

# Summary of Safety and Effectiveness Data

## I. General Information

<b>Device Generic Name:</b>	Continuous Glucose Monitor
<b>Device Trade Name:</b>	FreeStyle Navigator® Continuous Glucose Monitoring System
<b>Applicant's Name and Address:</b>	Abbott Diabetes Care 1360 South Loop Road Alameda, CA 94502
<b>PMA number:</b>	P050020
<b>Date of Panel recommendation:</b>	None
<b>Date of Notice of Approval to Applicant</b>	March 12, 2008

## II. Indications for Use

The FreeStyle Navigator® Continuous Glucose Monitoring System is indicated for continually recording interstitial fluid glucose levels in people (ages 18 and older) with diabetes mellitus for the purpose of improving diabetes management. Readings and alarms about glucose levels from FreeStyle Navigator® Continuous Glucose Monitoring System are not intended to replace traditional blood glucose monitoring. Before adjusting therapy for diabetes management based on the results and alarms from the FreeStyle Navigator® Continuous Glucose Monitoring System, traditional blood glucose tests must be performed. The FreeStyle Navigator® Continuous Glucose Monitoring System provides a built-in blood glucose meter to confirm the continuous glucose result.

The FreeStyle Navigator® Continuous Glucose Monitoring System provides real-time readings, graphs, trends and glucose alarms directly to the user. The FreeStyle Navigator® Continuous Glucose Monitoring System is intended to be used in home settings to aid people with diabetes in predicting and detecting episodes of hypoglycemia and hyperglycemia and in clinical settings to aid healthcare professionals in evaluating glucose control. The FreeStyle Navigator Continuous Glucose Monitoring System is available only by prescription.

## III. Contraindications

The FreeStyle Navigator Continuous Glucose Monitoring System must be removed prior to Magnetic Resonance Imaging.

#### IV. Warnings and Precautions

The warnings and precautions can be found in the FreeStyle Navigator Continuous Glucose Monitoring System labeling.

#### V. Device Description

The FreeStyle Navigator Continuous Glucose Monitoring System (hereinafter referred to as the System) provides an integrated approach to the need for the frequent measurement, display, and interpretation of the patient's glycemic status. The glycemic state can be correlated with carbohydrate intake, insulin dosage, oral medication dosage, exercise, or other factors that may be used by the patient and healthcare provider in the management of diabetes.

The System provides the following features to the user:

- On-demand continuous glucose information
- Glycemic trend information updated every minute
- User set alarm thresholds to alert the user when glucose concentrations reach a configured high or low glucose level
- Projected high glucose or projected low glucose alarm
- Functionality of a stand-alone blood glucose meter integrated into the receiver for performing calibration and confirmatory glucose measurements by fingerstick.

The System includes four components:

- 1) Single-use disposable electrochemical sensing element, or **Sensor**, which is designed for up to five days of continuous use (The Sensor is incorporated into the Sensor Delivery Unit and is not provided separately);
- 2) **Sensor Delivery Unit (SDU)**, which is a single-use disposable component designed to insert the Sensor at the proper depth in the subcutaneous tissue;
- 3) A reusable **Transmitter** that is the electrical interface to the Sensor; and
- 4) A reusable **Receiver**, which is a pager-like device that receives glucose measurement data from the Transmitter and calculates and stores the Continuous Monitor System readings. The Receiver also contains the functionality of a stand-alone blood glucose meter for determination of glucose by fingerstick.

## Description of System Components

### Sensor

The primary component of the System is the Sensor. It is a single-use disposable electrochemical sensing element designed for up to five days of continuous use. During the sensor equilibration period lasting ten hours, the data from the sensor is masked from the user. During this time period, the user will take his or her glucose measurements using conventional fingerstick methods.

The Sensor tail is inserted approximately 5 mm into the subcutaneous tissue of the abdomen or back of the upper arm, with a percutaneous electrical connection to the Transmitter. An electrical current is generated by the oxidation of glucose in the interstitial fluid. The conductive traces on the Sensor transfer the current from the Sensor tail to contact pads on the external portion of the Sensor.

The Sensor is maintained in its proper location on the surface of the skin by the Sensor Support Mount subcomponent of the Sensor Delivery Unit.

### Sensor Delivery Unit

The Sensor Delivery Unit (SDU) is a specially designed sterile single-use component of the System used to place the Sensor at the proper depth in the subcutaneous tissue.

The SDU also protects the Sensor from damage and provides a sharp-safe environment for the introducer sharp before and after use. The SDU is intended to be a single-use unit and has features to discourage reuse.

The SDU consists of 3 sub-systems:

- a. Inserter
- b. Sensor Support Mount Assembly
- c. Sensor (described previously)

The Sensor is located in a metal carrier (called an Introducer) which is spring loaded into the Inserter. The bottom portion of the SDU is the Sensor Support Mount that holds the Sensor and Transmitter in position on the skin using an adhesive patch. To insert a sensor, a locking pin is removed and the SDU is placed against the surface of the skin. The insertion button is pressed, and the Sensor is inserted into the subcutaneous tissue. After placement of the Sensor, the Introducer is automatically withdrawn back into the Inserter to protect the user or healthcare professional from exposure to the sharp tip of the Introducer. The Inserter is detached from its Sensor Support Mount base by squeezing plastic release tabs on the sides of the Inserter. The Transmitter is then snapped

into place on the Sensor Support Mount, thus completing the electrical connection to the Sensor.

At the end of Sensor life (up to five days), the Transmitter assembly is removed from the skin, automatically removing the Sensor. The Sensor Support Mount is detached from the bottom of the Transmitter and discarded, along with the Sensor.

### **Transmitter**

The Transmitter is the electrical interface to the Sensor. It measures and digitizes the Sensor output current and once per minute transmits the Sensor current value, temperature and other status information via a radiofrequency (RF) communication channel to the Receiver. The Transmitter is attached to the surface of the skin directly over the Sensor by means of the Sensor Support Mount described previously. After removing the Sensor at the end of the wear period, the Transmitter is detached from the mount and cleaned with soap and water, then reused with additional Sensors. The Transmitter is powered by a replaceable type 357 HZ silver oxide battery that lasts approximately 30 days.

### **Receiver**

The Receiver is a pager-like device that receives glucose measurement data from the Transmitter and calculates and stores the Continuous Monitor System readings. It also provides an LCD display for the system, and functions as a blood glucose meter. An internal antenna provides RF reception. Four input buttons on the Receiver allow for display of glucose information, changing Receiver configuration (e.g., audible vs. vibratory alarms) and initiating Receiver functions such as linking to a new Transmitter.

Additionally, the Receiver includes sound or vibratory alarms to:

- Warn of high or low glucose levels
- Remind user to perform various system maintenance functions, e.g., calibrate the Sensor
- Provide system status information, e.g., a Receiver that is out of range of the Transmitter

The Receiver also contains the functionality of a Blood Glucose Meter that can be used for blood glucose monitoring at any time. The integrated meter is also used for periodic calibration of the continuous glucose Sensor.

## **VI. Alternative Practices and Procedures**

Glucose self-monitoring using home blood glucose meters will provide glucose results. Traditional discrete home glucose monitors provide single glucose values for monitoring of glycemic state.

## VII. Marketing History

The FreeStyle Navigator Continuous Glucose Monitoring System has not been marketed in the United States or any country outside of the United States.

## VIII. Potential Adverse Effects of the Device on Health

Infection, inflammation, or bleeding at the glucose sensor insertion site are possible risks of inserting a sensor into your skin. Inaccurate glucose results and alarms may potentially lead to inappropriate insulin administration or carbohydrate intake.

## IX. Summary of Preclinical Studies

### 1. Component Level Testing

#### Sensor

Functional and environmental tests were performed on the Sensor, which is the primary component of the System. The capability of the sensor to meet functional requirements and support device features in a safe and effective manner was verified in several functional tests, including:

- Interference testing in accordance with NCCLS Document EP7-P, Vol. 6, No. 13 “Interference Testing in Clinical Chemistry”
- Linearity and temperature testing
- Sensitivity verification

*In-vitro* and *in-vivo* interference testing indicated that usual pharmacologic levels of ascorbic acid have no effect on the function of the Sensor but that salicylic acid has a minimal effect. *In vitro* testing indicated that Sensor function was not affected by normal physiologic levels of other potential interferents, including, but not limited to uric acid, lipids, bilirubin, Ibuprofen, and Acetaminophen. Linearity and temperature dependence testing verified that the Sensor gave proportional responses with acceptable sensitivity and met acceptance criteria across the range of glucose concentrations and expected skin

## Summary of Safety and Effectiveness Data

temperatures. The *in-vitro* and *in-vivo* sensitivity test verified the fundamental stability of the Sensor.

The Sensor was also tested after exposure to the following environmental stresses:

- Trace amounts of household soaps and toiletries
- Thermal cycling between -20°C to 45°C to simulate shipping conditions
- Shipping by common commercial air transport.

All acceptance criteria for Sensor performance were met during this testing.

### **Sensor Delivery Unit**

A series of functional and environmental tests were performed on the Sensor Delivery Unit (SDU). All SDU passed functional and environmental testing, including, but not limited to:

- User Assembly
- One Hand Operation
- Depth and Accuracy of Sensor Placement
- Drop Tests
- Hand Size and Dexterity Test
- Temperature and Humidity Tests
- Pressure
- Rapid Humidity and Temperature Changes

### **Transmitter**

A series of functional and environmental tests were performed on the Transmitter, which is the electrical interface to the Sensor. The Transmitter passed all tests in the functional design verification and environmental testing including but not limited to:

- Attachment
- Sensor Seal
- Electrical Connection
- Temperature and Humidity
- Extreme Temperature
- Pressure

## Summary of Safety and Effectiveness Data

- Submersion in Water
- Drop Tests
- Exposure to Cleaning Agents

### **Receiver**

A series of functional and environmental tests was performed on the Receiver, a device that receives glucose measurement data from the Transmitter and calculates and stores the System continuous glucose monitoring readings. The Receiver passed all tests in the functional design verification and environmental testing including but not limited to:

- Temperature Measurement
- Clock Accuracy
- Battery Replacement
- Glucose Measurement Capability
- Exposure to Cleaning Agents
- Ability to Operate after Dropping

The discrete glucose measurement testing, which included accuracy and precision evaluation, interference testing, dynamic range and operating environment robustness, indicated that the design and function of the integrated blood glucose meter met the established acceptance criteria.

## **2. System Level Testing**

### **System Function Verification**

Overall system functions were verified in a set of laboratory tests. These tests verified the system's ability to calibrate System Sensors using the integrated blood glucose meter measurements, to report continuous glucose results every minute over the specified sensor life of up to five days, and to raise alarms for low and high glucose results or projected low and high glucose results. Also verified were the functions of the key inter-component interfaces: the transmitter-to-sensor connection and the transmitter-to-receiver RF communications. The tests verified that the system provides feedback to users when interfaces are connected or disconnected and that the RF communication channel is robust and secure in the presence of multiple Systems.

### **System Environmental Verification**

Environmental testing verified the system's ability to measure glucose over its specified operating conditions:

## Summary of Safety and Effectiveness Data

- Temperatures from 40° to 113°F for continuous glucose monitor functionality (40° to 104°F for blood glucose functionality)
- Humidity up to 90%
- Air pressure down to 10.1 psia (~10,000 ft altitude)

The on-body components' tolerance to submersion in bathing conditions was evaluated in both hot and cold water to depths of one meter. In addition, the Transmitter measurement of skin temperature was evaluated to ensure that the system can correct reported glucose results for sensor response variations related to skin temperature.

### **Software Validation**

Extensive verification and validation testing was conducted to confirm that the software used in the System performed in accordance with established specifications. This testing confirmed that all major requirements were met. All identified deviations from desired or expected operation were carefully reviewed and determined to have no significant impact on the safe and effective use of the device.

### **Use and Labeling Verifications**

User interface and human factors were verified, including features such as user ability to display glucose results when a valid calibration is available, as well as user ability to enter and retrieve configuration parameters. The User's Guide was verified to provide the required information on how to operate the System safely.

## **3. Laboratory studies**

### **Biocompatibility Testing**

Biocompatibility testing was conducted for the sterilized Sensor that is inserted into the skin. Other components that come into contact with the user's skin surface are made from materials with established biocompatibility, including the introducer needle and the sensor mount adhesive patch.

Sensor biocompatibility testing was performed following ANSI/AAMI/ISO 10993-1 Standard (1997 Edition). All test protocols were performed following Good Laboratory Practice (GLP) as described in 21CFR Part 58. The results of the biocompatibility testing for the System Sensor component are listed in **Table 1** below.

**Table 1**  
**System Sensor Biocompatibility Testing**

<b>Test</b>	<b>Pass /Fail &amp; Results</b>
Cytotoxicity (MEM Elution)	Pass - Non-cytotoxic
Sensitization (Maximization Test)	Pass - No evidence of sensitization
Irritation (ISO Intracutaneous)	Pass - Primary irritation responses negligible
Systemic Toxicity (USP/ISO Systemic Injection Text)	Pass - Non-toxic
Subchronic Implantation	Pass - No gross evidence of local irritancy
Genotoxicity (Ames Test)	Pass - Non-mutagenic
Hemocompatibility (Hemolysis in vitro)	Pass - Non-hemolytic

The testing conducted in accordance with the ANSI/AAMI/ ISO 10993 Standard (1997 Edition) for Medical Devices demonstrated that overall product biocompatibility requirements are satisfied for the FreeStyle Navigator Continuous Glucose Monitoring System.

**Sterility**

The electron beam (EB) sterilization process used to sterilize the sensor assembly was validated according to the requirements of ISO 11137 and AAMI TIR27 Method VDmax.

**Sensor Shelf Life**

Sensor shelf life has been determined through real time (25°C) and accelerated studies. Under dry storage conditions, sensor performance has been shown to be acceptable for a shelf life of 6 months when stored at 2-25°C. Additional studies were carried out to verify that the packaging materials maintain a suitable dry environment for at least 6 months and have no deleterious effect on sensor stability.

**Packaging and Shipping Testing**

Final System and SDU kits were packaged using standard materials and methods and subjected to shipping testing per ASTM D 4169-05 including Altitude at 12,000 feet. All samples passed functional testing performed at the conclusion of the test.

### **EMI/EMC/ESD and Product Safety Testing**

A sequence of ESD/EMI/EMC and Product Safety testing for the System Receiver and Transmitter was performed by external accredited laboratories. The ESD/RF Immunity testing showed that the Transmitter and Receiver units functioned correctly after exposure to electromagnetic fields. Emissions from the Transmitter and Receiver were also tested for compliance and passed. Testing was conducted according to the following standards:

- a. CISPR 11 (requirements for medical devices)
- b. IEC 60601-1-2
- c. FCC Part 15 subpart B
- d. EN 300 220-3
- e. EN 301 489-3

Additional immunity testing was conducted beyond the standards listed to cover specific frequencies as follows: Frequency in Mhz, 124 (Air traffic control), 161.5 (Lo-jack, police, fire, etc.), 315 (remote control and security devices), 836.5 (US cell phones), 902.5 (EU cell phones), 915 (WLANS, Cordless phones), 1747.5 (EU cell phones), 1880 (US cell phones), and 2450 (WLANS, Cordless phones).

Additional special immunity testing was conducted beyond the listed standards, to cover interference generated by Electronic Article Surveillance Devices and Metal Detectors.

Electrical Safety was tested for compliance to the standards:

- a. UL 60601-1
- b. IEC 60601-1-1

FCC regulatory testing for the System Transmitter was conducted, according to the requirements prescribed by the design specification as they relate to electromagnetic emissions and compliance with the applicable FCC standards as listed in CFR 47, Part 15.231. The testing for the System Transmitter was performed by an external accredited laboratory and the Transmitter complies with the standards.

## X. Summary of Clinical Studies

### 1. Report of Prior Clinical Studies

The studies performed prior to the pivotal clinical studies are summarized in **Table 2**. Additionally, several other research clinical studies were performed to provide early evaluations of the device, which are not reflected in **Table 2**. During all of these studies, subjects were not using the FreeStyle Navigator Continuous Glucose Monitoring System data to diagnose, treat, nor manage their diabetes.

**Table 2**

**Summary of Prior Clinical Studies**

Study ID	Study Objective	Duration	Sites	No. of Subjects
TS01 005 (Phase 1)	Calibration and glucose calculation algorithm development	3 days	3 clinical sites	22 subjects with diabetes
TS02 049 (Phase 2A)	Evaluate accuracy, verify algorithm	3 days	3 clinical sites	30 subjects with diabetes
TS02 045 (Phase 2B)	Establish safety and efficacy in home use	21 days	7 clinical sites	102 subjects with diabetes
TS05 063	Feasibility of 5 day sensor	5 days	1 clinical site	42 subjects with diabetes
Design Verification Testing	Verify 5 day system performance	5 days	In-house	26 healthy subjects
TS05 065	Evaluate accuracy	5 days	3 clinical sites	29 subjects with diabetes

*Phase 1 and Phase 2 Clinical Studies:* Three studies were performed to demonstrate the safety and effectiveness of a previous version of the device with a 3-day sensor. The Phase 1 Study (TS01-005) collected frequent venous blood and sensor data over 3 days in-clinic for a wide range of glucose concentrations to develop the glucose calculation and calibration algorithms. The Phase 2A Study (TS02-049) determined the accuracy of the device using the algorithms developed with the Phase 1 data. The Phase 2B Study (TS02-045) evaluated the device under home use conditions over 21 days. Sensors were inserted by the subjects at home every 3 days during the study.

*Feasibility Study – Five-Day Sensor:* The feasibility study (TS05-063) evaluated performance of the updated 10-hour calibration scheme with a five

day sensor life. The study demonstrated good performance across five days of sensor wear in a home use setting, comparing continuous glucose results with the integrated FreeStyle Blood Glucose Meter. Results from 86 sensors (N=4597) had 77.6% of points in the A zone and 98.0% of points within the A+B zones on the Clarke Error Grid. There were no adverse events associated with five day sensor wear, the number of insertion site reactions was small, and they were all resolved without treatment.

*Design Verification Testing:* After feasibility of the 5-day sensor was confirmed, verification testing was conducted in-house to confirm system functional performance before beginning the pivotal external clinical studies. The 104-sensor study verified that the device met its functional requirements related to sensor insertion, calibration and five-day sensor wear. The few observed insertion site reactions resolved without treatment.

- 2. Initial In-Clinic Study TS05-065: This study was intended to determine the clinical accuracy of the device with respect to a glucose reference method (YSI). Study design problems related to the reference glucose measurements were identified that were corrected in the subsequent pivotal in-clinic study. Although the study did not meet its objective with regard to determining accuracy, it reflected excellent device safety, with few adverse events or sensor-related symptoms. FreeStyle Navigator Continuous Glucose Monitoring System In-Clinic Study (Protocol TS05-066 – PIVOTAL STUDY)**

### **Overview**

This was a multi-center, open-label study to evaluate the accuracy of the continuous glucose function of the System compared to a standard laboratory reference method, the YSI Blood Glucose Analyzer. The clinical trial was conducted at three U.S. clinical centers and enrolled subjects with type 1 diabetes who were at least 18 years of age. The objective of clinical trial TS05-066 was to determine the clinical accuracy of the FreeStyle Navigator Continuous Glucose Monitoring System at two anatomical sites (back of the upper arm and abdomen).

### **Patient Population**

Fifty-eight subjects were fitted with a total of 118 sensors in the In-Clinic Study. Subjects were required to stay at the healthcare facility for a total of about 50 hours over the course of the 5-day study. A total of 57 of the 58 subjects completed the entire 5-day study and one-week follow-up visit. One subject discontinued the study, apparently due to dislodged sensors.

**Subject Demographics**

Subjects ranged in age from 18 to 64 years (mean = 40.5 ± 11.2 years). Thirty-six of the subjects were male (62.1%) and 47 (81.0%) of the subjects were Caucasian. Subjects' Body Mass Index ranged from 20.9 to 45.3 with a mean of 27.8 ± 4.6. Time since the diagnosis of type 1 diabetes ranged from 0.6 to 43.5 years (with a mean of 21.7 ± 11.7 years).

**Clarke Error Grid Analysis**

According to the Clarke Error Grid Analysis, 81.7% of Navigator continuous mode (CM) results were in the clinically accurate Zone A. Refer to **Tables 3** through **5** and **Figure 1**.

**Table 3**  
**Clarke Error Grid**  
**by Sensor Location and Reference Glucose Level**

		<b>Abdomen</b>				
<b>Reference Glucose Level (mg/dL)</b>	<b>Number of Paired Readings</b>	<b>A (%)</b>	<b>B (%)</b>	<b>C (%)</b>	<b>D (%)</b>	<b>E (%)</b>
20-40	11	54.5	N/A*	N/A*	45.5	0.0
41-80	632	57.4	20.4	0.0	22.2	0.0
81-120	1878	68.7	31.2	0.2	N/A*	N/A*
121-240	5482	85.3	14.6	0.1	N/A*	0.0
241+	1841	91.8	7.7	0.0	0.5	0.0
Overall	9844	81.5	16.8	0.1	1.6	0.0
		<b>Arm</b>				
<b>Reference Glucose Level (mg/dL)</b>	<b>Number of Paired Readings</b>	<b>A (%)</b>	<b>B (%)</b>	<b>C (%)</b>	<b>D (%)</b>	<b>E (%)</b>
20-40	11	54.5	N/A*	N/A*	45.5	0.0
41-80	663	53.1	24.4	0.0	22.5	0.0
81-120	1942	70.3	29.7	0.0	N/A*	N/A*
121-240	5948	85.5	14.3	0.2	N/A*	0.0
241+	1954	91.7	7.8	0.0	0.4	0.1
Overall	10518	81.8	16.6	0.1	1.5	0.0

## Summary of Safety and Effectiveness Data

\*N/A means that the Clarke Error Grid does not consider the possibility of these zones in that concentration range.

Summary of Safety and Effectiveness Data

**Table 4**  
**Clarke Error Grid by Day and Reference Glucose Level**

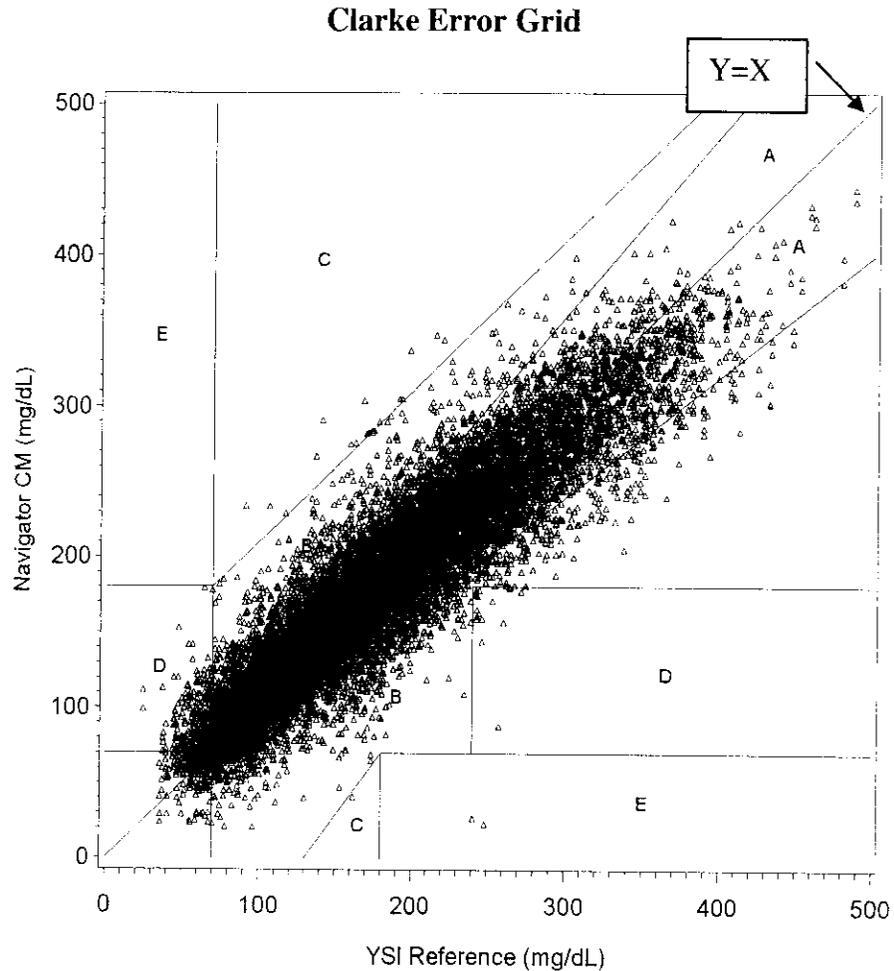
Reference Glucose Level	Day 1 (%)		Day 2 (%)		Day 3 (%)		Day 4 (%)		Day 5 (%)	
	A	A+B	A	A+B	A	A+B	A	A+B	A	A+B
20-40	50.0	50.0	50.0	50.0	66.7	66.7	N/A	N/A	50.0	50.0
41-80	71.6	89.6	45.4	74.8	40.1	65.6	56.9	74.3	49.5	74.5
81-120	70.7	100.0	73.1	99.8	62.4	100.0	72.5	100.0	69.6	99.8
121-240	86.1	99.6	83.7	99.9	85.1	100.0	87.7	100.0	85.3	100.0
241+	93.1	99.6	89.4	99.5	91.4	99.7	98.2	100.0	91.7	99.2
Overall	82.5	98.9	82.4	99.0	79.4	97.7	84.0	98.2	80.9	97.9

**Table 5**  
**Clarke Error Grid by Reference Glucose Level**

Reference Glucose Level (mg/dL)	Number of Paired Readings	A and B (%)	A (%)	B (%)	C (%)	D (%)	E (%)
20-40	22	54.5	54.5	N/A*	N/A*	45.5	0.0
41-80	1295	77.7	55.2	22.5	0.0	22.3	0.0
81-120	3820	99.9	69.5	30.4	0.1	N/A*	N/A*
121-240	11430	99.9	85.4	14.4	0.1	N/A*	0.0
241+	3795	99.5	91.7	7.8	0.0	0.4	0.1
Overall	<b>20362</b>	98.3	<b>81.7</b>	<b>16.7</b>	<b>0.1</b>	<b>1.6</b>	<b>0.0</b>

\*N/A means that the Clarke Error Grid does not consider the possibility of these zones in that concentration range.

Figure 1



In each of the Clarke Error Grid analyses, a majority of the clinical errors (Zones C, D and E) were at low glucose levels. On closer inspection of these errors, subsequent System CM readings often detected the hypoglycemic condition.

**Consensus Error Grid Analysis**

The Consensus Error Grid analysis of the System CM results classified 85.5% of paired points as clinically accurate (Zone A), 13.6% (2776/20362) as benign errors (Zone B), 0.8% (161/20362) as errors that are likely to affect clinical outcomes (Zone C), and 0.0% (6/20362) as errors that could have significant medical risk (Zone D). There were no results in Zone E. Refer to **Table 6**.

**Table 6**  
**Consensus Error Grid Analysis of System CM**

Zone	N	%
A	17419	85.5
B	2776	13.6
C	161	0.8
D	6	0.0
E	0	0.0
Total	20362	100.0

Of the 337 readings in Zone C, D, or E under the Clarke Error Grid analysis, nearly two-thirds were in the clinically acceptable Zones A and B under the Consensus Error Grid analysis.

**Bias Analysis**

The mean absolute difference for glucose < 100 mg/dL is 17.2 mg/dL, the mean absolute relative difference for glucose ≥ 100 mg/dL is 11.1%, and the overall absolute relative difference is 12.8%. Refer to **Tables 7** and **8**.

**Table 7**  
**Difference Analysis between System CM and YSI Reference**

	Level	Mean	SD	Median	Min	Max	N
Mean Difference (mg/dL)	< 100 mg/dL	10.7	20.5	8.8	-75.3	143.2	2961
Mean Absolute Difference (mg/dL)	< 100 mg/dL	17.2	15.4	13.0	0.0	143.2	2961
Mean Relative Difference (%)	≥ 100 mg/dL	1.0	15.0	-0.1	-90.7	120.4	17401
Mean Absolute Relative Difference (%)	≥ 100 mg/dL	11.1	10.0	8.6	0.0	120.4	17401
Mean Difference (mg/dL)	All results	0.8	26.8	1.6	-225.6	150.4	20362
Mean Absolute Difference (mg/dL)	All results	20.1	17.8	15.3	0.0	225.6	20362
Mean Relative Difference (%)	All results	3.0	18.4	1.0	-90.7	354.5	20362
Mean Absolute Relative Difference (%)	All results	12.8	13.6	9.3	0.0	354.5	20362

**Table 8**  
**Distribution of Difference between System CM and YSI Reference**

Glucose Range (mg/dL)	Number of Paired Readings	Percent within 20%	Percent within 30%	Percent within 40%
20-40*	22	31.8 %	54.5 %	72.7 %
41-80*	1295	65.9 %	82.0 %	90.7 %
81-120	3820	69.5 %	85.2 %	92.7 %
121-240	11430	85.4%	95.1%	98.3%
>240	3795	91.7%	98.8%	99.9%
Overall	20362	82.3%	93.1%	97.0%

\*The absolute difference from the YSI reading is measured in mg/dL if the YSI reading is 20-80 mg/dL.

**Regression Analysis**

The Deming regression analysis gives a slope of 0.92, an intercept of 14.3 mg/dL, and a correlation coefficient (r) of 0.93.

**Characterization of Precision**

The between sensor precision results are from the paired one-minute System CM readings from two sensors worn simultaneously (arm and abdomen). There were 312,953 paired readings evaluated for 57 subjects. The pooled sensor-to-sensor standard deviation is 10.7 mg/dL for glucose  $\leq$  100 mg/dL, and the pooled coefficient of variation is 9.2% for glucose  $>$  100 mg/dL. Refer to **Table 9**.

**Table 9**  
**Between Sensor Precision**

Level of Glucose (mg/dL)	Mean (mg/dL)	SD	%CV	N Pairs
20-60	50.4	10.8	22.1	4596
61-100	83.8	10.7	13.0	36924
101-200	150.3	15.5	10.5	147621
201-325	248.0	18.2	7.4	108610
326-450	360.0	22.4	6.2	15152
451+	454.8	12.8	2.8	50
All	185.1	16.3	10.0	312953

### Continuous Error Grid

The Continuous Error Grid evaluates the accuracy of the glucose value and the rate of glucose change. The point and rate accuracy were combined and stratified by glycemic status (hypoglycemia, euglycemia, and hyperglycemia) to complete the analysis. Under the Continuous Error Grid analysis, 97.5% of all Navigator readings were considered to be clinically accurate. Refer to **Table 10**.

**Table 10**

#### Continuous Error Grid Combined Point and Rate Rating by Glycemic State

	Hypoglycemia (BG ≤ 70 mg/dL) 3.2% of the data		Euglycemia (70 < BG ≤ 180 mg/dL) 53.6% of the data		Hyperglycemia (BG > 180 mg/dL) 43.2% of the data		All	
	N	%	N	%	N	%	N	%
Accurate Readings	369	59.5	10407	98.9	8364	98.6	19140	97.5
Benign Errors	5	0.8	99	0.9	74	0.9	178	0.9
Erroneous Readings	246	39.7	22	0.2	41	0.5	309	1.6
All	620	100.0	10528	100.0	8479	100.0	19627	100.0

### Determination of Alarm Performance

The performance of low and high glucose alarms was assessed in an in-clinic study using 58 subjects with type 1 diabetes wearing one FreeStyle Navigator sensor on the arm and one sensor on the abdomen. FreeStyle Navigator continuous data were masked from the subjects and investigators and the alarms were not turned on. During 50 hours the subjects' venous glucose was tested with a YSI 2300 Stat Plus glucose analyzer at 15 minute intervals. Arm and abdomen data were pooled in the alarm analysis. Alarm performance was evaluated in a retrospective analysis of the study data. As alarm performance was developed retrospectively, your results may vary from those reported below.

#### Definitions:

Hypoglycemic event – two or more successive YSI measurements below the alarm threshold or one YSI measurement 6 mg/dL below the alarm threshold.

Hyperglycemic event - two or more successive YSI measurements above the alarm threshold or one YSI measurement 6% above the alarm threshold.

True Threshold Alarm – a threshold alarm that occurred ± 30 minutes from the start of a hypoglycemic or hyperglycemic event

## Summary of Safety and Effectiveness Data

True Alarm Rate – the percentage of time the glucose level was beyond the threshold and an alarm was activated

$$\frac{\text{Events Detected by True Threshold Alarms}}{\text{Total Events}} \times 100$$

Missed Alarm Rate – the percentage of time the glucose level was beyond the threshold and an alarm was not activated

$$\frac{\text{Events Not Detected By True Threshold Alarms}}{\text{Total Events}} \times 100$$

False Threshold Alarm – a threshold alarm that occurred when a YSI measurement within  $\pm 30$  minutes was not beyond the threshold setting

False Alarm Rate – the percentage of time an alarm occurred when glucose level was not beyond the threshold setting

$$\frac{\text{False Threshold Alarms}}{\text{Total Threshold Alarms}} \times 100$$

Projected alarms occur when glucose value and the rate of change of glucose predict the crossing of an alarm threshold at a future time determined by the sensitivity setting – the low sensitivity is 10 minutes; the medium sensitivity is 20 minutes; and the high sensitivity is 30 minutes. Projected alarms are designed to alert the patient to the possibility of a future high or low glucose event. **Note: The performance of projected alarms has not yet been established.**

### Detection of Low Glucose

See **Table 11** below for detection of low glucose. As an example, when the threshold alarm was set at 70 mg/dL (during the day), 56 % of the low glucose events were detected by FreeStyle Navigator.

**Table 11 Low Glucose Detection**

Low Alarm Setting (mg/dL)	Day True Alarms*	Day Missed Alarms**	Night True Alarms*	Night Missed Alarms**	Day False Alarms***	Night False Alarms***
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
65	46 (51/121)	54 (65/121)	80 (12/15)	20 (3/15)	19 (18/95)	41 (11/27)
70	56 (98/176)	44 (78/176)	79 (19/24)	21 (5/24)	16 (21/132)	40 (14/35)
75	59 (130/219)	41 (89/219)	72 (23/32)	28 (9/32)	9 (15/161)	37 (14/38)
85	61 (189/308)	39 (119/308)	65 (22/34)	35 (12/34)	7 (17/228)	33 (14/43)

\* True Alarms are the percentage of time the glucose level was below the threshold and an alarm was activated

\*\*Missed Alarms are the percentage of time the glucose level was below the threshold and an alarm was not activated.

\*\*\*False Alarms are the percentage of time an alarm occurred but the glucose level was not below the threshold setting.

**Detection of High Glucose**

See **Table 12** for detection of high glucose. As an example, when the threshold alarm was set at 240 mg/dL (during the day), 78 % of the high glucose events were detected by FreeStyle Navigator.

**Table 12 High Glucose Detection**

High Alarm Setting (mg/dL)	Day True Alarms*	Day Missed Alarms**	Night True Alarms*	Night Missed Alarms**	Day False Alarms***	Night False Alarms***
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
180	89 (561/630)	11 (69/630)	69 (29/42)	31 (13/42)	11 (68/628)	7 (3/44)
240	78 (295/376)	22 (81/376)	41 (12/29)	59 (17/29)	12 (47/393)	25 (7/28)
270	70 (193/274)	30 (81/274)	21 (3/14)	79 (11/14)	12 (32/265)	36 (5/14)
300	61 (117/192)	39 (75/192)	12 (1/8)	88 (7/8)	12 (20/161)	33 (1/3)

\* True Alarms are the percentage of time the glucose level was above the threshold and an alarm was activated

\*\*Missed Alarms are the percentage of time the glucose level was above the threshold and an alarm was not activated.

\*\*\*False Alarms are the percentage of time an alarm occurred but the glucose level was not above the threshold setting

**Calibration Stability**

The FreeStyle Navigator system is typically calibrated at 10, 12, 24 and 72 hours following sensor insertion. To demonstrate performance of the FreeStyle Navigator system across each calibration cycle 115 sensors were evaluated to verify that performance remains consistent in time increments after calibration. Performance is assessed by comparing the percent of FreeStyle Navigator sensor readings falling within 20, 30 and 40 % of the YSI readings throughout each interval. Results in **Table 13** indicate that there is minimal deterioration in accuracy during the calibration periods.

**Table 13**  
**Percentage of FreeStyle Navigator Readings Falling Within 20, 30 and 40% of YSI Reading by Time of Use**

Calibration Period		% of FreeStyle Navigator Readings Within 20% *	% of FreeStyle Navigator Readings Within 30% *	% of FreeStyle Navigator Readings Within 40% *
Cal 1 (typically occurs 10 hrs after sensor insertion)	First Calibration Period	80	88	94
Cal 2 (typically occurs 12 hours after sensor insertion)	First Third of Second Calibration Period	83	94	98
	Second Third of Second Calibration Period	83	94	98
	Final Third of Second Calibration Period	84	95	98
Cal 3 (typically occurs 24 hours after sensor insertion)	First Third of Third Calibration Period	84	94	98
	Second Third of Third Calibration Period	80	92	97
	Final Third of Third Calibration Period	80	91	95
Cal 4 (typically occurs 72 hours after sensor insertion)	First Quarter of Final Calibration Period	86	93	96
	Second Quarter of Final Calibration Period	84	92	96
	Third Quarter of Final Calibration Period	80	93	98
	Final Quarter of Final Calibration Period	82	93	97

\*The absolute difference from the YSI reading is measured in mg/dL if the YSI reading is at or below 75 mg/dL.

**Sensor Stability**

The FreeStyle Navigator sensor provides glucose information for up to 122 hours. Performance of the FreeStyle Navigator system was evaluated according to length of time from sensor insertion. Performance was assessed by comparing the percent of FreeStyle Navigator sensor readings falling within 20, 30 and 40 % of the YSI readings throughout the sensor wear. Results in **Table 14** indicate that there is no significant change in accuracy during the sensor wear.

**Table 14**

**Percentage of FreeStyle Navigator Readings Falling Within 20, 30 and 40% of YSI Reading by Time After Insertion**

<b>Time After Insertion (hours)</b>	<b>% of FreeStyle Navigator Readings Within 20% *</b>	<b>% of FreeStyle Navigator Readings Within 30% *</b>	<b>% of FreeStyle Navigator Readings Within 40% *</b>
10-12	86	92	96
12-24	82	93	97
24-72	81	92	97
72-122	82	93	97

\*The absolute difference from the YSI reading is measured in mg/dL if the YSI reading is at or below 75 mg/dL.

**Insertion Site Examinations / Adverse Events**

Thirty-four of 58 subjects (58.6%) were reported as experiencing a sign or symptom relating to a sensor insertion site. Mild erythema (27.6%, 16/58) and mild itching (17.2%, 10/58) were the most common symptoms seen after removal of the sensor. All of these reactions were transient resolving without recourse to treatment. Furthermore, one Adverse Event was reported related to the device: one subject had moderate blistering under the sensor mount that resolved within a week without medication. No Serious Adverse Events were reported.

### 3. Home-Use Study (Protocol TS05-064 – PIVOTAL STUDY)

#### Overview

This was a multi-center, open-label study to evaluate the Navigator Continuous Glucose Monitoring System in a home-use setting. The clinical trial was conducted at six U.S. clinical centers. A total of 137 subjects with type 1 or 2 diabetes were enrolled in the study between September 7, 2005 and November 4, 2005. Subjects wore individual sensors for a series of 5-day durations for a total of 40 days. The first 20 days (approximately four 5-day sensor durations) was the blinded phase during which the subjects could not see display of the continuous glucose data. After 20 days was the unblinded phase, during which the subjects could view the continuous data but used the integrated Blood Glucose Meter (BG) to monitor their glucose, just as they had done during the prior 20 days.

#### Patient Population

Of the 137 subjects enrolled in the investigation, 123 completed the 41-day monitoring period and returned for the final follow-up visit. Of the 14 subjects discontinued prior to study completion, the primary reasons were unwillingness or inability to follow protocol, difficulty understanding the system and non-compliance with the study. Thirteen (13) subjects discontinued prior to the 21-day study visit and one subject discontinued at the 21-day study visit. None of these 14 discontinued subjects used unblinded Navigator CM systems.

#### Subject Demographics

Subjects ranged in age from 19.5 to 72.6 years (mean of  $48.6 \pm 13.0$  years). Sixty-five (47.4%) of the subjects were male and 108 (78.8%) were Caucasian. Subjects' Body Mass Indices ranged from 18.9 to 52.6 with a mean of  $28.7 \pm 5.8$ . Time since the diagnosis of diabetes ranged from 1.3 to 55.8 years with a mean of  $22.0 \pm 11.9$  years. Daily total insulin dosage ranged from 12.0 to 160.0 units, with a mean of  $51.7 \pm 28.7$  units. Of the 137 subjects, the majority (73.0%, 100/137) had type 1 diabetes.

#### Sensor Usability Performance

Sensor insertions and removals were performed by study subjects during the Home Use Study. Sensor calibrations were performed by the study subjects using the built-in FreeStyle blood glucose meter. Success rates are summarized below. In some cases, use errors led to usability failures. Success rates that exclude these use errors provide an indication of the potential device usability when it is used according to the operating instructions.

*Insertion:* Out of 1307 total reported insertion attempts, 1275 were evaluable. Of these, 1168 (91.6%) were successful. If only the 1215 insertion attempts that

were completed according to the device instructions are considered, 1168 (96.1%) were successful.

*Calibration:* Out of 1168 successfully inserted sensors for which calibration attempts were made, 1043 (89.3%) were successfully calibrated and produced continuous glucose measurements. Of the 1121 sensors for which calibration attempts were made according to the device instructions, 1043 (93.0%) were successfully calibrated and produced continuous glucose measurements.

*Duration:* Once glucose values were obtained, most sensors completed the target 5 days of sensor wear. Excluding 155 sensors that were intentionally removed early for study-related reasons or for user discretion not related to the device, the remaining 892 sensors had a median sensor life of 119.6 hours; 664 (74.4%) of them provided glucose results for 5 days (108 to 122 hours). Considering only those sensors that were used according to the device instructions, a total of 808 sensors had a median sensor life of 120.0 hours; 664 (82.2%) of them provided glucose results for 5 days.

### **Glycemic Excursions**

The change in glycemic status between the blinded and unblinded phases of the study was stratified by type 1 and type 2 diabetes. In various measures of hypoglycemia the type 1 diabetes subjects improved in the unblinded phase compared with the blinded phase. The time spent below the 70 mg/dL threshold for hypoglycemia for type 1 patients was reduced by 42% from 1.4 hours/day to 0.8 hours/day ( $p < 0.0001$ ), and the time spent below the more dangerous 55 mg/dL threshold was reduced by 54% ( $p < 0.0001$ ). There was a 15% decrease in the time spent severely hyperglycemic (glucose  $> 240$  mg/dL) ( $p=0.0049$ ). Although the frequency of hyperglycemia did not change for type 2 subjects, all measures of duration and severity improved in the unblinded phase. The time spent in the euglycemic range for type 2 patients increased by 12% ( $p=0.0027$ ), the time spent  $> 180$  mg/dL decreased by 18% ( $p=0.0057$ ), and the time spent  $> 240$  mg/dL decreased by 33% ( $p=0.0077$ ). As anticipated, the measures of hypoglycemia for type 2 subjects, which were low in the blinded phase, were largely unchanged in the unblinded phase.

### **User Satisfaction Questionnaire**

At the conclusion of the study, subjects were asked to complete a user satisfaction and experience questionnaire; 131 of 137 subjects (95.6%) responded to the questionnaire. User satisfaction was based on an evaluation category of 1 to 6, with 1 corresponding to strongly agree and 6 corresponding to strongly disagree. The majority of subjects (88.5%; 115/130) indicated that the System was easy to learn, and 87.7% (114/130) of subjects found that conducting blood glucose tests with FreeStyle strips from the System receiver's integrated BG meter was easily accomplished. Ninety percent of subjects (90.2%; 110/122) indicated that changing the settings was also an easy process.

## Summary of Safety and Effectiveness Data

Eighty percent of subjects (104/130) found the insertion site choices (back of upper arm, abdomen) acceptable. Additionally, 93.8% (121/129) of the study subjects indicated that the information from the System helped them better understand their blood glucose.

## **XI. Conclusions Drawn From the Studies**

The results of the pre-clinical verification/validation testing and clinical trials to assess the performance of the FreeStyle Navigator Continuous Glucose Monitoring System establish reasonable assurance that this system is safe and effective for its intended use when utilized in accordance with product labeling.

## **XII. Panel Recommendation**

In accordance with the provisions of Section 515(c) (2) 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 this PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CDRH Decision**

FDA issued an approval order on March 12, 2008.

The applicant's manufacturing facility was inspected on 9/15/05 (Santa Fe Springs, CA), 3/29/06 (Hayward, CA), 5/3/06 (Morton Grove, IL), 3/17/06 (Rochester, NY), 3/13/07 (Alameda, CA) & 12/21/07 (Marietta, GA) and found to be in compliance with the Quality Systems regulation (21 CFR 820).

## **XIV. Approval Specification**

Directions for use: See labeling.

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

Postapproval requirements and Restrictions: See approval order.