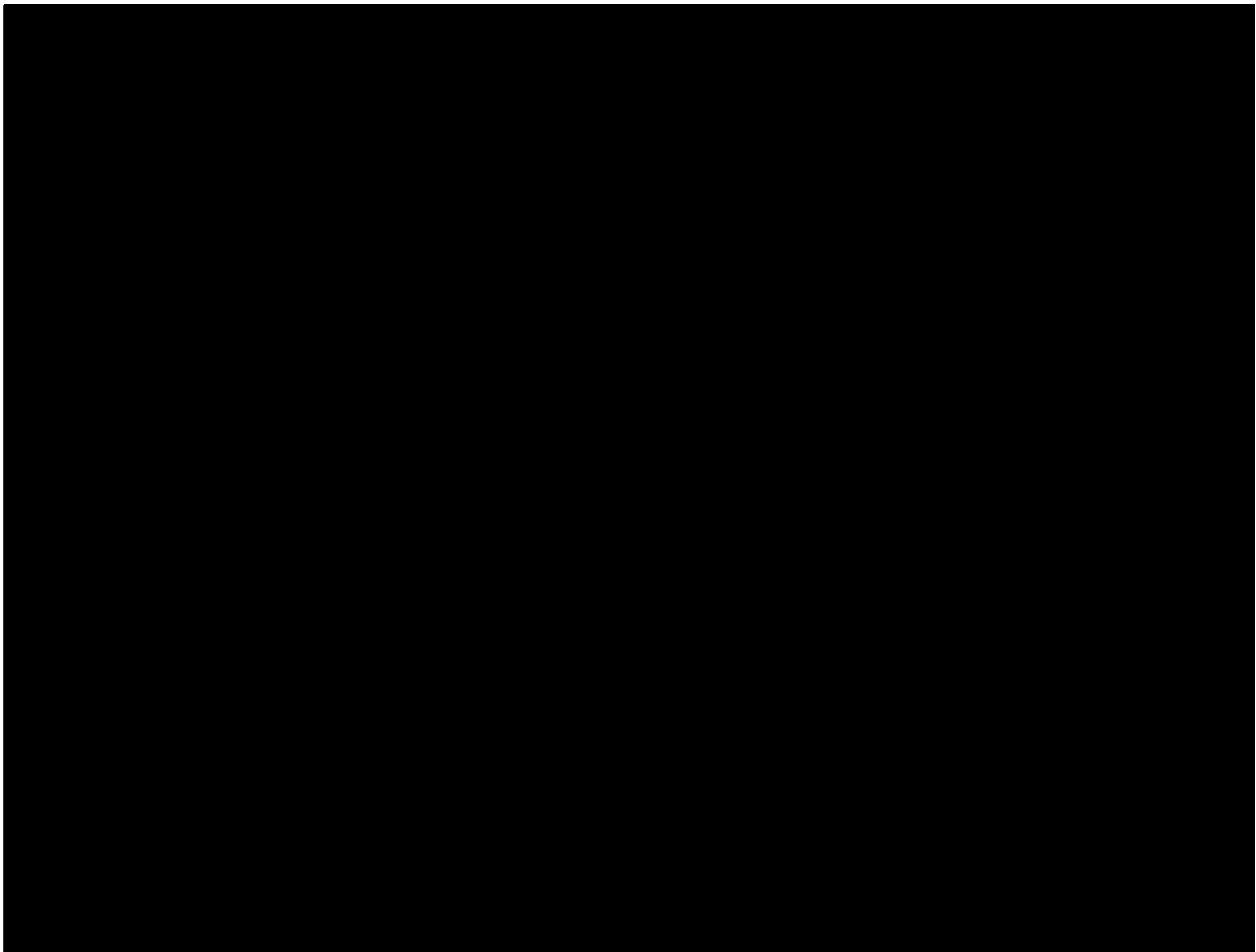
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1. Version History

Version	Summary of Changes	Author(s)/Title
V1.0	Not applicable	[REDACTED]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
ARD	Absolute Relative Difference
BG	Blood Glucose
BMI	Body Mass Index
CEC	Clinical Events Committee
CFDA	China Food and Drug Administration
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CIP	Clinical Investigation Plan
CTA	Clinical Trial Approval
CV	Curriculum Vitae
DKA	Diabetic Ketoacidosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EGA	Error Grid Analysis
ER	Emergency Room
EOS	End of Study
FST	Frequent Sample Testing
Hct	Hematocrit
ICF	Informed Consent Form
ISIG	Interstitial Signal
IV	Intravenous
MARD	Mean Absolute Relative Difference
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
POC	Point of Care
QC	Quality Control
SAE	Serious Adverse Event
SGV	Sensor Glucose Value

SID	Subject Identification
SMBG	Self-Monitoring of Blood Glucose
SQ	Subcutaneous
SSL	Secure Socket Layer
UADE	Unanticipated Adverse Device Effect
USB	Universal Serial Bus
YSI	Yellow Springs Instrument

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3. Introduction

The iPro2 recorder is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace, blood glucose (BG) information obtained using standard home glucose monitoring devices. The information collected by the iPro2 recorder may be downloaded to a computer and reviewed by healthcare professionals. The information may allow identification of patterns of glucose-level excursions above and below a desired range, facilitating therapy adjustments, which may minimize these excursions.

The study is designed to demonstrate the performance of the Enlite Sensors used with the iPro2 when inserted in the abdomen of subjects ages 14 – 75 years and used for 6 days.

Accuracy data will be calculated based on comparing values from the iPro2 and Enlite Sensor to a “gold standard” (Yellow Springs Instrument [YSI™] plasma glucose values) in subjects during YSI frequent sample testing (FST). YSI glucose analyzers have been recognized standards for the measurement of BG and will be utilized across the investigational centers for the tests.

The purpose of this study is to demonstrate the performance and safety of the Enlite Sensor over 6 days when inserted in the abdomen and used with the iPro2 in subjects age 14 – 75 years.

This document provides details of the statistical analysis plan (SAP) for the clinical trial of evaluating the performance and safety of the Enlite Sensor over 6 days when inserted in the abdomen and used with the iPro2 in subjects age 14 – 75 years. The statistical analysis report will be issued for registration and declaration after the subjects complete study or terminate the trial early and the database is locked. See the table, listing and figure in the statistical analysis plan.

4. Study Objectives

The primary objective of the study is to demonstrate the accuracy of Enlite Sensor when connected to iPro2 when used over a period of 6 days.

5. Investigation Plan

5.1 Study Design

This study is a multi-center, randomized, prospective single-sample correlational design without controls. Up to 72 subjects will be enrolled in order to have approximately 60 subjects complete the study. Three investigational centers in China will be used during this study.

Each subject will wear the following devices:

- Two Enlite Sensors each connected to an iPro2 for approximately 6 days

Sensor Location:

- The 2 Enlite Sensors will be worn in the abdomen area. Investigational center staff will insert sensors and connect to the iPro2s.

During the study, each subject will be randomized and undergo one Yellow Springs Instrument (YSI™) frequent sample testing (FST) (Day 1, 3-4, or 6).

On the evening prior to FST, subjects will be asked to fast for approximately 12 hours and adjust their insulin and medications according to routine care (for example as they would do for fasting lipid panel). Subjects may fast for shorter period of time **based on investigator discretion**.

The subject should be in fasting status upon arrival hospital to start FST process. **The feeding protocol may be modified based on investigator discretion**. The duration of FST will be approximately 7 hours.

During the study, subjects will continue with their current diabetes regimen independent of the study devices. Subjects will be instructed by the investigational center that they are not to use the study devices (except for the study meter) for the management of their diabetes. The Study Meter may be used for treatment decisions and calibration of Enlite Sensor.

Fingerstick Testing: A minimum of 4 fingerstick glucose readings per day will be requested for subjects. Subjects should test prior to meals and at bedtime.

5.2 Primary Endpoint

The primary endpoint is 20/20% consistency evaluation with the reference value which is expressed by the agreement rate.

Sensor values from primary sensor will be compared to YSI plasma glucose values during YSI FSTs to analyze the agreement rate. Consistency rate = A + B:

A = (the number of pairs of the deviation of sensor value from primary sensor minus YSI value is within $\pm 20\%$ /total number of pairs) * 100% (when the blood glucose concentration is greater than 4.4 mmol/L (80 mg/dL), percentage of results with deviations from the reference value within $\pm 20\%$);

B = the number of pairs of the deviation of sensor value from primary sensor minus YSI value is within ± 20 mg/dL /total number of pairs) * 100% (when the blood glucose concentration is less than or equal to 4.4 mmol/L (80 mg / dL), percentage of results with deviations from the reference value within ± 1.1 mmol/L (20mg/dL).

5.3 Secondary Endpoints

The secondary endpoints are including mean absolute relative difference (MARD), mean rate in Zone A+B of Clarke Error Grid and Consensus Error Grid.

The MARD is calculated by the following formula:

$$ARD_k = 100\% \frac{|y_{CGM}(t_k) - y_{ref}(t_k)|}{y_{ref}(t_k)}$$

$$MARD = \frac{1}{N} \sum_{k=1}^N ARD_k$$

5.4 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Subject is 14 - 75 years of age at time of screening
2. Subject has a clinical diagnosis of type 1 or 2 diabetes as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
3. Subject has adequate venous access as assessed by investigator or appropriate staff
4. Subject is willing to follow the study procedures and willing to come to study visits.
5. Subject is willing to perform at least 4 self-monitoring of blood glucose (SMBG) per day for 6 days

Exclusion Criteria:

1. Subject will not tolerate tape adhesive in the area of Enlite Sensor placement as assessed by qualified individual.
2. Subject has any unresolved adverse skin condition in the area of study device or device placement (e.g., psoriasis, rash, *Staphylococcus* infection)
3. Subject is actively participating in an investigational study (drug or device) wherein they have received treatment from an investigational study (drug or device) in the last 2 weeks
4. Subject is female and has a positive pregnancy screening test
5. Females of child bearing age and who are sexually active should be excluded if they are not using a form of contraception deemed reliable by investigator
6. Subject is female and plans to become pregnant during the course of the study
7. Subject has a hematocrit (Hct) lower than the normal reference range

Subject may not be on the research staff of those performing this study

5.5 Study Timeline

The subject's participation from study start to completion is approximately 1 – 3 weeks (including replacement sensor wear and repeat in clinic procedures).

Additional rescheduled visits could occur if Enlite Sensors dislodge and new Enlite Sensors must be re-inserted.

- Visit 1: Consent and Screening
- Visit 2: Randomization
 - Visit 1 and 2 can be combined, however all eligibility criteria on Visit 1 should be met, including review of Hct prior to Visit 2.
 - Visit 1 and Visit 2 should be no more than 2 weeks apart.
- Visit 3: Study Training and iPro2 Placement & Sensors Insertion
 - Two Enlite Sensors each connected to an iPro2
 - Dispense Patient Log Sheet
- Visit 4: YSI FST.
 - Study training and iPro2 placement & sensors insertion (Day 1 subjects who have not already received study training and iPro2 placement and sensor insertion from Visit 3)
 - Subjects will undergo one YSI FST on any one of the following sensor wear days:
 - Day 1 (1 – 25 hours)
 - Day 3 – 4 (49 – 97 hours)
 - Day 6 (121 – 145 hours)
- Visit 5: End of Study (EOS) Visit
 - iPro2 removed (**Please note that the subject should target wearing the device for 145 hours or longer from time of insertion**)
 - Investigational center staff will:
 - Download the iPro2 data from CareLink iPro following completion of the study devices wear
 - Obtain subject's Study Meter BG values and enter into CareLink iPro
 - Collect subject's Patient Log Sheet
 - Provide iPro2 data to sponsor
 - Return study devices
 - Subject complete questionnaires
 - Random assignment for primary sensor and secondary sensor via RDC

Guidelines for Combining Visits:

- All subjects meeting eligibility criteria:

- Visit 1 and 2 can be combined, however all eligibility criteria on Visit 1 should be met, including review of Hct prior to Visit 2.
- Subjects randomized to FST Day 1
 - Subjects doing FST on Day 1 may combine Visit 2 and Visit 3 as long as they are able to perform Visit 4 FST in the second half of FST day.
 - For example, subject does Visit 1 and 2 in the morning and performs Visit 3 in the afternoon. Subjects comes in the next day for Visit 4 in the morning within approximately 25 hours from time of insertion.
- Subjects randomized to FST Day 3-4
 - May combine Visit 2 and Visit 3
- Subjects randomized to FST Day 6
 - May combine Visit 2 and Visit 3
 - May combine Visit 4 and Visit 5 as long as the subject has worn N=145 hours.

6. General Statistical Considerations

6.1 Study Hypothesis

The primary endpoint in this study is 20/20% consistency evaluation with the reference value which is expressed by the agreement rate. Single-armed comparison against target value will be used for the study design, the corresponding hypothesis is:

$$H_0: \mu \leq 60\%$$

$$H_1: \mu > 60\%$$

Where μ represents the expected mean agreement rate for 20/20% consistency evaluation, 60% represents the target rate. The 97.5% lower confidence limit of the mean agreement rate will be tested against corresponding threshold.

6.2 Sample Size Determination

The sample size selected is based on the primary effectiveness endpoint (i.e., accuracy), agreement in comparative readings of paired sensor and YSI glucose readings.

Based on pervious study, using one sample T test (formula provided below) with α level of 0.975 (one sided), β of 0.8, μ_0 is 0.6, μ_α is 0.72 and σ is 0.32:

$$n = \sigma^2 \frac{(t_\alpha + t_\beta)^2}{(\mu_0 - \mu_\alpha)^2}$$

it is indicated that a sample size of 58 will have power greater than or equal to 80% to demonstrate that the overall agreement rate is greater than 0.6. Considering 20% drop out, we need to enroll 72 subjects.

6.3 Analysis Population

Full analysis set (FAS^{#1}): a set of subjects who have a Enlite Sensor inserted.

Full analysis set (FAS^{#2}): a set of subjects who have a Enlite Sensor inserted and have at least one paired Enlite Sensor and YSI measurement.

Per-Protocol Set (PPS) refer to the subgroup population of FAS^{#2} who have no major protocol violations (subjects that violate the inclusion criteria, meet the exclusion criteria, etc.).

Safety Set (SS) will use the same definition method of FAS^{#1}, hence it will not be defined alone in the analysis.

Primary efficacy analysis and secondary efficacy analysis will be analyzed based on both the FAS^{#2} and PPS. All the baseline demographic data and safety evaluation will be analyzed based on the FAS^{#1}.

6.4 Analysis Population Set Determination Details

(1) No Enlite Sensor inserted: Subjects obtain randomization number, but have no Enlite Sensor inserted.

(2) No paired Enlite Sensor and YSI measurement: Subjects obtain randomization number and have a Enlite Sensor inserted, but have no paired Enlite Sensor and YSI measurement.

(3) Violation of Inclusion/Exclusion criteria: Subjects do not meet the inclusion criteria or meet the exclusion criteria pre-specified in the protocol, and this protocol deviation may severely affect the results of primary effective endpoint. Whether protocol deviation severely affect the results of primary effective endpoints will be judged together by sponsor, investigators and statistician through discussion;

(4) $FAS^{#1}$ = Number of the randomized subjects – Number of subjects who have no Enlite Sensor inserted;

$FAS^{#2}$ = Number of $FAS^{#1}$ – Number of subjects who have no paired Enlite Sensor and YSI measurement;

PPS = Number of $FAS^{#2}$ - Number of subjects who severely violate study protocol (i.e. violate inclusion and exclusion criteria, etc.).

The listing of subjects who have no Enlite Sensor inserted or severely violate study protocol will be listed, including the center number, registration number, gender, age, type, details, $FAS^{#1}$, $FAS^{#2}$ and PPS.

6.5 Missing Values, Abnormal Value and Outliers

Data entry error or non-reasonable values will be cleaned before data analysis. No imputations will be done for missing data.

All withdrawals subjects will be included in the final statistical analysis. For the missing primary endpoint data due to early withdrawal, no imputations will be done for missing data.

For the dates collected during the trail, if the day or month or year is filled with "UK" or "NA" , they will not be processed.

6.6 General Considerations for Data Analysis

6.6.1 Data Collection

(1) Primary endpoint, secondary endpoints, and other descriptive endpoints will be based on retrospective data collected from primary sensor.

(2) Precision analysis will be based on data collected from both sensors.

6.6.2 Pairing Scheme

(1) All YSI and fingerstick values collected will be presented. Most of descriptive analyses will include all YSI values, such as those less than ($<$) 40 mg/dL, or greater than ($>$) 400 mg/dL as long as Enlite Sensor values are greater than or equal to (\geq) 40 mg/dL or less than or equal to (\leq) 400 mg/dL (displayed to users as Low or High without numerical numbers).

Reference glucose values (YSI values or fingerstick values) will be paired with the closest Enlite Sensor value between [0, 5) minutes.

(2) The primary Enlite Sensor will be used as a reference for precision analysis. Reference glucose values (primary Enlite Sensor) will be paired with the closest Enlite Sensor value between [0, 5) minutes

(3) Clarke EGA will be restricted to YSI values of 40-400 mg/dL. The same pairing scheme will be utilized.

6.6.3 YSI Retention

All YSI values will be captured and retained in OC-RDC database. However, if the difference between Result A (black) and Result B (white) is greater than ($>$) 5%, the YSI values will not be included in the analysis dataset. The corresponding details in analysis of YSI are as following:

(1) At first, delete observations which were identified as deletion according to “deletion flag” collected in OC-RDC database;

(2) Calculate absolute relative difference between Result A (black) and Result B (white) by the formula: $|\text{Result A (black)} - \text{Result B (white)}| / \text{Result A (black)} * 100\%$. If the ARD% is greater than 5%, then this observation will be deleted.

(3) The mean of Result A (black) and Result B (white) will be used in paired data analysis finally.

6.6.4 Sensor Data Retention

Any sensor data beyond 144 hours of functional life time will be removed from all analysis including functional sensor life time, primary endpoints, secondary endpoints, other accuracy analysis, precision analysis, etc. (For the function sensor life time calculation methods, please see section 7.3.).

6.7 Center Pooling

Data will be pooled for analysis.

6.8 Adjustments for Multiple Comparisons

No adjustments will be made.

6.9 Significance Level and Statistical Analysis Software

For the statistical analysis of the primary endpoint and secondary endpoints, the level of significance will be set at one-sided 0.025. The level of significance of tests performed on other indicators will be set at two-sided 0.05 level (except special cases). SAS® 9.4 statistical software and R3.5.2 are applied for statistical analysis.

7. Indicators and Statistical Analysis Methods

7.1 Subject Disposition

The number of subjects enrolled in the study will be presented by study phase. The reasons for discontinuing prior to study completion will be summarized.

- (1) Subjects Enrolled: Subjects who were enrolled in study.
- (2) Screening Failure: The subject did not meet eligibility criteria on visit 1 and did not enter visit 2: randomization. (Is the subject qualified to be randomized into the study collected in CRF was “No”).
- (3) Randomization: The subject entered visit 2: randomization. (Is the subject qualified to be randomized into the study collected in CRF was “Yes”).
- (4) Subjects entering FST: The subject inserted Enlite Sensor successfully and entered visit 4: FST with YSI. (This item is determined based on the subjects’ YSI information).
- (5) Subjects completing Study: Subjects completing Study: The subject completed the last visit. (This item is determined by the section study exit collected in CRF).
- (6) Subjects discontinuing from study phase: The subject did not complete the last visit. (This item is determined by the section study exit collected in CRF).

7.2 Subject Demographics and Baseline Characteristics

Subject demographics and characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, BMI, Type of diabetes, diabetes history, pregnancy test, baseline Hct and baseline A1C will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

$$\text{Age} = (\text{Informed Consent Date} - \text{Date of Birth}) / 365.25;$$

$$\text{BMI} = \text{Weight (kg)} / (\text{Height (m)})^2.$$

7.3 Sensor Disposition

The number of Enlite Sensor insertions and Enlite Sensor removals for every subject enrolled in the study will be presented.

A descriptive analysis of Enlite Sensor disposition including Enlite Sensor dislodgement and reasons why it dislodged will be included in the Final Report. Enlite Sensor insertion and removals will be characterized by the following:

- Enlite Sensor location.
- Duration of Enlite Sensor wear by investigational center subject report.
- The number and percentage of Enlite Sensors remaining in place at study end.
- Duration of Enlite Sensor wear (subject report) by insertion site.
- Reason for removal: for example, scheduled removal, AE, fell out.

The functional life of the Enlite Sensor will also be characterized. The duration of Enlite Sensor performance from the time of first valid Interstitial Signal (ISIG) to the last glucose reading (i.e., time to end of Enlite Sensor life) will be described with Kaplan-Meier curves.

For the duration of Enlite Sensor analysis, both the physical sensor life time and functional sensor life time based on sensor level will be provided. The corresponding calculation method are as following:

(1) Physical sensor life time (hours) = (Removal time- Insertion time) /3600, the insertion time and removal time collected in OC-RDC database.

(2) Functional sensor life time (hours): The analysis data collected in iPro2 database. Related calculation method is as following:

- 1) Find the first valid Interstitial Signal (ISIG) value (i.e. first sensor glucose value), and its corresponding time will be considered as beginning time.
- 2) Find the last available Sensor value, and its corresponding time will be considered as ending time.
- 3) Functional sensor life time (hours) = (Ending time- Beginning time) /3600.

7.4 Treatment Characteristics

The total number of YSI collected and deleted will be calculated. In addition, the detailed reason for YSI deletion will also be provided.

7.5 Interim Analyses

Not Applicable.

7.6 Primary Endpoint

For the primary endpoint 20/20% consistency rate analysis, both the analyses based on measurement level and subject level will be provided. One sample T test will be used for the analysis of the primary endpoint based on subject level. Both the approximate normal distribution method and Clopper-Pearson method will be used to estimate primary endpoint based on measurement level. The 95% confidence limit of mean agreement rate will be calculated and tested against corresponding threshold pre-specified in protocol.

7.7 Secondary Endpoints

For the secondary endpoints including:

- a) a mean rate in Zone A+B of Consensus Error Grid between Enlite Sensor values and YSI plasma glucose values during YSI FST days.
- b) a mean rate in Zone A+B of Clarke Error Grid between Enlite Sensor values and YSI plasma glucose values during YSI FST days.
- c) Mean absolute relative difference (MARD) between Enlite Sensor values and YSI plasma glucose values during YSI FST days.

The analyses of a) and b) based on measurement level will be provided. One sample T test will be used for the analysis of c) mean absolute relative difference (MARD) based on subject level. The 95% confidence limit of a), b) and c) will be calculated and tested against corresponding threshold pre-specified in guideline principles.

7.8 Numbers of Reading in the Low and High Ranges

Every effort to safely collect data in the low and high range via the hyperglycemic and hypoglycemic challenge will be made.

The number and percentage of YSI values collected when Sensor readings displayed 'Low' (less than 40 mg/dL) and 'High' (greater than 400 mg/dL) will be provided.

This part of indicators will be summarized by descriptive statistics. The analysis method will be referred to section 7.2.

7.9 Other Descriptive Endpoints

- Data from the home-use portion will be described. Analysis will include but not be limited to: 20% mean agreement rate (± 20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (\leq) 80 mg/dL (4.4 mmol/L)) for all fingersticks (capillary SMBG) collected, Clarke Error Grid Analysis (EGA), Consensus Error Grid analysis, Absolute Relative Difference (ARD), bias, correlation between Enlite Sensor and fingersticks (capillary SMBG), and Bland-Altman plots. In addition, 20% mean agreement rate (± 20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (\leq) 80 mg/dL (4.4 mmol/L)) will be described by the subgroups mentioned below: frequent sampling. The number of actual calibrations performed per day by study subjects will be tabulated and presented.
- Similar descriptive subgroup analysis of Enlite Sensor performance with YSI in all devices will be performed.
 - **FST:**
 - Day 1
 - Day 3-4
 - Day 6
- Precision analysis: ARD, bias, and 20% mean agreement rate (± 20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (\leq) 80 mg/dL (4.4 mmol/L)) will be performed.

This part of indicators will be summarized by descriptive statistics. The analysis method will be referred to section 7.2.

7.9.1 Difference Tables Comparing Sensor and Reference Readings

Number and percentage of paired data points within 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% of the reference method (YSI for in-clinic portion and meter BG for home-use portion) will be summarized.

Number and percentage of paired data within 10 mg/dL, 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL and 100 mg/dL Of the reference method (YSI for in-clinic portion and meter BG for home-use portion) will be summarized.

This part of indicators will be summarized by descriptive statistics. The analysis method will be referred to section 7.2.

7.9.2 Sensor Calibration

Characteristics of Enlite Sensor calibration will be evaluated by:

- Rate of change (less than (<)-4.0 mg/dL/min, -4.0 to -2.5 mg/dL/min, -2.5 to -2.0 mg/dL/min, -2.0 to -1.5 mg/dL/min, -1.5 to -1.0 mg/dL/min, -1.0 to +1.0 mg/dL/min, +1 to +1.5 mg/dL/min, +1.5 to +2.0 mg/dL/min, +2.0 to +2.5 mg/dL/min, +2.5 to +4.0 mg/dL/min, and greater than (>) +4.0 mg/dL/min).

The detailed calculation is as following:

Rate of change for each SG point can be calculated using the SGs within +/- 20 minutes of that SG point. The rate of change is calculated by the formula below:

For each of SGs before SG of interest:

$$(SG_interest - SG_before(i))/time_interval, i=1, 2, 3, 4, \dots\dots$$

For each of SGs after SG of interest:

$$(SG_after(i) - SG_interest)/time_interval, i=1, 2, 3, 4, \dots\dots$$

Then we average all values to get the rate of change and it can be summarized into different categories.

- Rate of change arrows that are displayed to users.

7.9.3 Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI and Reference Values

1) Description

Clarke EGA separates paired observations into five zones of clinical significance. The presence and severity of possible treatment error based on interstitial glucose assay evaluated by the sensor defines the five zones. Zone A represents the absence of treatment error, where the evaluation method and the reference method are within 20% of one another or in which both methods indicate hypoglycemia. Zone B represents cases where the two methods disagree by more than 20%, but do not lead to treatment error. Zones C, D, and E represent increasingly large and potentially harmful discrepancies between the evaluation and the reference method. If the method under evaluation has a high percentage (greater than (>) 90%) of its pairs in Zones A and B, then it is considered clinically acceptable [Clarke et al, 1987].

2) Statistical analysis

Summary statistics (N, %) for each of the zones, as well as combined Zones A and B, will be calculated.

In order to evaluate differing levels of accuracy at various YSI defined glucose levels, the number and percentage of paired observations falling into Zones A, B, A+B, C, D, and E will be provide form YSI glucose ranges of 40-80 mg/dL, greater than (>) 80-120 mg/dL, greater than (>)120-240 mg/dL, and greater than (>) 240 mg/dL.

All analysis performed using the Clarke Error Grid comparing the paired sensor and YSI reference glucose values will be duplicated using the Consensus Error Grid [Parkes et al, 2000].

7.9.4 Precision Analysis

Precision analysis will be performed for the two sensors worn by the same subject in the same location. This part of indicators will be summarized by descriptive statistics. The analysis method will be referred to section 7.2.

7.9.5 Other Accuracy Analyses

The ARD, the absolute differences between the sensor and YSI relative to the YSI reference will be calculated for each day separately. Summary statistics will include its mean, standard deviation, min, median, and max.

The mean numerical bias, which is the difference between the sensor and YSI values, will be calculated for each day. Summary statistics will include its mean, standard deviation, min, median, and max.

Bland-Altman plots, with 95% CI, will be provided for each of the 3 study days. The paired differences between the sensor and YSI rating will be plotted against the X-axis reference of mean YSI and sensor values.

Descriptive subgroup analysis of Enlite Sensor performance (20% mean agreement rate (± 20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (\leq) 80 mg/dL (4.4 mmol/L))) will be performed in the following cohorts:

- **FST:**
 - Day 1
 - Day 3-4
 - Day 6

All analysis follow the definitions provided in: Performance Metrics for Continuous Interstitial Glucose Monitoring: Approved Guideline, CLSI POCT05-A [Klonoff et al. 2008].

This part of indicators will be summarized by descriptive statistics. The analysis method will be referred to section 7.1.

7.10 Safety Evaluation

For Safety analysis, no formal hypothesis testing will be performed. Descriptive analytics will be used to summarize safety events. Safety events which will be characterized include:

- Skin assessment of Enlite Sensor insertion sites
- All adverse events (AEs) to include but not limited to:
 - Device Related AE
 - Procedure Related AE
 - Serious Adverse Event (SAE)
 - Serious Adverse Device Effects (SADE)
 - UADE

- Severe Hypoglycemia
- Diabetic Ketoacidosis (DKA)

7.11 Device Deficiencies and Subject Feedback

Descriptive summary will be used to characterize device deficiencies. Descriptive summary will be used to characterize study questionnaire results. The questionnaire will use a Likert scale rating to assess their Enlite Sensor experience.

7.12 Health Outcomes Analyses

Descriptive summary will be used to characterize data from questionnaires that are given to subjects to record feedback.

7.13 Changes to Planned Analysis

1. Analysis result of Continuous Error Grid will not be provided in statistical analysis report as there is no requirement in CFDA registration technical review guideline.
2. Evaluation of “First calibration SMBG value ranges (40 - 70 mg/dL, 70 – 180 mg/dL and 180 - 400 mg/dL): the numerical Sensor Glucose Value (SGV) accuracy will be evaluated against YSI stratified by the first calibration SMBG value up to the second calibration SMBG.” will not be provided in the analysis report as there is no requirement in CFDA registration technical review guideline.

8. Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. Mock Tables, Listings and Figures

See SAP appendix tables, listings and figures.

