SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sensor, glucose, invasive, non-adjunctive, factory-calibrated, user-initiated

Device Trade Name: FreeStyle Libre 14 Day Flash Glucose Monitoring System

Device Procode: PZE

Applicant's Name and Address: Abbott Diabetes Care Inc.
1360 South Loop Road
Alameda, CA 94502

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160030/S017

Date of FDA Notice of Approval: July 23, 2018

II. INDICATIONS FOR USE

The FreeStyle Libre 14 Day Flash Glucose Monitoring System is a continuous glucose monitoring (CGM) device indicated for the management of diabetes in persons age 18 and older. It is designed to replace blood glucose testing for diabetes treatment decisions.

The System detects trends and tracks patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of the System readings should be based on the glucose trends and several sequential readings over time. The System is intended for single patient use and requires a prescription.

III. CONTRAINDICATIONS

The FreeStyle Libre 14 Day Flash Glucose Monitoring System must be removed prior to Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment. The effect of MRI, CT scans, or diathermy on the performance of the system has not been evaluated. The exposure may damage the Sensor and may impact proper function of the device to detect trends and track patterns in the user's glucose values during the wear period.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Freestyle Libre 14 Day Flash Glucose Monitoring System labeling.

V. DEVICE DESCRIPTION

The FreeStyle Libre 14 Day Flash Glucose Monitoring System (FreeStyle Libre 14 Day System, Libre 14 Day, or System) is the same physical device as the Abbott Freestyle Libre Flash Glucose Monitoring System approved under the original PMA P160030. The previously approved device was approved for use starting 12 hours after insertion up to 10 days. In this supplement, the sponsor has provided information sufficient to expand the use claims by extending glucose measurement to include the first 11 hours of wear following a 1 hour warm up period and 3 additional days of wear (i.e., up to 14 days after insertion). The subject device of this supplement provides glucose values following the intial 1 hour warm up period and values within the first 11 hours of use may not be used to calculate insulin dose; however, following the first 11 hours of use, users may use glucose values to calculate insulin dose if values are available.

The Libre 14 Day uses an electrochemical sensor to monitor glucose levels in interstitial fluid (ISF). The sensor is held in place by an adhesive and incorporates both the subcutaneously implanted sensor and associated electronics. The sensor uses a glucose oxidase enzyme to oxidize glucose and transfer electrons to a metal electrode, producing a current. The strength of the current is proportional to the amount of glucose present in the subcutaneous space. The system converts the electrical current signal to a glucose value for display to the user on a handheld Reader.

The FreeStyle Libre 14 Day System consists of three primary components:

Sensor
The disposable Sensor can be worn for up to 14 days following the initial 1-hour warm-up period and consists of three primary elements:

- An outer casing that contains the electronics required to power the Sensor, measure temperature, maintain a memory of Sensor data, and facilitate wireless transmission of Sensor data to the Reader via radiofrequency communication.
- A medical grade adhesive layer that adheres the Sensor to the surface of the skin for the duration of wear.
- A sensor tail that is inserted into the subcutaneous tissue on the back of the patient's upper arm and generates an electrical current via the oxidation of glucose from the interstitial fluid. The sensor tail is electrically connected to the Sensor electronics to allow measurement of Sensor data.

Sensor insertion device
The Sensor insertion device consists of two secondary disposable single use components (Sensor Pack and Sensor Applicator) that require user assembly prior to Sensor application. The Sensor Pack is sterilized and is preloaded with the sensor tail

loaded into an introducer needle while the Sensor Applicator is preloaded with the Sensor outer casing, internal electronics, and skin adhesive. To assemble these components, the Sensor Applicator is aligned and pressed firmly into the Sensor Pack, which results in an assembled Sensor contained within the Sensor Applicator. After Sensor application the introducer needle is automatically retracted into the Sensor Applicator, which serves as a container for disposal.

Reader

The Reader is a small hand-held device that contains an antenna and the associated electrical circuitry to receive raw Sensor measurement data from up to 1.5" (4cm) away through wireless radiofrequency (RF) communication. The Reader collects glucose data from the Sensor and can store up to 90 days of information including glucose readings and notes. The Reader employs signal processing algorithms to convert the measurement data into glucose results. The Reader supports functionality of the single front button and a touchscreen color display for user interface navigation, user settings, power management, and a micro-USB port for battery charging and data upload to a computer installed with the FreeStyle Libre 14 Day data management software. The Reader incorporates a built-in blood glucose meter, which can be used in combination with FreeStyle Precision Neo Blood Glucose Test Strips (K171941) to test blood glucose in a whole blood sample drawn from the fingertip or to test a control solution to assess functionality of the built-in blood glucose meter and compatible test strips.

The user assembles and applies the Sensor to the back of the upper arm, and uses the Reader to activate the Sensor. One hour after the Sensor is successfully activated, the Reader can be used to check glucose. The FreeStyle Libre 14 Day System is factory calibrated and does not require, or allow, calibration with blood glucose values, for example as obtained from a blood glucose monitoring system (glucose meter) typically used for glucose self-monitoring for diabetes management.

The FreeStyle Libre 14 Day System allows the user to wirelessly query glucose data from the Sensor by bringing the handheld Reader in close proximity (within 1.5" or 4cm) of the Sensor; i.e., scanning a Sensor. The act of scanning a Sensor initiates Reader calculations of real-time glucose measurements (glucose values) accompanied by trend information (glucose arrows) and historic eight-hour glucose results (glucose graph) that are presented on the Reader display. The Reader does not passively capture glucose information in the absence of a scan. Therefore, glucose values, trend information, and system messages are completely dependent on user-initiated action (a scan). In the absence of a scan; for example, when a user is sleeping, or otherwise occupied or distracted, and unable to scan their Sensor, the Reader is not able to alert users to high or low glucose levels, or changing glucose levels. Users must scan the sensor in order for the Reader to display current glucose levels and trends and provide any appropriate glucose-level or trend related messages. However, users can configure the Reader to provide reminders at specific times of the day, or on a timer (e.g., a specific amount of time after the current time). Reminders will be activated even if the Reader is turned off.

The FreeStyle Libre 14 Day System is intended for single patient use and the Reader can only pair with one Sensor at a time. If the Reader activates a Sensor it cannot activate a second Sensor without discontinuing interaction with the first.

The Sensor may be scanned by the Reader as frequently as a user desires, and a current glucose value will be displayed in one minute increments. If consecutive scans occur within one minute, the same glucose result may be displayed as the previous scan.

The Sensor automatically stores glucose data every fifteen minutes. During a scan, the preceding eight hours of glucose data are transferred to the Reader, where those data are logged and may be viewed by the user. The Sensor has an eight-hour memory capacity and must be scanned every eight hours to ensure complete data capture by the Reader. If the Sensor is not scanned every eight hours then only the most recent eight hours of data will be captured and any data generated outside of an eight-hour period covered by a scan will be lost and not available to the user. For example, if a user scans their Sensor before going to sleep, and then sleeps for ten hours before scanning the Sensor again, historic glucose information during the first two hours of sleep will be lost. The Sensor is disposable and may be worn for up to fourteen days before it must be replaced.

The Reader stores up to about ninety total days of information including glucose readings and notes and provides several options to review the information. The user also has the option to review the information by connecting the Reader USB port to a computer with appropriate software to generate and print additional reports.

The Reader also incorporates a built-in blood glucose meter, which uses a hardware and software design based on the FreeStyle Precision Neo Blood Glucose Monitoring System (K142928). Use of the Freestyle Precision Neo test strips with the Freestyle Libre built-in glucose meter was reviewed concurrently with this PMA, in K171941. The built-in test strip port can be used to test blood glucose or to test the meter and strip functionality using a control solution.

The glucose values obtained from the FreeStyle Libre 14 Day Flash Glucose Monitoring System may be used to non-adjunctively (i.e., without confirming readings using a blood glucose meter) to make diabetes treatment decions (including calculation of insulin dose) except when the System displays the “non-actionable icon.” When this icon is displayed, information from the System should not be used to make diabetes treatment decisions (including to dose insulin). The icon is displayed under the following conditions:

- The glucose as reported by the Sensor is below 70 mg/dL (when the “low glucose” message is displayed);
- The glucose will be below 70 mg/dL within 15 minutes (when the “glucose is going low” message is displayed);

- The glucose is rapidly changing (when the glucose trend arrow as reported by the Reader is rising quickly or falling quickly);
- The glucose trend arrow is not displayed;
- The glucose as reported by the Sensor is above 500 mg/dL (when the HI message is displayed); and
- During the first 12 hours of sensor life.

Additional information about the device components and their function can be found in the Freestyle Libre 14 Day Flash Glucose Monitoring System User's Manual.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the control of diabetes. Control of diabetes can be achieved through a combination of methods and behaviors. Self-behaviors include healthy eating, taking medications as appropriate, and being active. Methods of controlling glucose levels (glycemic control) have been shown to reduce severe diabetes-related complications. Methods of monitoring glycemic control include periodic measurement of Hemoglobin A1c (HbA1c), which reflects average blood glucose levels over a three month period. Self-monitoring of blood glucose using glucose meters and test strips provides quantitative measurements of fingerstick blood glucose at a single point in time for patients and their healthcare providers to monitor the effectiveness of glycemic control and make more immediate treatment modifications. Continuous glucose monitors can be used for detecting glycemic control trends and patterns when used as adjunctive devices to complement, not replace, information obtained from glucose meters; All other currently approved continuous glucose monitors can also provide real-time passive alerts and alarms to users in the absence of user initiated action. Information from some continuous glucose monitors can be used to make diabetes treatment decisions. Automated insulin delivery devices can be used to automatically adjust insulin delivery from an insulin pump based on glucose data generated from a continuous glucose monitor.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their healthcare provider to select the method that best meets their needs, expectations and lifestyle.

VII. MARKETING HISTORY

A previous version of the FreeStyle Libre 14 Day System has been marketed in the US since October 2017 under P160030. This previous version has a claimed sensor wear time of 10 days and a blinded warm up period of 12 hours after sensor initialization. The FreeStyle Libre 14 Day System has a wear time of 14 days and a blinded warm up period of 1 hour after sensor initialization.

A different version of the System has also been marketed in the following countries – Australia, Austria, Belgium, Brazil, Chile, Finland, France, Germany, Greece, Japan, Kuwait, Israel, Italy, Netherlands, Norway, Saudi Arabia, Spain, Sweden, Switzerland,

United Arab Emirates, and United Kingdom since September 2014. A different version has been marketed in Canada since July 2017.

The device has not been withdrawn from marketing in any of these countries for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects associated with the use of the device:

The following are possible adverse effects of inserting a sensor and wearing the adhesive patch: local erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin.

There are potential adverse effects associated with making diabetes treatment decisions when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

Inaccurate calculation of the rate of change of glucose by the device could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose by the device could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

There are potential adverse effects associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney,

nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The device also provides glucose threshold and predictive messages (alerts) when the Sensor is scanned; these alerts may cause a user to take action to prevent potential future glycemic events (e.g., set reminders for future glucose checks or future action, or take immediate treatment-based action). Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts, or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia.

In the absence of a user-initiated action (scan) the system cannot provide glucose-related alerts, which could serve to notify users of an actual or impending glucose value above or below glucose thresholds. The lack, compared to currently approved continuous glucose sensors, of alerts in the absence of user-imitated action (scan) could increase the risk of severe hypoglycemia or diabetic ketoacidosis through decreased opportunities for detection of hypoglycemia or hyperglycemia relative to other similar currently marketed continuous glucose sensors.

For the specific adverse events that occurred in the clinical studies please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The changes from the approved Abbott FreeStyle Libre System (P160030) are limited to the wear time, duration of the warm-up period, an update in the algorithm in the reader software, creation of a new brand name, and labeling. The preclinical studies included applicable software verification and validation testing. A summary of the testing performed is summarized below.

A. Laboratory Studies

Bench Performance Testing

Bench testing that was conducted to support safety of the system is provided in the SSED for P160030.

Software Validation and Verification:

Testing was performed to support the algorithm changes in the reader software.

Verification of the software implementation was accomplished through software code reviews, unit testing, and integration testing. These evaluations verify that the software implementation satisfies the design implementation as defined in the Software Requirements Specifications.

Validation of the software implementation is completed and confirmed by examination and provision of objective evidence that the software end products conform to user needs and intended users, and that the software requirements are consistently fulfilled.

Specific test methods, acceptance criteria, and test results include proprietary information.

B. Animal Studies

No animal studies were conducted in support of the FreeStyle Libre 14 Day System .

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

To validate the clinical performance of the System, Abbott performed clinical study ADC-US-VAL-17166 to determine system accuracy.

Primary Objective
The sponsor's primary objective of the study was to characterize System performance relative to measurement of glucose using a laboratory comparator method (YSI 2300 analyzer) in venous plasma samples. System performance was primarily evaluated in terms of point and rate accuracy of the FreeStyle Libre 14 Day Flash Glucose Monitoring System interstitial continuous glucose measurements (CGM) in reference to the comparator method.

Secondary Objective
The sponsor's secondary objective was to evaluate the trend and point accuracy of the System at different glucose rates of change and in different glucose ranges.

The safety of the device was examined through the number and percentage of subjects experiencing adverse events as well as anticipated application signs and symptoms related to the Sensor insertion site.

The clinical measurement performance characteristics established in this study included the accuracy across the claimed measuring range (40 to 500 mg/dL glucose), precision, performance of glucose messages (messages are only available for this device when the user initiates a scan), and the number of readings displayed across the wear period.

Data from this US clinical study supported the approval decision. Results from the pivotal study were the primary source of performance information used to support a decision of safety and effectiveness for the device. Key measures of the accuracy and precision of the device demonstrated in the pivotal US clinical study conducted by the applicant are presented in additional detail in Tables 5-15 in Section X.D.2 below.

A. Study Design

This was a non-randomized, single arm, multi-center, prospective, pivotal, non-significant risk study, without controls. Three production Sensor lots that conformed to the factory calibration release process were used in the study. Data to support the current device modification was analyzed after 14 days, but the study was continued for 21 days. Subjects wore two Sensors (one on the back of each upper arm) for up to twenty-one (21) consecutive days following Sensor application. For this analysis, only CGM data generated between the onset of the 1st hour from the time of sensor activation and the end of the 336th hour (14th day) and the corresponding glucose comparator results are included. Analysis presented here is based on the first-applied sensor for each subject.

The protocol and informed consent forms were reviewed and approved by an Institutional Review Board (IRB) and all subjects were required to provide written informed consent before enrollment in the study.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the clinical study was limited to patients who met the following inclusion criteria:

   - Subject must be at least 18 years of age.
   - Subject must have type 1 or type 2 diabetes.
   - Subject must require insulin therapy through an insulin pump and/or multiple daily insulin injections (at least 3 injections daily).
   - Willing to perform a minimum of 8 finger sticks per day during the study.
   - Subject must be willing to fast five individual times prior to in-clinic visits, each fast lasting a minimum of eight hours.
   - Subject must be able to read and understand English.
   - In the investigator's opinion, the subject must be able to follow the instructions provided to him/her by the study site and perform all study tasks as specified by the protocol.
   - Subject must be available to participate in all study visits.
   - Subject must be willing and able to provide written signed and dated informed consent..

   Patients were not permitted to enroll in the clinical study if they met any of the following exclusion criteria:

   - Subject has known allergy to medical grade adhesive or isopropyl alcohol used to disinfect skin.
   - Subject is pregnant, attempting to conceive or not willing and able to practice birth control during the study duration (applicable to female subjects only).
   - Subject has extensive skin changes/diseases at the proposed application sites that could interfere with device placement or the accuracy of interstitial glucose measurements. Such conditions include, but are not limited to extensive psoriasis, recent burns or severe sunburn, extensive eczema,

extensive scarring, dermatitis herpetiformis, skin lesions, redness, infection or edema.

- Subject is currently participating in another clinical trial.
- Subject has donated blood within 112 days (3.7 months) prior to the beginning of the study activities.
- Subject is anemic as determined by the Investigator.
- Subject has concomitant medical condition which, in the opinion of the investigator, could interfere with the study or present a risk to the safety or welfare of the subject or study staff. Such conditions include but are not limited to:
    - History of HIV, Hepatitis B or C
- Subject has X-ray, MRI or CT appointment scheduled during the period of study participation, and the appointment cannot be rescheduled for a time before study participation starts or after study participation ends.
- Subject is unsuitable for participation due to any other cause as determined by the Investigator.Have known allergy to medical grade adhesive or isopropyl alcohol used to disinfect the skin.

2. Follow-up Schedule

   Subjects were scheduled to make eight (8) visits to the clinical study site, including the Enrollment/ Screening visit (Visit 1) and Sensor application visit (Visit 2). Subjects had a total of five (5) in-clinic visits (Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7) during the 21-day Sensor wear period.

   Subjects either underwent plasma venous comparator measurements during the first 12 hours or second 12 hours of each in-clinic visit.

3. Clinical Endpoints

   The study characterized the performance of the System in comparison with laboratory comparator method venous plasma sample measurements and assessed system-comparator matched pairs obtained in the in-clinic sessions.

   During each in-clinic visit, study staff performed intravenous (IV) blood draws to obtain venous blood for comparator reference glucose measurements, in duplicate, approximately every 15 minutes for a total of approximately 7 hours, yeilding a total of 28 samples per subject per visit.

   During the home use period, the sponsor instructed subjects to maintain their diabetes management plan already established prior to initiation of the study, including using a blood glucose meter to provide glucose information for making diabetes treatment decisions. Results of the System were masked and subjects could not see glucose results from the System on the screen.

   Safety data for the FreeStyle Libre 14 Day System were also collected and characterized by incidence, severity and relatedness. Device incidents and malfunctions were also collected.

B. Accountability of PMA Cohort

One hundred and four subjects were enrolled in the study; eight subjects were discontinued due to screen failure and one subject experienced an unrelated adverse event prior to visit 2 (Sensor insertion) and was then discontinued from the study. Therefore, ninety-five subjects were available for analysis at the completion of the study. A total of ninety-five primary sensors with attempted insertion were used in the study. Please note that the primary sensor was defined as the first applied sensor (95 sensors total for first applied) as each subject wore two sensors throughout the study. All 95 Sensors generated Real-time glucose readings that were able to be paired with reference glucose results, and thus included in the effectiveness analysis.

It should be noted that the labeling for the Freestyle Libre Flash 14 Day Glucose Monitoring System presents a different performance analsysis than what is provided in this document. The analysis provided in the labeling presents data from the longest lived sensors per each subject; this analysis could include either the primary sensor or the second applied sensor for each subject (whichever sensor lasted the longest). We have provided analysis below for the primary sensor, and this analysis would most closely represent the user expeience with the device.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical accuracy and precision study for this type of device performed in the US. See Tables 1 through 4 for a description of the demographics and baseline characteristics of the study population of evaluable subjects.

Table 1: Demographic Information

Demographic		Overall	
		N	%
Sex	Female	51	53.7
	Male	44	46.3
Race	White - Not Hispanic or Latino	80	84.2
	White - Hispanic or Latino	7	7.4
	Black or African American	3	3.2
	Asian	2	2.1
	American Indian or Alaskan Native	1	1.1
	Native Hawaiian or Pacific Islander	1	1.1
	Other†	1	1.1
Education	College Education and above	40	42.1
	Some College	47	49.5
	Further Education not completed	8	8.4
Type of Diabetes	Type 1	80	84.2
	Type 2	15	15.8
Insulin pump use	Yes	43	45.3
	No	52	54.7

†Race was reported as ‘mixed race’.

Table 2: Participant Baseline Characteristics

Characteristic		Mean ± SD	Median	Range
Age (years)		49.7 ± 16.1	51.0	19 to 76
Weight	pounds	186.1 ± 47.6	187.0	106.2 to 426.0
	kilograms	84.4± 21.6	84.8	48.2 to 193.2
Height	inches	67.1 ± 3.6	67.0	59.0 to 77.0
	meters	1.70 ± 0.09	1.70	1.50 to 1.96
Body Mass Index		29.1 ± 7.5	29.0	17.7 to 66.7
Duration of Insulin Use (years)		24.0 ± 12.9	21.8	2.2 to 57.0
Total number of injections per day (N subjects=22)		4.7 ± 1.5	4.0	3 to 10
HbA1c (%)		7.7 ± 1.5	7.3	5.1 to 13.6

Table 3: Participant HbA1c distribution

HbA1c Range	N	%
HbA1c < 7%	31	32.6
7% ≤ HbA1c ≤ 8.5%	44	46.3
HbA1c > 8.5%	20	21.1
Total	95	100.0

Table 4: Participant BMI distribution

Body Type Category (BMI Range)	N	%
Underweight (< 18.50)	1	1.1
Normal (18.50 - 24.99)	33	34.7
Overweight (25.00 - 29.99)	22	23.2
Obese Class I (30.00 - 34.99)	25	26.3
Obese Class II (35.00 - 39.99)	10	10.5
Obese Class III (≥ 40.00)	4	4.2
Total	95	100.0

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all subjects enrolled. The key safety outcomes for this study are presented below. All one-hundred and four enrolled subjects were included in the safety analysis. No serious adverse events or unexpected adverse device effects were reported during the clinical study.

Adverse effects that occurred in the PMA clinical study:

There were a total of thirty adverse events that occurred in 16 subjects during the course of the study. These were separated into application site and non-application site adverse events as follows:

Eight (8) of the 95 subjects who had a Sensor inserted reported experiencing an adverse event relating to a Sensor application site. A total of 9 application site adverse events were reported during the study, all of which were mild in severity. There was one report of mild bruising at the sensor insertion site in one subject, two reports of mild bruising at the sensor site in two subjects, 4 reports of slight pink redness erythema at the sensor insertion site in four subjects, one report of mild infection at the insertion site in one subject, and one report of a papule at the sensor insertion site in one subject.

Twenty-one adverse events aside from those related to a Sensor application site were reported by eight subjects. One of these were related to study procedures and was reported to be a vasovagal syncopal episode, and was considered to be anticipated. The twenty remaining events were considered to be both unrelated to the study device and unrelated to the study procedures. These consisted of the following: two reports of hypoglycemia, one report of hypoglycemia symptoms, one report of upper respiratory infection, one report of gastroenteritis, one report of emesis, one report of worsening carpal tunnel syndrome bilateral , three reports of headache, five reports of head cold, one report of back pain, one report of left hip soreness, one report of flu, one report of cold sores, one report of basal cell carcinoma, and one report of skin rash.

2. Effectiveness Results

The analysis of effectiveness with regards to device accuracy was based on all paired data points collected during all study visits for primary sensors worn by study subjects during the study that matched with comparator values ("reference") from a laboratory measurement method (YSI 2300 analyzer). Each subject had their blood glucose analyzed up to 140 times using the laboratory measurement method over five separate visits to the clinical center. This resulted in a total of 9075 paired data points across all subjects. Analysis of sensor wear duration was based on the use lifetime of all primary sensors applied to subjects in the study. Key effectiveness outcomes are presented below in Tables 5 to 15.

Agreement Relative to Reference

Agreement was characterized using paired FreeStyle Libre 14 Day System values and reference laboratory glucose values. These values were compared by pairing the reference blood glucose value to the Libre glucose reading that occurred immediately after the reference glucose value was collected. For values greater than 80 mg/dL, the absolute percent difference (%) from the reference values was calculated and the agreement of the FreeStyle Libre 14 Day System to blood glucose values was assessed by calculating the percentage of FreeStyle Libre 14 Day System readings that were within 15%, 20%, 30%, 40% and more than 40% different from the reference values. For readings less than or equal to 80 mg/dL, the absolute difference in mg/dL between the two glucose results was calculated and the agreement of the FreeStyle Libre 14 Day System to blood glucose values was assessed by calculating the percentage of FreeStyle Libre 14 Day System

readings that were within 15 mg/dL, 20 mg/dL, 30mg/dL, 40 mg/dL and greater than 40mg/dL different from the reference values. The results are presented below in Table 5 for all paired data points in the study and broken down by glucose concentration range (as measured by the FreeStyle Libre 14 Day System).

Table 5: FreeStyle Libre 14 Day System Agreement with Reference Glucose Measurements within Freestyle Libre 14 Day Glucose ranges

Libre Glucose Range (mg/dL)	Number of Libre-Reference Pairs	Within ±15% / ±15mg/dL	Within ±20% / ±20mg/ dL	Within ±30% / ±30mg/ dL	Within ±40% / ±40mg/ dL	Outside ±40% / ±40mg/ dL
Overall	9075	80.8	89.8	97.0	99.1	0.9
40-50	47	38.3	46.8	76.6	87.2	12.8
51-80	638	52.8	65.0	87.9	95.8	4.2
81-180	5785	80.3	90.2	97.2	99.3	0.7
181-300	2292	89.6	95.8	99.1	99.7	0.3
301-400	283	87.6	95.1	100.0	100.0	0.0
401-500	30	80.8	100.0	100.0	100.0	0.0

Agreement When the FreeStyle Libre 14 Day System Reads "LO" or "HI"
The System reports glucose readings between 40 and 500 mg/dL. When the System determines the glucose reading is below 40 mg/dL, it displays "LO" on the Reader display. When the System determines that the glucose reading is above 500 mg/dL, it displays "HI" on the Reader display. Because the System does not display glucose readings below 40 mg/dL or above 500 mg/dL, the comparisons to the actual blood glucose readings (as determined by a laboratory reference analyzer) when the FreeStyle Libre 14 Day System Reader displays "LO" or "HI" are included separately in Tables 6 and 7. Tables 6 and 7 include the total number of values and the cumulative percentages when reference values were less than specific glucose readings when "LO" and "HI" was displayed on the FreeStyle Libre 14 Day System Reader.

When the System displayed "LO" (17 occasions during the clinical study), none of the reference values was less than 40 mg/dL. 100% of the reference values were greater than 40 mg/dL, 82.4% were greater than 50 mg/dL, 58.8% were greater than 60 mg/dL, 41.2% were greater than 70 mg/dL and 23.5% were greater than 80 mg/dL (all of these values greater than 80mg/dL were between 81 and 96 mg/dL).

Table 6: % of Reference Readings in Specific Glucose Ranges When the Freestyle Libre 14 Day Reader Displayed "LO"

Libre Reading	Reference glucose values (mg/dL)						N
	<40	≥40	>50	>60	>70	>80	
"LO"	0.0	100.0	82.4	58.8	41.2	23.5	17

When the System displayed "HI" (13 occasions during the clinical study), none of the reference values were less than 200 mg/dL. 100% of the reference values were greater than 200 mg/dL, 100% were greater than 300 mg/dL, 100.0% were greater than 400 mg/dL, and 7.7% were greater than 500 mg/dL (all of these values greater than 500 mg/dL were between 501 and 513 mg/dL) .

Table 7: % Of Reference Readings in Specific Glucose Ranges When the Freestyle Libre 14 Day Reader Displayed "HI

Libre Reading	Reference glucose values (mg/dL)					N
	<200	≥200	>300	>400	>500	
"HI"	0.0	100.0	100.0	100.00	7.7	13

Concurrence of System and Laboratory Reference

The percentage of concurring glucose values for each reference glucose range with each Freestyle Libre 14 Day glucose range is presented in Table 8 below. This table describes the percentage of paired reference values that were in the same glucose range (shaded) or in glucose ranges above and below the paired Libre-reference readings. For example, when readings from the FreeStyle Libre 14 Day System were within 81 to 120 mg/dL, reference measurements of blood glucose in the clinical study were also within 81 to 120 mg/dL 67.1% of time. The table also indicates the total number (N) of paired Libre-reference data points within each Libre glucose range.

Table 8: Concurrence of Freestyle Libre 14 Day Readings and Reference Values

Libre Glucose Range (mg/dL)	Reference Glucose Range (mg/dL)												
	<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	401-500	>500	N
<40	0	41.2	35.3	23.5	0	0	0	0	0	0	0	0	17
40-60	1.9	24.7	48.7	24.7	0	0	0	0	0	0	0	0	154
61-80	0.4	6.0	33.9	58.2	1.5	0	0	0	0	0	0	0	531
81-120	0	0.2	3.5	67.1	28.1	1.0	0.1	0	0	0	0	0	2394
121-160	0	0	0	7.9	70.1	20.8	1.1	0.2	0	0	0	0	2442
161-200	0	0	0	0.3	13.3	66.2	18.8	1.1	0.3	0	0	0	1610
201-250	0	0	0	0	0.6	16.7	68.2	13.9	0.6	0	0	0	1110
251-300	0	0	0	0	0	0.8	26.5	61.0	11.7	0	0	0	521
301-350	0	0	0	0	0	0	2.8	34.0	55.3	7.9	0	0	215
351-400	0	0	0	0	0	0	0	1.5	20.6	69.1	8.8	0	68
401-500	0	0	0	0	0	0	0	0	0	20.0	80.0	0	30
>500	0	0	0	0	0	0	0	0	0	0	92.3	7.7	13

Difference Relative to Reference

Difference between matched data pairs was calculated as difference between FreeStyle Libre 14 Day System reading and reference glucose value. FreeStyle Libre 14 Day System and reference values were compared by pairing the FreeStyle Libre 14 Day System reading that was obtained closest in time to when the reference sample was collected.

For the FreeStyle Libre 14 Day System , the mean absolute difference is 15.1 mg/dL, or 10.1%; therefore, on average across all glucose measurements in the clinical study, the FreeStyle Libre 14 Day System read 15.1mg/dL or 10.1% different than the reference method. The Median Absolute Difference (in % units) shows that half of the time the System read within 7.8% of the reference blood glucose values.

Difference measurements are based on 9075 paired glucose results; the data are summarized in Table 9 below. Table 9 presents results across all glucose levels combined.

Table 9. Differences between FreeStyle Libre 14 Day System and Reference Glucose Measurements

units	mean difference	median difference	mean absolute difference	median absolute difference	Number of paired data points
mg/dL	-6.0 mg/dL	-5.3 mg/dL	15.1 mg/dL	11.8 mg/dL	9075
%	-4.0%	-3.6%	10.1%	7.8%	9075

Detection of Hypoglycemic and Hyperglycemic Events
When a user performs a scan the FreeStyle Libre 14 Day System displays, when appropriate, Glucose Messages to inform them that their glucose levels are currently low or high (Low Glucose or High Glucose messages), or that their glucose levels are predicted to be low or high within the next 15 minutes (Glucose Going Low or Glucose Going High messages). As described above, these messages differ from the alerts and alarms in most other approved continuous glucose sensors because the user will only be alerted if a scan is initiated (i.e., no message will be provided when the user is wearing the Sensor but has not actively scanned it using the reader).

In the clinical study, the Low Glucose and High Glucose messages were set to appear when the glucose levels reported by the FreeStyle Libre 14 Day System were less than 70 mg/dL or more than 240 mg/dL, respectively. The same thresholds were used for the Glucose Going Low or Glucose Going High messages, for glucose levels projected 15 minutes into the future. These glucose thresholds levels can be set by users, but performance at other thresholds was not evaluated in the study. The ability of the System to appropriately provide these messages was assessed by comparing a reference blood glucose result with a Glucose Messages displayed within 15 minutes (before or after the reference result) and determining if appropriate Glucose Message was displayed when the Sensor was scanned.

Table 10 displays percentages for three different parameters:

- Detection Rate – the percent of cases where a Glucose Message *was displayed correctly.*
- Missed Detection Rate – the percent of cases where a Glucose Message *was not displayed but should have been.*
- False Notification Rate – the percent of cases where a Glucose Message *was displayed but it should not have been*.

For example, in the clinical study with the low glucose target set at <70 mg/dL, the System correctly displayed a Low Glucose message within 15 minutes (before or after) for 71.1% of reference glucose measurements <70 mg/dL (detection rate). However, 28.9% of the time that a reference glucose measurement was <70mg/dL a Low Glucose message was not displayed within 15 minutes before or after this (missed detection rate). Finally, 71.6% of the times that a Low Glucose message was displayed it should not have been (false notification rate) because the reference glucose level was not <70mg/dL within 15 minutes (before or after) of the message being displayed.

Table 10: Detection of Hypoglycemic and Hyperglycemic Events

Type of Notification	Parameter	Rate (%)
Notification of Low Glucose Events (Low Glucose message)	Detection Rate	71.1
	Missed Detection Rate	28.9
	False Notification Rate	71.6
Notification of High Glucose Events (High Glucose message)	Detection Rate	82.3
	Missed Detection Rate	17.7
	False Notification Rate	20.9
Impending Notification of Low Glucose Events (Glucose Going Low message)	Detection Rate	91.6
	Missed Detection Rate	8.4
	False Notification Rate	60.1
Impending Notification of High Glucose Events (Glucose Going High message)	Detection Rate	89.0
	Missed Detection Rate	11.0
	False Notification Rate	15.5

Accuracy After warm-up period

After a user inserts a Sensor and activates a Sensor session using the Reader, the FreeStyle Libre 14 Day System enters a 1 hour warm-up period during which no readings are provided to a user when the Sensor is scanned. Once the warm-up period is complete the Sensor can be scanned and provides data to the user for up to 14 days. The accuracy of the FreeStyle Libre 14 Day System relative to a laboratory reference measurement in the first twenty-four hours of sensor wear following the completion of the warm-up period was assessed by calculating the percentage of System readings that were within 15%, 20%, 30%, 40%, and beyond 40% of reference measurements for glucose values 80 mg/dL and above; and within 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, and beyond 40 mg/dL of reference measurements for glucose values below 80 mg/dL, in intervals of two hours. The results are presented below in Table 11.

Table 11: Number and Percent of Results within Reference

Time Interval (hours)	Number of paired data points	Within ±15% or ±15mg/dL	Within ±20% or ±20mg/dL	Within ±30% or ±30mg/dL	Within ±40% / ±40mg/dL	Outside ±40% / ±40mg/dL
(0-2)	180	71.7	82.2	95.6	98.9	1.1
(2-4)	386	69.7	82.6	94.3	98.4	1.6
(4-6)	376	79.8	89.1	94.4	96.3	3.7
(6-8)	373	73.5	85.8	95.4	99.2	0.8
(8-16)	102	71.6	79.4	95.1	99.0	1.0
(16-18)	292	78.1	87.7	96.2	99.0	1.0
(18-20)	212	78.6	85.4	94.9	99.7	0.3
(20-22)	201	78.6	88.9	98.5	99.4	0.6
(22-24)	101	82.1	93.6	98.7	100.0	0

Sensor Stability Relative to Reference

Sensors can be worn for up to 14 days following the completion of the 1-hour warm-up period. During the clinical study, Libre System performance was evaluated in comparison to a laboratory glucose measurement method at the beginning (Day 1), middle (Day 6 and Day 11) and end (Day 14) of the wear period (Table 12). Additionally, the percentage of System readings were calculated that were within 15%, 20%, 30%, 40%, and beyond 40% of reference measurements for glucose values 80 mg/dL and above; and within 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, and beyond 40 mg/dL of reference measurements for glucose values below 80 mg/dL, at the beginning (Day 1), middle (Day 6 and Day 11) and end (Day 14) of the wear period (Table 13).

Table 12: Differences Measures Between FreeStyle Libre 14 Day System and Reference Readings

Day	Number of Paired Data Points	Median Absolute Relative Difference (%)	Mean Absolute Relative Difference (%)
1	2538	8.5	11.1
6	2377	7.6	9.5
11	2205	7.6	9.7
14	1955	7.5	9.4

Table 13: Number and Percent of FreeStyle Libre 14 Day System Results within Reference Measurements by Day of Wear

Day	Number or Paired Data Points	Within ±15% / ±15mg/dL	Within ±20% / ±20mg/dL	Within ±30% / ±30mg/dL	Within ±40% / ±40mg/dL	Outside ±40% / ±40mg/dL
1	2538	76.0	86.3	95.7	98.7	1.3
6	2377	82.2	92.0	98.1	99.5	0.5
11	2205	81.8	88.9	97.4	99.7	0.3
14	1955	83.9	92.2	97.0	99.5	0.5

Accuracy of Glucose Trends

The FreeStyle Libre 14 Day System displays arrows to indicate the rate and direction of change of glucose levels. Table 14, below, shows the percentage of time in the clinical study that a specific trend arrow displayed by the FreeStyle Libre 14 Day System was observed as it corresponds to the true direction and rate of change in glucose levels as measured using a laboratory glucose measurement method. For example, in the clinical study, when the trend arrow indicated that glucose was changing slowly (-1 to 1 mg/dL/min (→)), actual glucose levels in the body were falling quickly (↓) 0.3% of the time, falling (↘) 2.5% of the time,

↗

changing slowly (→) 50.3% of the time, rising ( ) 4.4% of the time, and rising quickly (↑) 0.6% of the time.

Table 14: FreeStyle Libre 14 Day System Trend Arrow Concurrence

Libre trend arrow	**Reference Rate of Change (mg/dL/min)**							
(mg/dL/min)	**<-2**	**[-2, -1)**	**[-1, 0)**	**[0, 1]**	**(1, 2]**	**>2**	**NA***	**N**
<-2 (↓)	37.7	40.4	11.6	0.7	0	0	9.6	146
-2 to -1 (↘)	4.2	27.8	55.4	6.1	0	0	6.6	623
-1 to 1 (→)	0.3	2.5	50.3	36.0	4.4	0.6	5.9	7304
1 to 2 (↗)	0	0.5	6.5	41.3	36.9	10.2	4.6	629
>2 (↑)	0	0	0.4	16.1	38.3	40.4	4.8	230
NA†	2.3	12.1	29.5	33.5	11	3.5	8.1	173

*Glucose rate of change not available due to the time difference between laboratory reference measurement of glucose readings exceeding 30 minutes.
†Glucose Trend Arrow not available.

Precision of System Readings
In the clinical study all subjects wore two Sensors, each paired with a separate Reader. The purpose of this was to determine the similarly with which two Sensors functioned on the same subject (sensor precision). Precision was evaluated by comparing the glucose readings from the two Systems worn on the same subject at the same time. Results based on 15283 paired readings between two sensors worn on the same subject showed that System readings from the two sensors agreed with each other with a 4.2% coefficient of variation.

Sensor Life
After the 1 hour warm-up period, the Sensor can be worn for up to 14 days. To estimate how long a Sensor will work over the wear duration, 95 Sensors were evaluated in the clinical study to determine how many days of readings each Sensor provided.

Of these 95 sensors, 72 (75.8%) lasted until the final day of use. 86 sensors (90.5%) lasted more than 7 days. There were 8 (8.4%) sensors that failed early, of which 8 (8.4%) failed on or before the sixth day of wear, and 4 (4.2%) failed on or before the third day of wear. Table 15 provides the data below:

Table 15: Operational Hours by Sensor

Operational Hours	Number of Remaining Sensors	Number of Failed Sensors	Survival Percentage (%)
0	95	0	100.0
12	94	1	98.9
24	93	2	97.9
36	91	4	95.8
48	88	7	92.6
60	87	8	91.6
72	87	8	91.6
84	87	8	91.6
96	87	8	91.6
108	87	8	91.6
120	87	8	91.6
132	87	8	91.6
144	87	8	91.6
156	87	8	91.6
168	86	9	90.5
180	84	11	88.4
192	84	11	88.4
204	84	11	88.4
216	81	14	85.3
228	80	15	84.2
240	80	15	84.2
252	80	15	84.2
264	80	15	84.2
276	78	17	82.1
288	77	18	81.1
300	75	20	78.9
312	74	21	77.9
324	72	23	75.8

System Glucose Availability

The System is designed to produce a glucose reading after each user initiated scan that is performed after the warm-up time throughout the entire wear period. To assess the availability of glucose readings, all scans were analyzed for all Sensors which produced at least one reading during the clinical study over the total wear period. The percentage of available FreeStyle Libre 14 Day System readings was calculated in comparison to the number of scans attempted. Overall, 99.3% of Freestyle Libre Scans produced a reading (17,253 readings from 17,370 scans).

4. Pediatric Extrapolation

The applicant provided information to support their claim that the device could be used in people with diabetes aged 18 and up. The FreeStyle Libre 14 Day System is not approved for use in people less than 18 years of age. The labeling states that Sensor readings in people less than 18 years old may be inaccurate and that in general, continuous glucose monitoring systems are recognized to be less accurate in children than in adults. Therefore existing clinical data generated with this device in adults was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Clinical Chemistry and Toxicology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The results of the pivotal clinical study performed by the applicant establish a reasonable assurance of effectiveness of the FreeStyle Libre 14 Day System to be used as intended in the intended use population. The primary effectiveness measurements for this study were based on the accuracy performance evaluation of

the FreeStyle Libre 14 Day System compared to the blood glucose values measured by a laboratory glucose analyzer during in-clinic sessions that spanned the wear period of the device (days 1, 4, 7 and 10).

The performance data presented above (Tables 5-15) are comparable to the performance of current generation CGM systems accepted in the field of diabetes management to provide information that can be used for diabetes treatment decision-making; and therefore support the effectiveness conclusions. These data establish the accuracy across the claimed measuring range (40 to 500 mg/dL glucose), precision, the 14 day wear period (following the 1 hour warm-up period) for the sensor, the notifications (Glucose Messages), and the number of readings displayed during the wear period.

However, system accuracy is lower during the for 12 hours after insertion, and though glucose values are generated for the user during that time period, the non-actionable icon will be displayed. During the first 12 hours of use, the system should be used adjunctively to blood glucose measurementsm, and Libre values should not be used to make treatment decisions.

The clinical study data demonstrate that the FreeStyle Libre 14 Day System was effective in the study population designed to be reflective of the intended use population.

B. Safety Conclusions

The risks of the device are based on the adverse events observed in the clinical study which are described in Section X.D.1 above and the potential adverse effects of the device on health described below.

The following are possible adverse effects of inserting a sensor and wearing the adhesive patch: local erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin.

There are potential adverse effects associated with making diabetes treatment decisions when glucose values and rates of change provided by the device are inaccurate, as follows:

The risks of making treatment decisions based on falsely high readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong existing hypoglycemia which can result in seizures, loss of consciousness, and rarely, death.

The risks of making treatment decisions based on falsely low readings include inappropriate administration of carbohydrates. These inappropriate treatments could increase the risk of hyperglycemia or prolong existing hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and acute diabetic ketoacidosis (DKA) which can result in weakness, seizures, and death.

Inaccurate calculation of the rate of change of glucose by the device could increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. Inaccurate calculation of the rate of change of glucose by the device could also prevent a patient from taking measures to prevent a sustained increase or decrease in glucose levels, which could lead to serious hypoglycemia or hyperglycemia.

There are potential adverse effects associated with making acute and long-term therapy adjustments when glucose values and rates of change provided by the device are inaccurate. The risks of making therapy adjustments based on inaccurate device information include inappropriate adjustment of diabetes medication regimens. This could increase the risk of hypoglycemia and corresponding risk of seizures, loss of consciousness, and rarely, death; it may also increase the risk of hyperglycemia, increasing exposure to long-term microvascular complications of diabetes (eye, kidney, nerve and heart disease) and risk of acute diabetic ketoacidosis (DKA) which can cause weakness, seizures, and death.

The device also provides glucose threshold and predictive messages (alerts) when the Sensor is scanned; these alerts may cause a user to take action to prevent future potential future glycemic events (e.g., set reminders for future glucose checks or future action, or take immediate treatment-based action). Potential adverse events may therefore also result from inaccuracies that cause a failure to trigger alerts, or cause false alerts. This may cause users to take an inappropriate action, or incorrectly take no action, and result in increased risk or prolongation of hyperglycemia or hypoglycemia. In the absence of a user-initiated action (scan) the system cannot provide glucose-related alerts, which could serve to notify users of an actual or impending glucose value above or below glucose thresholds. The lack of alerts in the absence of user-imitated action (scan) could increase the risk of severe hypoglycemia or diabetic ketoacidosis through decreased opportunities for detection of hypoglycemia or hyperglycemia relative to other similar currently marketed continuous glucose sensors.

Users may experience different levels of performance from each sensor inserted (e.g., based on the specific insertion site and individual physiology), at different times of use (e.g., days of wear) or under different conditions (e.g., before or after meals or exercise). User understanding that each sensor may perform differently and that for any given sensor the performance may be affected by multiple factors and may vary throughout a wear session, depends on a user checking glucose information provided by the FreeStyle Libre 14 Day System against blood glucose values obtained using a

glucose meter. Because the FreeStyle Libre 14 Day System is factory calibrated, there is not a minimum number of daily glucose meter checks that a user should make (i.e., to calibrate the system, as for other currently marketed similar systems). Factory calibration may therefore reduce the opportunity of some patients using the device to become familiar with the performance of any given sensor or the performance of the system at specific times during a sensor session by checking readings from the device using a self-monitoring blood glucose device (glucose meter).

These risks are mitigated by warnings in the labeling and through required patient training. In the labeling, users are advised that if their symptoms do not match readings from the FreeStyle Libre 14 Day System , they should perform blood glucose testing and make treatment decisions based on the blood glucose reading, not the FreeStyle Libre 14 Day System reading. The frequency with which user symptoms did not match FreeStyle Libre 14 Day System readings, as assessed in clinical studies, is sufficiently low to be adequately mitigated through labeling warnings.

There is a potential for overtreatment, especially with insulin, for FreeStyle Libre 14 Day System users because glucose values are less burdensome to obtain than by performing a typical glucose meter test. The ready availability of glucose information at all times could prompt some users to incorrectly react to a post-meal increase in glucose levels by taking an insulin dose without accounting for a previously delivered meal insulin does (this is known as insulin stacking). This could result in subsequent hypoglycemia. Users are therefore advised in the labeling to avoid stacking insulin (re-administration of insulin within a 2 hour timeframe).

Users are also advised in the labeling to use their FreeStyle Libre 14 Day System concurrently with a blood glucose meter for a period of time until they are comfortable with how the device is best used. The Reader incorporates a built-in blood glucose meter that can be used with compatible test strips to conduct blood glucose tests.The Reader also displays a non-actionable icon under conditions when the device should not be used for treatment decisions to inform patients that blood glucose testing with a glucose meter should be performed prior to making a diabetes treatment decision. The icon is displayed under the following conditions:

- The glucose as reported by the Sensor is below 70 mg/dL (when the “low glucose” message is displayed);
- The glucose will be below 70 mg/dL within 15 minutes (when the “glucose is going low” message is displayed);
- The glucose is rapidly changing (when the glucose trend arrow as reported by the Reader is rising quickly or falling quickly);
- The glucose trend arrow is not displayed;
- The glucose as reported by the Sensor is above 500 mg/dL (when the HI message is displayed); and
- During the first 12 hours of sensor life.

C. Benefit-Risk Determination

The probable benefits of the device were assessed using data collected in clinical studies conducted to support PMA approval as described above in Section X. Risks of the device were assessed using data collected in clinical studies conducted to support PMA approval as described above in Section X and potential adverse effects of the device on health as described above in Section VIII. A summary of the Benefits and Risks of the device is presented below.

The FreeStyle Libre Flash Glucose Monitoring System is a continuous glucose monitoring system which is intended to replace blood glucose testing for diabetes treatment decisions. The system does not require user calibration with blood glucose values.

The FreeStyle Libre 14 Day System is intended to detect trends and track patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of FreeStyle Libre 14 Day System readings should be based on the glucose trends and several sequential readings over time.

The system is intended for single patient use and requires a prescription. The user begins scanning with the FreeStyle Libre 14 Day System after a 1 hour warm-up period and uses the Sensor for up to 14 days.

Benefits of FreeStyle Libre 14 Day System, when used as intended, include real-time knowledge of glucose levels, whether glucose levels are increasing or decreasing, and the identification and/or confirmation of patterns of glycemic excursions throughout the day and night, when patients may be unable to test their blood glucose. Access to retrospective glucose trend information for diabetes treatment decisions with this device may allow patients to make more informed diabetes treatment decisions than relying solely on glucose point information as provided by self-monitoring of blood glucose (SMBG) devices.

Non-adjunctive use (i.e., use to make real-time therapy adjustment decisions) of the FreeStyle Libre 14 Day System can be expected to provide the benefit of decreased pain relative to fingerstick measurements. Factory calibration of the FreeStyle Libre 14 Day System provides the additional benefit that the system does not require calibration with fingersticks, further decreasing the burden, pain, and discomfort associated with blood glucose meter use. Factory calibration also provides the benefit of avoiding potential errors or delays that could arise during user calibration and which can negatively influence performance of CGM systems that require calibration. Non-adjunctive use of the FreeStyle Libre 14 Day device is expected to be associated with increased access to glucose information and decreased burden of SMBG-based diabetes treatment decisions. The decreased daily burden of use of the FreeStyle

Libre 14 Day System to replace fingerstick glucose measurements can additionally have psychosocial benefit (e.g. reduced burnout and perceived stigma). SMBG adherence is known to be suboptimal, and non-adjunctive use of the FreeStyle Libre 14 Day System could increase adoption of continuous glucose monitor use and provide opportunities for easier and more convenient glucose monitoring to patients with diabetes, while providing the added benefits of this device.

The longer intended duration of use of this device (14 days) is beneficial to patients, in that less frequent sensor insertions are required relative to similar systems with a shorter use life, and patients may endure pain and other symptoms associated with sensor insertion less frequently.

The clinical performance study demonstrated that the performance of the FreeStyle Libre 14 Day is comparable to the performance of current generation CGM systems accepted in the field of diabetes management to provide information that can be used to make diabetes treatment decisions starting 12 hours after insertion. During the first 12 hours of sensor life, the glucose values should not be used to alone to make treatment decisions.

Risks of treatment decisions made from falsely high CGM readings include inappropriate or excessive administration of insulin. These inappropriate treatments could increase the risk of hypoglycemia or prolong hypoglycemia which can result in seizures, loss of consciousness, or rarely, death. Risks of treatment decisions made from falsely low CGM readings include inappropriate administration of carbohydrate. These inappropriate treatments could increase the risk of hyperglycemia or prolong hyperglycemia.

Inaccurate calculation of the rate of change of glucose by the device could prevent a patient from taking measures to stop a trend of increasing or decreasing glucose levels which could lead to serious hypoglycemia or hyperglycemia. This could also lead patients to make inappropriate adjustments to their treatment, resulting in serious hypoglycemia or hyperglycemia. Inaccurate calculation of the rate of change of glucose by the device could also increase the risk of serious hypoglycemia or hyperglycemia if treatment is influenced by the inaccurate rate of change. However, labeling specifically advises not to make changes in dosing based solely on the arrows indicating rate of change.

The risks of these uses above are mitigated by strong warnings in the label and training. In the labeling, users are advised that if their symptoms do not match their CGM reading, they should perform blood glucose testing and make treatment decisions based on the blood glucose reading, not the CGM reading. Users are also advised to avoid stacking insulin (avoid re-administration of within a 2 hour timeframe). Users are also advised to use their CGM concurrently with SMBG for a period of time until they are comfortable with how the device is best used. In addition, at specific glucose levels and rates of change and during the first 12 hours of sensor life, the Reader displays a non-actionable icon, which informs patients that SMBG should be performed prior to making a diabetes treatment decision.

Labeling specifies that users should gain experience with the device prior to using it to make diabetes treatment decisions and that patients should work with their healthcare professionals to incorporate the use of the Libre 14 Day System into their diabetes management plan. Gaining experience with the use of the device prior to using it to make treatment decisions will be helpful to provide additional risk mitigations and optimize safety and usability of the device, including use of the non-actionable icon described above.

Further, the factory calibration could potentially reduce the opportunity of some patients using the device to become familiar with the performance of any given sensor or the performance of the system at specific times during a sensor session by checking readings from the device using a self-monitoring blood glucose device (blood glucose meter).

There are warnings and precautions in the labeling relating to use of the device in populations in which the device has not been studied (e.g., critically ill patients, dialysis patients, and hypoglycemia unaware patients) and in populations in which device performance is not established but generally accepted to be less accurate (i.e., pediatric population).

The lack of passive alerts in the absence of a user initiated action (as compared to other marketed systems with the same intended use) notifying patients of a glucose value above or below (or predicted to reach above or below) user-specified thresholds could increase the risk of severe hypoglycemia and DKA through decreased opportunities for detection of hypoglycemia or hyperglycemia. The lack of passive alerts is conveyed to users and healthcare providers through a warning in the labeling. There are also risks associated with inaccuracies in the performance of glucose messages, including false messages that cause users to take an inappropriate action, or missed messages that cause users to incorrectly take no action, resulting in increased risk or prolongation of hyperglycemia or hypoglycemia. Labeling includes a warning about the lack of passive alerts in the absence of user-initiated action for patients using the device and for healthcare providers potentially prescribing the device.

There is a minor risk of local skin erythema (redness), local infection, inflammation, pain or discomfort, bleeding at the glucose sensor insertion site, bruising, itching, scarring or skin discoloration, hematoma, and adhesive irritation. There is also a remote risk of sensor or needle fracture during insertion, wear or removal, with fragments retained under the skin. This event was not observed during the clinical studies reviewed for this submission.

Despite the differences in accuracy of this device relative to blood glucose meters, it provides benefits not available from blood glucose meters. If the expected performance of the device is understood, the benefits of additional information gained from this device outweigh the risk of inaccurate results, rates of change, and false negative and positive messages.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

FDA considered that patients want a variety of devices that provide information and aid in management of their glucose control to inform decision making with their health care providers on lifestyle changes and treatment decisions. Patients have also expressed at patient centered forums, on social media outlets, and in personal conversations with FDA staff that they want availability of a variety of glucose monitoring devices (continuous or otherwise) that address patients specific needs because not all devices suit all patients, and are willing to accept reasonable risks related to such devices. This information was gathered during patient oriented conferences and face-to-face meetings with patients.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits of this System, as discussed above, outweigh the risks.

XIII. CDRH DECISION

CDRH issued an approval order on July 23, 2018. The final conditions of approval cited in the approval order are described below.

The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience users need in order to use the device.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

None.