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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Evaluation of Updated Continuous Glucose Monitoring (CGM) Form Factor in Adults, Adolescents and Pediatrics
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Sponsor/Local Sponsor	U.S.A. Medtronic MiniMed, Inc. (“Medtronic”) 18000 Devonshire St Northridge, CA 91325 866.948.6633 China Medtronic (Shanghai) Management Co., Ltd. Room 2106A, 2106F, 2106G, 2106H, Floor 21, Donghua Financial Building, No. 28 Maji Road, China (Shanghai) Pilot Free Trade Zone, 200120, Shanghai, P.R.China

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 27-OCT-2020	Not Applicable, New Document	[redacted]
2.0 19-NOV-2021	Updated the following sections to reflect changes from the Version C protocol • Section 3.1 Background • Section 7.9.1.1 Primary Endpoints • Section 7.9.1.2 Secondary Endpoints	[redacted]

3.0
30-MAR-2022
	Updated document template
	Updated List of Abbreviations and Definitions of Terms
	Updated the following sections to reflect changes from the Version D protocol
	• Updated Background section
	• Updated definition of two study reports in Section 7.2 General Methodology
	• Updated Section 7.3 Center Pooling
	• Specified primary and secondary datasets in Section 7.9 Evaluation of Objectives
	• Updated Section 7.9 which will be performed on primary and secondary datasets:
	  ○ Primary Endpoints
	  ○ Secondary Endpoints
	  ○ Agreement, ARD, Bias (Accuracy Analyses)
	• Updated Section 7.9 which will be performed on primary datasets only:
	  ○ Descriptive Endpoints
		[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ARD	Absolute Relative Difference
AR1	Auto-regressive
BG	Blood Glucose
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CI	Confidence Interval
DS5	Disposable Sensor
EC	Ethics Committee
eCRF	Electronic Case Report Form
EGA	Error Grid Analysis
exch	Exchangeable
EtO	Ethylene Oxide
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GEE	Generalized Estimating Equation
GST	Glucose Sensor Transmitter
HbA1c	Glycosylated hemoglobin
iCGM	Integrated Continuous Glucose Monitoring
IND	Independence
ISIG	Interstitial Signal
IV	Intravenous
NMPA	National Medical Products Administration
QIC	Quasi-AIC
RF	Radio Frequency
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SQ	Subcutaneous
TDD	Total Daily Dose
TS	Technical Support
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization
YSI™*	Yellow Springs Instrument

3. Introduction

3.1 Background

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous (SQ) glucose sensors worn by the user, which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. A CGM sensor is attached to a transmitter, which typically sends interstitial glucose information to a monitor (e.g., the Guardian™ Connect App) as radio frequency (RF) signals. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The monitor is the data collection/user interface of the system and provides continuous real-time glucose values to the user, as well as the option to set high/low glucose alerts according to the individual patient's needs.

The Medtronic MiniMed™, Inc. (d/b/a "Medtronic Diabetes") family of Continuous Glucose Monitoring Systems (CGMS) measures SQ glucose continuously over various ranges of time. The newest generation Medtronic MiniMed™ SQ Glucose Sensor (Guardian™ Sensor [3]) was approved by the United States Food and Drug Administration (FDA) for commercialization as part of the MiniMed™ 670G System in September 2016. The Medtronic MiniMed Glucose Sensor is a glucose sensor designed to work in Medtronic CGM systems to help users manage their diabetes.

Medtronic has developed the Disposable Sensor (DS5), which is a single-use integrated disposable device, integrating the sensor and transmitter. The DS5 is packaged into the single-use insertion device, minimizing the number of components. The DS5 CGM reduces user burden by minimizing the form factor of the device and simplifying the insertion process.

The portion of the DS5 sensor flex that is implanted beneath the skin is the same design as the Guardian™ Sensor (3) sensor flex. As a result of the integration of sensor and the electronic components, the DS5 will require a new sterilization method, ethylene oxide (EtO) sterilization, as opposed to ebeam sterilization used on Guardian™ Sensor (3). The Zeus Algorithm, which is the algorithm platform developed for Guardian Sensor (3) and housed in GST5G transmitter, has been modified to benefit performance with the DS5. This modified version of Zeus is called the Athena algorithm.

The Athena Plus algorithm is a further refinement of the Athena algorithm. The only design difference between Athena and Athena Plus is the sensor glucose model coefficients resulting from the utilization of YSI intravenous blood glucose reference data to train part of the sensor glucose model instead of SMBG reference data. The expected benefit is to improve overall sensor accuracy.

In this study, sensor data will be collected in a blinded approach, where the DS5 sensor will be used as a recorder for the purposes of data collection. There will not be any real-time receiver used during the study as no mobile application or pump display will be used. At the end of the study, raw sensor data

collected by the DS5 sensor will be processed using the Athena and Athena Plus algorithms and various calibration schemes through the post-processing tool. The Athena and Athena Plus algorithms will be implemented in the final code format which will be included in the post-processing analysis tools to support this study. The values used for these calibration schemes will be collected using the commercially available CONTOUR® NEXT LINK 2.4 study meter (**US only**) and CONTOUR® PLUS study meter (**China only**).

Testing on human subjects is necessary to characterize the accuracy of DS5 with the Athena and Athena Plus algorithms. For purposes of this study, subjects will wear the DS5 sensors. Subjects will manage their diabetes independent of the DS5 sensor values. During YSI™*/ Self-Monitoring of Blood Glucose (SMBG) frequent sample testing (FST), venous blood glucose concentrations or SMBG (subjects 2-6 years only) will be measured periodically; these values will be compared to sensor glucose (SG) values in order to determine sensor accuracy.

Accuracy data will be calculated based on comparing calibrated glucose sensor values to a "gold standard" (Yellow Springs Instrument [YSI™*] plasma glucose values) in subjects during YSI™* FST. The YSI™* glucose analyzer, Model 2300, has been the recognized standard for the measurement of blood glucose and will be utilized across the investigational centers for the tests. Accuracy data will be calculated based on comparing calibrated glucose sensor values to SMBG during SMBG FST in the 2-6 age group.

3.2 Purpose

The purpose of this study is to demonstrate the performance of the Disposable Sensor (DS5) in subjects age 2 – 80 years, for the span of 170 hours (7 days).

4. Study Objectives

4.1 Primary Objective(s)

The primary objective of the study is to demonstrate the accuracy of Disposable Sensor (DS5) when used over a period of 7 days (i.e., 170 hours) in subjects 2-80 years of age.

5. Investigation Plan

The study is a multi-center, prospective, single-arm study without controls, and random assignments of sensor location, frequent sample testing (FST) day, and FST time.

A total of up to 376 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. and China will be enrolled in order to have 260 subjects complete the study.

Up to 22 investigational centers in the US and China will be used during the study.

5.1 Study Design: Subjects 14-80 years

Subjects will wear sensors in the following configurations and follow the FST schedule:

- Sensor Location
  - 14-17 years
    - Arm/Arm/Buttock
    - Buttock/Buttock/Arm
  - 18-80 years
    - Arm/Arm
- FST Schedule
  - 4 x 8 hours FST
  - Challenges
    - Two Hyperglycemic Challenges
    - Two Hypoglycemic Challenges
    - If challenges are performed, the following are recommended:
      - **US only:** Investigator discretion may be used in selecting which challenge is to be performed for each FST as long as 2 hyperglycemic challenges and 2 hypoglycemic challenges are met.
      - **China only**: Whether performing recommended challenges or not will be based on Ethics Committee (EC) suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

Subjects will be assigned to FST Timing (random assignment) according to their age:

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of FST from Sensor Insertion T=0
A1	Day 1, 3, 4 and 7	2-10 hours (+2), 50-58 hours (±6), 74-82 hours (±6), 146-154 hours (±6)
A2	Day 1, 3, 4 and 7	10-18 hours (±2), 58-66 hours (±6), 82-90 hours (±6), 154-162 hours (±6)
B1	Day 1, 3, 4 and 7	18-26 hours (±2), 66-74 hours (±6), 90-98 hours (±6), 162-170 hours (-6, +2)
B2	Day 2, 4, 5 and 6	24-32 hours (±2), 74-82 hours (±6), 98-106 hours (±6), 122-130 hours (±6)
C1	Day 2, 4, 5 and 6	32-40 hours (±2), 82-90 hours (±6), 106-114 hours (±6), 130-138 hours (±6)
C2	Day 2, 4, 5 and 6	40-48 hours (±2), 90-98 hours (±6), 114-122 hours (±6), 138-146 hours (±6)

Sensors worn in the same insertion site location may be inserted on same side or opposite sides.

Sensors may be inserted with the assistance of a caretaker.

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.

Subjects will wear the devices up to 7-day training period, followed by a 7-day study period. Investigational center staff will ensure 176-188 hours of sensor wear (sensors may be removed at that time or after that time to ensure that the devices are not removed pre-maturely). In the event that early sensor removal occurs during the training period, the subject can continue to the study period based on PI discretion.

During the study period, each subject will undergo four YSI™* FSTs.
During the YSI™* FST, intravenous (IV) blood samples will be drawn every 5-15 minutes and analyzed using the YSI™*.
The YSI™* FST will be approximately 8 hours during the in-clinic visit. For details on maximum amount of blood drawn refer to Synopsis and Stopping Rules for Subjects for FST (section 20.1.1 in the protocol).
For device troubleshooting and device complaints (See Section 24 in the protocol):

- **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
- **China only:** Subjects are to call Investigational Center staff

Hypoglycemic and Hyperglycemic Challenges:

US only: During the YSI™* FST, subjects with a known insulin sensitivity factor and insulin carbohydrate ratio will undergo hypoglycemic and hyperglycemic challenges.
China only: Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

5.2 Study Design: Subjects 2-13 years

It is expected that subjects 7 - 13 years will complete 2 days of YSI™* FST with the sensors and subjects 2 - 6 years will complete 2 days of SMBG FST with the sensors. Subjects ages 2 – 6 years will only do SMBG during their FST.

Subjects will wear sensors in the following configurations and follow the FST schedule:

Subjects 7 - 13 years

- Sensor Location
  - Arm/Arm/Buttock
  - Buttock/Buttock/Arm
- FST Schedule

- 2 x 6 hours FST

Subjects 2 - 6 years

- Sensor Location
  - Arm/Buttock
  - Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement
- FST Schedule
  - 2 x 4 hours FST
  - SMBG only

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of FST from Sensor Insertion T=0
A1	Day 1, 7	2-8 hours (+2), 146-152 hours (±6)
A2	Day 1, 7	20- 26 hours (±2), 164-170 hours (-6, +2)
B1	Day 2, 5	26-32 hours (±2), 116-122 hours (±6)
B2	Day 2, 5	44-50 hours (±2), 98-104 hours (±6)
C1	Day 3, 5	50-56 hours (±6), 116-122 hours (±6)
C2	Day 3, 5	68-74 hours (±6), 98-104 hours (±6)
D1	Day 4, 6	74 -80 hours (±6), 140-146 hours (±6)
D2	Day 4, 6	92-98 hours (±6), 122-128 hours (±6)

FST Timing for 2-6 years old:

Group	Sensor Wear Day	Timing of FST from Sensor Insertion T=0
A1	Day 1, 7	2-6 hours (+2), 148-152 hours (±6)
A2	Day 1, 7	20- 24 hours (±2), 166-170 hours (-6, +2)
B1	Day 2, 5	26-30 hours (±2), 118-122 hours (±6)
B2	Day 2, 5	44-48 hours (±2), 100-104 hours (±6)
C1	Day 3, 5	50-54 hours (±6), 118-122 hours (±6)
C2	Day 3, 5	68-72 hours (±6), 100-104 hours (±6)
D1	Day 4, 6	74 -78 hours (±6), 142-146 hours (±6)
D2	Day 4, 6	92-96 hours (±6), 124-128 hours (±6)

Sensors worn in the same insertion site location may be inserted on same side or opposite sides.
Sensors may be inserted with the assistance of a caretaker.

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.

Subjects will wear the devices up to 7-day training period, followed by a 7-day study period. Investigational center staff will ensure 176-188 hours of sensor wear (sensors may be removed at that time or after that time to ensure that the devices are not removed pre-maturely). In the event early sensor removal occurs during the training period, the subject can continue to study period based on PI discretion.

During the YSI™* FST, IV blood samples will be drawn every 5-15 minutes and analyzed using the YSI™* for subjects 7-13 years. For subjects aged 2 – 6 years, the frequency of blood draws with SMBG is every 5 – 30 minutes.

The YSI™* FST will be approximately 6 hours during the in-clinic visit for subjects 7- 13 years. The SMBG FST will be approximately 4 hours during the in-clinic visit for subjects 2-6 years. For details on maximum amount of blood drawn refer to Synopsis and Stopping Rules for Subjects for FST (section 20.1.1 in the protocol).

For device troubleshooting and device complaints (See Section 24 in the protocol):

- **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
- **China only:** Subjects are to call Investigational Center staff

Hypoglycemic and Hyperglycemic Challenges

Subjects 2 - 13 years:

During the day of FST, subjects will not participate in hypoglycemic and hyperglycemic challenges.

6. Determination of Sample Size

A total of up to 376 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. and China will be enrolled in order to have 260 subjects complete the study.

Up to 22 investigational centers in the US and China will be used during the study.

US:

A total of up to 300 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. will be enrolled in order to have 200 subjects complete study.

Up to 17 investigational centers in the US will be used during the study.

Number of subjects to complete study:

- N= 100 subjects 18-80 years old
- N= 100 subjects 2-17 years old

The US investigational centers will be encouraged to include subjects of different ethnicities including Hispanic, Native American, Asian, and African-American.

China:

A total of up to 76 previously-diagnosed type 1 or type 2 diabetes subjects in China will be enrolled in order to have 60 subjects complete study.

Up to 5 investigational centers in China will be used during the study.

Number of subjects to complete study:

- N= 40 subjects 18-80 years old
- N= 20 subjects 2-17 years old

A minimum of 6 subjects and a maximum of 24 subjects is expected to be enrolled at each investigational center.

6.1 DS5 sensor accuracy, Threshold of 75%

The sample size selected is based on the primary effectiveness endpoint, which is the within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) in comparative readings of paired sensor and YSI™* glucose readings in FST days. On those 4 days, 8 hours of paired testing will be recorded.
Data from CIP318 and ERP2018-11254 study was used for power estimation via simulation.

The simulation was performed 1000 times and one sided 95% lower confidence limit of the mean agreement rate was tested against the threshold of 75%. The results of the simulation indicated that a sample size of 100 will yield greater than 80% power.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

All enrolled subjects who have at least one paired sensor and YSI™* measurement will be included in the efficacy analysis population. All enrolled subjects who have a sensor inserted will be included in the safety analysis population. Others who don't have sensors inserted will also be included in the safety analysis population.

7.2 General Methodology

All data collected from the time of screening until the end of the study will be collected either on eCRFs, subject survey or electronically by downloading the various devices and used as source data for analysis. Data and analysis will be summarized in a Clinical Study Report. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

Two study reports will be generated: one study report including data from US and all analyses except National Medical Products administration (NMPA) CGM for DS5; another study report including data from US and China and all analyses.

China only: The Clinical Study Report will be compliant with the elements from the NMPA 2016 No. 58 Announcement Annex 5 "Template of Clinical Trial Report of Medical Devices". There are no criteria and/ reasons for trial termination based on statistics.

7.3 Center Pooling

For each report, the relevant data will be pooled for analysis.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

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

7.5 Adjustments for Multiple Comparisons

Secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity.

7.6 Demographic and Other Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis (includes duration of diabetes diagnosis and type of diabetes), height, weight, BMI, CGM experience, pump experience, baseline HbA1c, and TDD will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

7.7 Treatment Characteristics

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

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

- Sensor location
- Duration of sensor wear by investigational center subject report
- The number and percentage of sensors remaining in place at study end.
- Duration of sensor wear (subject report) by insertion site.
- Reason for removal: e.g., scheduled removal, adverse event, fell out.

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

7.8 Interim Analyses

Not applicable.

7.9 Evaluation of Objectives

All datasets are categorized into primary datasets and secondary datasets for endpoints.

Primary datasets will be evaluated for

- Primary endpoints
- Secondary endpoints
- Agreement, ARD, Bias (Accuracy Analyses)
- Descriptive endpoints

Secondary datasets will be evaluated for

- Primary endpoints
- Secondary endpoints
- Agreement, ARD, Bias (Accuracy Analyses)

Datasets are described below:

Primary Datasets

Athena Plus algorithm

- Dataset 1: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 2: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 3: Peds (2 to 17 years), arm insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 4: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 5: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 6: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 7: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Peds (2 to 17 years), arm insertion location and 0 Calibration
- Dataset 9: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 10: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 11: Adult (18 – 80 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 12: Adult (18 – 80 years), arm insertion location and daily Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Dataset 13: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 14: Peds (2 to 17 years), buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration
- Dataset 15: Peds (2 to 17 years), buttock insertion location and daily Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Dataset 16: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

- Dataset 17: Peds (2 to 17 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 18: Peds (2 to 17 years), arm insertion location and daily Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

Datasets (NMPA CGM for DS5 only) are described below**:**

Primary Datasets

Athena Plus algorithm

- Dataset 1: Arm insertion location and 0 Calibration
- Dataset 2: Buttock insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 3: Arm insertion location and 0 Calibration
- Dataset 4: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 5: Buttock insertion location and 0 Calibration
- Dataset 6: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 7: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 9: Arm insertion location and daily Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Dataset 10: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

- Dataset 11: Buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 12: Buttock insertion location and daily Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

7.9.1 Endpoints

7.9.1.1 Primary Endpoints

Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), μ, between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated against the null Hypothesis:

H0: $\mu \leq 75\%$

H1: $\mu > 75\%$

Statistical Testing:

A generalized estimating equation (GEE) method model will be used. The one sided 95% lower confidence limit of the mean agreement rate will be tested against the threshold of 75%. For the GEE model, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC).

Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model. Sites with less than 6 subjects will be pooled into 'pseudo-sites' of at least 10 subject per pseudo-site. Pseudo-sites will be pooled by ranking those sites with less than 6 subjects by site number and pooling those sites in order of site number until the number of subjects reaches at least 10.

The primary endpoint will be independently evaluated for each of the 3 primary and 15 secondary datasets.

Pass/Fail Criteria:
The study pass/fail criteria is based on statistical hypothesis of the primary endpoints per dataset. The study will be considered as success when the evaluation criteria meets the predefined threshold.

Justification for Exclusion of Particular Information from the testing of the Hypothesis:
Not Applicable.

Secondary endpoints will be evaluated only if the primary endpoint meets the predefined threshold.

7.9.1.2 Secondary Endpoints

7.9.1.2.1 National Medical Products Administration (NMPA) CGM for DS5

The four secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the NMPA CGM criteria for sensor accuracy (SG limit of 50-400 mg/dL [2.8-22.2 mmol/L]):

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% agreement rate (±20 mg/dL [1.1 mmol/L] when Reference BG less than or equal to (≤) 80 mg/dL [4.4 mmol/L]) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 60\%$

  H1: $p > 60\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Consensus Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Clarke Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis.

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean absolute relative difference (MARD) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as μ will be evaluated against the null Hypothesis.

  H0: $\mu \geq 20\%$

H1: μ < 20%

- Statistical testing

  One proportion Z test will be used to obtain 97.5% lower confidence limit of the agreement rate, the mean rate in Zone A+B of Consensus Error Grid, and the mean rate in Zone A+B of Clarke Error Grid, which will be tested against corresponding threshold, respectively.

  One sample T test will be used to obtain the 97.5% upper confidence limit of the MARD, which will be tested against corresponding threshold.

The secondary endpoints will be independently evaluated for each of the 2 primary and 10 secondary datasets (NMPA CGM for DS5 only).

7.9.1.2.2 Integrated Continuous Glucose Monitoring (iCGM) for DS5

The 11 secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 50-400 mg/dL [2.8-22.2 mmol/L]). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements
- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- When iCGM values are greater than 180 mg/dL (10.0 mmol/L), the number of corresponding blood glucose values that read less than 70 mg/dL (3.9 mmol/L).

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- When iCGM values are less than 70 mg/dL (3.9 mmol/L), the number of corresponding blood glucose values that read above 180 mg/dL (10.0 mmol/L).
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL (0.8 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL (2.2 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

The iCGM secondary endpoints will be independently evaluated for each of the 3 primary and 15 secondary datasets.

7.9.1.3 Agreement, ARD, Bias (Accuracy Analyses)

The following will be evaluated for each of the 3 primary and 15 secondary datasets.

The agreement, ARD (the absolute differences), and bias 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.

7.9.1.4 Descriptive Endpoints

The following descriptive endpoints will be independently evaluated for each of the 3 primary datasets.

7.9.1.4.1 Numbers of Readings 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.

7.9.1.4.2 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 (0.6 mmol/L), 15 mg/dL (0.8 mmol/L), 20 mg/dL (1.1 mmol/L), 30 mg/dL (1.7 mmol/L), 40 mg/dL (2.2 mmol/L), 50 mg/dL (2.8 mmol/L), 60 mg/dL (3.3 mmol/L), 70 mg/dL (3.9 mmol/L), 80 mg/dL (4.4 mmol/L), 90 mg/dL (5.0 mmol/L) and 100 mg/dL (5.6 mmol/L) of the reference method (YSI™* for in-clinic portion and meter BG for home-use portion) will be summarized.

7.9.1.4.3 Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI™* and Reference Values

1) Description

Clarke Error Grid Analysis (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 provided by YSI™* glucose ranges of 40-80 mg/dL (2.2 – 4.4 mmol/L), greater than (>) 80-120 mg/dL (4.4 – 6.7 mmol/L), greater than (>) 120-240 mg/dL (6.7 – 13.3 mmol/L), and greater than (>) 240 mg/dL (13.3 mmol/L).

All analysis performed using the Clarke Error Grid comparing the paired sensor and YSI™* reference glucose values will be duplicated using the Continuous Error Grid [Clarke et al, 1987] and the Consensus Error Grid [Parkes et al, 2000].

7.9.1.4.4 Precision Analysis

Precision analysis will be performed for the two sensors worn by the same subject in the same location.

7.9.1.4.5 Comparison of CGM Performance to Reference under conditions leadings to Alert

The alert will be triggered when the sensor BG value reaches the threshold glucose value. Predictive alerts will be evaluated by using the predicted sensor BG value based on current sensor BG and sensor BG readings within the previous 30 minutes.

In the in-clinic portion, the threshold and predictive alert analysis will be performed retrospectively with theoretical hypoglycemia threshold setting at 50 mg/dL (2.8 mmol/L), 60 mg/dL (3.3 mmol/L), 70 mg/dL (3.9 mmol/L), 80 mg/dL (4.4 mmol/L), 90 mg/dL (5.0 mmol/L) and 100 mg/dL (5.6 mmol/L) and theoretical hyperglycemia threshold setting at 180 mg/dL (10.0 mmol/L), 220 mg/dL (12.2 mmol/L), 250 mg/dL (13.9 mmol/L) and 300 mg/dL (16.7 mmol/L).

The threshold alert performance will be evaluated for in-clinic portion by true alert rate, missed alert rate and false alert rate within 15 and 30 minutes windows of the reference event. Predictive alert performance will only be evaluated for the in-clinic portion by true predictive alert rate, missed predictive alert rate and false predictive alert rate within 15 and 30 minutes windows. All reference BG values will be used, including those less than (<) 40 mg/dL (2.2 mmol/L) and greater than (>) 400 mg/dL (22.2 mmol/L).

The comparison of CGM performance to reference under conditions leading to alert will be evaluated by true alert rate, missed alert rate and false alert rate within 15 and 30 minutes window of the reference event.

The alert rates will be defined as follows:

Alert Rate Type	Column Label	Label Definition
Detection Rate	Hypo/Hyper Events Correctly Detected (%)	The device alarmed at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.
Missed Detection Rate	Hypo/Hyper Events Not Detected (%)	The device did not alarm at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.
True Alert	Alerts Verified by Hypo/Hyper Events (%)	There is at least one reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.

Alert Rate Type	Column Label	Label Definition
False Alert	False Alerts (%)	There is no reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.

7.9.1.4.6 Other Accuracy Analyses

A correlation between the sensor and YSI™* values will be performed. As this statistic ignores any data dependency, it will be used only as a descriptive measure of association.

A linear model, in which YSI™* is predicted by sensor values, using a repeated measures model, will be performed. The models solution will provide the intercept and slope, while adjusting for dependence in the data within day. An intercept of 0, along with a slope of 1, would indicate the absence of bias in predicting YSI™* from sensor readings. The residuals of the model will be inspected to determine if transformation of either variable is required.

Bland-Altman plots, with 95% confidence interval (CI), will be provided. 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 DS5 sensor performance (20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) will be performed in the following cohorts:

- **Diabetes cohorts based on insulin requirement:**
  - Type 1 insulin requiring
  - Type 2 insulin requiring
  - Type 2 non-insulin requiring
- **Diabetes cohorts based on Centers for Disease Control and Prevention (CDC) classification for younger than 20 years old:**

  A description of the following 4 groups will be performed:

  - Underweight subjects (less than (<) 5th percentile)
  - Normal weight subjects (5th percentile to less than (<) 85th percentile)
  - Overweight (85th to less than (<) the 95th percentile)
  - Obese subjects (greater than or equal to (≥) the 95th percentile)

- **Diabetes cohorts based on BMI according to WHO criteria [World Health Organization, 2011] for subjects equal to or greater than 20 years old:**

  A description of the following 5 groups will be performed:

  - Underweight subjects (BMI less than (<)18.5 kg/m²)
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²)
  - Overweight and obese subjects (BMI 25.00 to 40 kg/m²)
    - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
    - Obese subjects (BMI 30.00 to 39.99 kg/m²)
  - Morbidly obese subjects (BMI greater than or equal to (≥)40 kg/m²)

- **Diabetes cohorts based on prior real-time CGM experience (by self-report)**
  - CGM naïve
  - CGM experienced

- **Diabetes cohorts based on prior pump experience (by self-report)**
  - Pump naïve
  - Pump experienced

- **Diabetes cohorts based on HbA1c:**
  - Baseline HbA1c (by certified National Glycohemoglobin Standardization Program, NGSP, method) will be collected:
    - A description of the following 3 groups will be performed: HbA1c less than (<) 7%, HbA1c 7-9%, HbA1c greater than (>) 9%
  - Quartile comparison (lowest to the highest) based on HbA1c

- **Diabetes cohort based on exercise activity:**
  - Per Investigator's discretion, subjects may participate in the exercise in order to obtain low glucose values.

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

7.9.1.4.7 Home-Use Portion Data Analysis

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 SG less than (<) 80 mg/dL [4.4 mmol/L]) for all fingersticks (capillary SMBG) collected, Clark Error Grid, other accuracy analysis, absolute relative difference (ARD), bias, correlation between sensor and SMBG and Bland-Altman plots. In addition, 20%

mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) will be described by subgroups of: age, YSI™* FST, diabetes classification, BMI/weight, CGM experience, HbA1c and exercise activity (if applicable).

7.9.2 Safety
Descriptive summary will be used to characterize adverse events:

- Skin assessment at sensor insertion sites
- All adverse events

7.9.3 Device Deficiencies
Descriptive device deficiencies will include all reports of sensor damage, breakage or fracture.

7.9.4 Subject Feedback
Descriptive summary will be used to characterize study survey results

7.10 Safety Evaluation
The safety of the study will be evaluated and summarized per all enrolled subjects, including but not limited to the following:

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

7.11 Health Outcomes Analyses
Not applicable.

7.12 Changes to Planned Analysis
Not applicable.

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. References

David Klonoff et al. CLSI. Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline. CLSI Document POT05-A. Wayne,PA, Clinical and Laboratory Standards Institute. 2008;28(33).

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World Health Organization, Global Database on Body Mass Index. Accessed May 11, 2011.

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