510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:
k043158

B. Purpose for Submission:
New product

C. Measurand:
Glucose, home glucose monitoring test

D. Type of Test:
Quantitative

E. Applicant:
Bayer Healthcare LLC

F. Proprietary and Established Names:
Ascensia BRIO Blood Glucose Monitoring System: blood glucose monitor

G. Regulatory Information:

1. Regulation section:
   21 CFR §862.1345, Blood Glucose Test System, Over-the-Counter
2. Classification:
   Class II
3. Product code:
   NBW, CGA
4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   A glucose test system is intended to measure glucose quantitatively in blood and other bodily fluids. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and pancreatic islet cell tumors.
2. Indication(s) for use:
   "The Ascensia BRIO Blood Glucose Meter is used with Ascensia EASYFILL Blood Glucose Test Strips and Ascensia EASYFILL Control Solutions (Low, Normal, and High) for the measurement of glucose in whole blood. The Ascensia BRIO Blood Glucose Monitoring System is an Over-the-Counter (OTC) device used by persons with diabetes and by healthcare professionals in home settings and in healthcare facilities.

   The Ascensia BRIO Blood Glucose Monitoring System is indicated for use with fingertip capillary whole blood specimens.

   The frequent monitoring of blood glucose is an adjunct to the care of persons with diabetes."

3. Special conditions for use statement(s):
   This product is intended for over-the-counter and point-of-care use.
4. Special instrument requirements:
   None; this is a complete blood glucose monitoring system.

I. Device Description:

The Ascensia BRIO Blood Glucose Monitoring System consists of a hand-held blood glucose meter, test strips, and control materials. Each lot of test strips has a code chip containing lot-specific calibration information that the machine reads automatically. The meter is turned on by strip insertion; the user then supplies finger-tip blood or control solution to the strip and the meter makes an audible tone and starts the assay, which completes in ten seconds. The meter's software converts the results read off the test strip into a plasma glucose concentration and displays the value on the meter's LCD screen.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Ascensia Elite Diabetes Care System (including Ascensia Elite Blood Glucose Meter, Ascensia Elite Test Strips, and Ascensia Elite controls (low, normal, and high).
2. Predicate 510(k) number(s):
   k020208, k990649, k991242
3. Comparison with predicate:

Similarities		
Item	**Ascensia BRIO**	**Ascensia ELITE**
Intended Use	Blood glucose monitoring for home and point-of-care	Same
System Components	Meter, calibration code strip, test strip, check strip, battery, control solutions	Same
Specimen	Capillary blood	Same, and approved for arterial and neonatal specimens
Test Principle/ Enzyme/ Mediator	Electrochemical/ Glucose oxidase/ Potassium ferricyanide	Same/ same/ same
Calibration	Automatic	Same
Stability	Strips and controls, 3 mo after opening	Same
Power Source	3V lithium battery	Same

Differences		
Item	**Ascensia BRIO**	**Ascensia ELITE**
Test Range	30 – 550 mg/dL	20 – 600 mg/dL
Sample Volume	2.5 ul	2.0 ul
Test Time	10 seconds	30 seconds
Hematocrit Range	30 – 55%	20 – 60%
Operating Range	57 – 104^{o} F, relative humidity < 80%	50 – 104^{o} F, relative humidity 20 - 80%
Memory Capability	10 test results	20 test results
Size	100x58x21 (mm)	81x51x14 (mm)
Weight	64 grams	50 grams

K. Standard/Guidance Document Referenced (if applicable):

Area of Study	Reference Procedure	Procedure Title
Method Comparison/ Anticoagulant Studies	NCCLS EP9-A	User Comparison of Quantitative Clinical Laboratory Methods Using Patient Samples
Precision	NCCLS EP5-A	User Evaluation of Precision Performance of Clinical Chemistry Devices
Linearity	NCCLS EP6-A	Evaluation of the Linearity of Quantitative Methods
Interferences/ Cross-Reactivity	NCCLS EP7-A	Interference Testing in Clinical Chemistry
Stability	Chemistry/Reagent Development Procedures	Reagent Stability Guidelines for Access
Guidance	ISO 15197	In vitro diagnostic test systems- Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus
Clinical Outcome Effects	Parkes JL et al., *Diabetes Care* 23:1143 (2000)	"A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose"

L. Test Principle:

The test is based on the release of electrical potential after a two-step reaction where glucose and ferricyanide, in the presence of glucose oxidase, are converted into gluconolactone and ferrocyanide. Ferrocyanide, when electrical current is applied, becomes ferricyanide and releases electrons; the increase in current measured after 10 seconds by the meter is proportional to the glucose concentration. As the rate of the chemical reaction is proportional to temperature, the meter also takes the temperature into account when calculating the glucose concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within-run and between-run precision were tested with three test strip lots for 10 days. Whole blood was glycolyzed for 18 hours at 25°C, then spiked with glucose (see below) and tested once a day. Ten replicates of each of level of whole blood samples were tested in each run. Three replicates of each of the control solutions were tested twice a day (20 total runs).

Precision in 3 Lots of Ascensia BRIO Test Strips

Whole Blood Samples							
		Within-Run		**Between Run**		**Overall**	
Strip Lot	**Mean (mg/dL)**	**Std Dev**	**%CV**	**Std Dev**	**%CV**	**Std Dev**	**%CV**
CS700D	55	2.4	4.4	3.6	6.5	4.3	7.9
	131	4.1	3.1	3.0	2.3	5.0	3.9
	458	12.0	2.6	9.8	2.1	15.5	3.4
CS700E	61	2.9	4.7	4.0	6.5	5.0	8.0
	143	4.3	3.0	4.4	3.1	6.2	4.3
	502	11.3	2.2	11.7	2.3	16.2	3.2
CS700F	66	2.9	4.5	3.0	4.6	4.2	6.4
	144	5.6	3.9	4.0	2.8	6.9	4.8
	496	11.8	2.4	10.3	2.1	15.6	3.2
Control Samples							
		Within-Run		**Between Run**		**Overall**	
Strip Lot	**Mean (mg/dL)**	**Std Dev**	**%CV**	**Std Dev**	**%CV**	**Std Dev**	**%CV**
CS700D	46	1.8	3.9	2.7	5.8	3.2	6.9
	100	2.2	2.2	1.6	1.5	2.7	2.7
	297	6.4	2.1	6.2	2.1	8.8	3.0
CS700E	48	1.9	4	2.8	5.9	3.4	7.1
	105	2.3	2.2	1.9	1.8	3.0	2.8
	312	8.1	2.6	7.1	2.3	10.8	3.4
CS700F	53	1.7	3.3	2.6	5.0	3.1	5.9
	107	2.8	2.6	1.9	1.8	3.4	3.2
	314	6.8	2.2	7.2	2.3	9.9	3.2

These results met Bayer's internal specification for whole-blood precision.

b. Linearity/assay reportable range:

Upper range linearity study: Plasma was extracted from whole blood samples that had been spiked with glucose. The resulting seven samples, ranging from 36 to 548 mg/dL glucose and each read forty times, were compared to results obtained with the YSI Glucose Analyzer which was calibrated with a set of glucose standards in serum. Three test strip lots were linear over the range

tested ($r^2 \geq 0.996$) although there was substantial negative bias compared to the YSI values in the two lowest data points (36 and 56 mg/dL).

Lower range linearity study: Heparinized blood was allowed to glycolyze at 25°C for 18 hours then spiked with glucose to concentrations of approximately 0, 20, 30, 40, and 50 mg/dL. Plasma was extracted, and forty replicates of each concentration were tested with an Ascensia BRIO meter without the glucose cut-off limits set. Regression analysis of the three lots tested showed that they all had a slope of 1.00, but an r^2 value between 0.830 and 0.911.

The low and high detection limits for the Ascensia BRIO system have been set at 30 and 550 mg/dL glucose. Readings below or above these values will generate a "LO" or "HI" result respectively.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Control solutions are made by gravimetrically adding glucose to the control base solution. The glucose concentration for each control bulk solution is verified by a glucose hexokinase assay using glucose standards that are traceable to SRM917a, a NIST standard reference material. Value assignments for each lot of control are determined using 10 replicates of randomly selected test strips each on 10 meters to determine mean, standard deviation, and %CV. Control ranges estimates include consideration of the estimated stability shifts of the test strips, control solution, and temperature/humidity effect of the test results at the outer ranges of the operating parameters.

Shelf life studies performed by the manufacturer indicate that unopened sensors have a 15 month life-span. Unopened controls have a 24-month shelf life and are stable for 3 months after opening.

d. *Detection limit:*
The sensitivity of the Ascensia BRIO assay, defined as the minimum glucose concentration that can be distinguished from a zero concentration sample, was calculated using the low-end linearity data described above. Using twice the standard error of the estimate (Sy,x) calculated from the regression analysis, the average sensitivity for the three test lots was 15 mg/dL glucose.

e. *Analytical specificity:*
Assay interferents were tested in a dose-response manner following NCCLS EP7-A guidelines. A pool of whole blood was allowed to glycolyze for 18 hours at 25°C. Aliquots of the blood were supplemented with glucose to a final concentration of 100 mg/dL and measured on an YSI analyzer. The interferent was prepared with an appropriate solvent, and spiked into the 100 mg/dL blood. A control pool was prepared by supplementing the blood with solvent minus the interferent. A series of four to five levels that included the

maximum concentration of the substance that would be expected to be encountered in clinical practice were used for each interferent.

The table below shows the effect of common interferents at the upper end of normal or therapeutic levels on Ascensia BRIO test levels, however, some substances (acetaminophen, ascorbic acid, dopamine, sodium gentisate, iodoacetate, and uric acid) had large biases (≥±20%) at supernormal (≥ 5X normal) concentrations.

Interference at High-Normal or High Therapeutic Levels
Ascensia BRIO System

Interferent	Upper End of Therapeutic or Normal Range	% Bias from Normal or Zero		
		Lot CS700A	Lot CS700B	Lot CS700C
Acetaminophen	2 mg/dL	4.3	3.9	3.8
Ascorbic Acid	2 mg/dL	1.4	1.4	1.4
Bilirubin	1.2 mg/dL	0	0.2	0.2
Cholesterol	300 mg/dL	-1.5	-1.4	-1.4
Dopamine	0.037 mg/dL	0.2	0.2	0.2
Gentisate	0.6 mg/dL	1.2	0.3	0.8
Iodoacetate	100 mg/dL	24.7	29.3	30.6
L-dopa	No established therapeutic range, no sig effect at ≤1 mg/dL			
Methyl-Dopa	0.75 mg/dL	4.0	3.4	2.9
Tolazamide	3 mg/dL	3.0	2.0	2.7
Triglycerides	190 mg/dL	-0.13	-0.15	-0.14
Uric Acid	7.7 mg/dL	5.3	5.1	4.6

The anticoagulants EDTA, heparin, and oxalate, and the glycolytic inhibitors fluoride and iodoacetic acid were tested for interference bias. EDTA and heparin are acceptable anticoagulants, but oxalate and the two glycolytic inhibitors gave unacceptably high bias. Therefore, the sponsor does not recommend the use of glycolytic inhibitors with the Ascensia BRIO system.

Hematocrit Effect:
The effect of sample hemoglobin variation on the Ascensia BRIO system was tested experimentally by preparing samples of known hematocrit (Hct) and spiking aliquots of these samples with different levels of glucose. The calibration information stored in the meter's code chip was established using 40% Hct whole blood. Studies where the Hct of the blood varied but the glucose concentration was the same showed that the Ascensia Brio system will have an average change of 1.0% in the reported glucose value for every percent deviation in the sample hematocrit away from 40% Hct.

Glucose concentrations were shown to affect hemoglobin bias of a sample. For example, samples containing low levels of glucose (≤50 mg/dL) did not

show a significant hematocrit bias. However, samples in the normal range and above normal range demonstrated that if the sample had a hematocrit greater than 40% there was a substantial negative bias and if the sample had a hematocrit less than 40% there was a positive bias in the meter reading. Bayer has set an internal product specification of mean % Hct bias ≤ ±20% for samples >75 mg/dL glucose when compared to 40% Hct values and ≤ ±15 mg/dL bias for samples ≤ 75 mg/dL; this product meets this specification.

This bias was confirmed in clinical testing with patient samples, as shown in the table below. Whole blood samples were collected at three clinical sites by lay users and health care providers (HCP). Blood glucose levels of these samples were read on the BRIO meter with two test strip lots; a sample was collected for laboratory method determination of blood glucose levels and determination of the subject's Hct. An estimate of the potential bias at six different Hct levels was obtained by least square linear regression analysis.

Hematocrit Effect on Ascensia BRIO Glucose Results

Glucose Range	n = *	30% Hct	35% Hct	40% Hct	45% Hct	50% Hct	55% Hct.	% ± 20% YSI
All (42 to 394)	1280	7.7%	3.1%	-1.3%	-5.7%	-10%	-14.4%	97.1%
>220 mg/dL	240	4.5%	1.3%	-2.3%	-5.6%	-9%	-12.3%	99.6%
127 to 220 mg/dL	560	11.5%	6.2%	0.9%	-4.5%	-9.8%	-15.1%	97.9%
42 to 126 mg/dL	480	4.7%	1.8%	1.8%	-4.0%	-6.8%	-9.7%	95.0

* The n is composed of four measurements of each sample; 320 total, 60 above 220 mg/dL, 140 samples between 127 and 220 mg/dL, and 120 samples between 42 to 126 mg/dL

f. Assay cut-off:
Not applicable.

2. Comparison studies:
   a. Method comparison with predicate device:
   Performance of the Ascensia BRIO and YSI were compared in two studies performed by Bayer. In each study, duplicate donor capillary fingerstick blood samples were applied to three different strip test lots (a total of six samples applied to test strips). Sufficient blood was also collected in microtubes

containing sodium heparin and tested on the YSI instrument in duplicate. The results of the two studies are shown below:

Correlation of 2 Studies to Reference Method: Laboratory Studies

Study	Test Strip Lots	Donors	Samples	Slope	Intercept	R^2	Sample Range
1	CS700A, B, C	93	555	0.999	1.5	0.988	35 – 522
2	CS700D, E, F	103	618	0.975	2.5	0.980	62 – 387

97% of the meter results obtained from the six lots of test strip were within the ISO 15197:2003(E) accuracy criteria: ± 15 mg/dL bias for glucose samples ≤ 75 mg/dL and ± 20% bias for glucose samples > 75 mg/dL

b. Matrix comparison:
Not applicable. The meter's software adjusts the whole-blood glucose reading to a plasma-equivalent reading.

3. Clinical studies:
Clinical evaluations of Ascensia BRIO system performance were performed at three clinical sites. At least 100 lay-users users and three health-care professionals participated at each site. The lay-users ranged in age, education, and years of diabetes; subjects were about equally divided between males and females, and type-2 diabetes was more common in the participant groups. Duplicate readings were obtained for each of three different strip lots.

a. Clinical Sensitivity:
The relationship between the Ascensia BRIO system results and laboratory glucose results were evaluated using the Passing-Bablok linear regression method which does not assume that the reference method has no variability. The regression equations for all three clinical sites are shown below.

Regression Analysis of Ascensia BRIO Clinical Studies

		Lay-Users vs. Lab		HCP vs. Lab	
Clinical Site	Strip Lot	Equation	r value	Equation	r value
1 (n=103)	D	1.013x-7.38	0.98	0.996x-4.73	0.98
	E	0.959x+4.21	0.97	0.969x+1.65	0.97
2 (n=109)	D	0.996x-3.00	0.98	1.007x-4.84	0.98
	E	0.988x+0.22	0.98	0.996x-0.90	0.98
3 (n=108)	D	0.995x-3.13	0.97	1.014x-6.83	0.97
	E	0.996x+0.67	0.97	0.968x+2.14	0.98

One method of comparing the significance of variability between clinical laboratory results and meter systems such as the Ascensia BRIO is to determine how close the values are to each other. A widely accepted criteria, ISO 15197:2003, suggests that ≥95% of all values be within ±20% of the reference value if the sample is >75 mg/dL and ±15 mg/dL if the sample is ≤75 mg/dL. However, differences between the two measurement systems may or may not affect clinical decisions; the Parkes Consensus Error Grid method was used to determine if differences between the methods might affect clinical outcome.

Summary of Accuracy Analysis of Ascensia BRIO Clinical Studies

Site	n=	Tester	% ±20% Reference	% of Results in Parkes Error Grid Zone				
				A	B	C	D	E
1	206	SUB	96.6	95.6	4.4	0	0	0
		HCP	96.1	96.6	3.4	0	0	0
2	218	SUB	97.7	97.7	2.3	0	0	0
		HCP	97.7	98.2	1.8	0	0	0
3	216	SUB	96.3	96.8	3.2	0	0	0
		HCP	98.2	97.7	2.3	0	0	0
ALL	**640**	**SUB**	**96.9**	**96.7**	**3.3**	**0**	**0**	**0**
		HCP	**97.7**	**97.5**	**2.5**	**0**	**0**	**0**

b. *Clinical specificity**:***
Lay users and HCP at each site performed a precision and quality control assessment each day of the study. Each operator performed duplicate measurements with each of three levels of controls using two reagent strip lots. The subjects performed their 12 control replicates immediately after a competence assessment and just before the collection of capillary blood sampling. The table below shows the precision measurements for the lay-users at trial sites 1, 2, and 3; HCP values were similar at all sites.

Clinical Precision of Ascensia BRIO

Clinical Site	Strip Lot	Control Level	Mean (mg/dL)	Overall % CV
1 (n=105 users, 210 samples)	D	Low	52.4	6.8
	E	Low	54.6	7.4
	D	Normal	112.1	4.2
	E	Normal	116.7	4.3
	D	High	310.6	3.5
	E	High	321.7	3.8
2 (n=110 users, 220 samples)	D	Low	53.0	6.4
	E	Low	54.7	6.2
	D	Normal	113.2	3.9
	E	Normal	116.8	4.1
	D	High	308.8	3.9
	E	High	321.8	3.9

3 (n=111 users, 222 samples)	D	Low	53.2	5.9
	E	Low	54.7	5.9
	D	Normal	111.8	5.0
	E	Normal	115.9	4.8
	D	High	308.4	3.4
	E	High	323.0	3.7
Control Level Targets:		**Low**	**Normal**	**High**
	D	44 – 72	91 – 134	264 – 357
	E	43 - 70	93 - 136	268 – 362

c. *Other clinical supportive data (when a. and b. are not applicable):*
The meter was evaluated at high altitude (10,200 ft.) to assess the effect of low oxygen levels on meter performance. Fingerstick samples from 55 people with diabetes were tested in duplicate with three lots of test strips (110 tests/lot, 330 total samples) by a HCP. Hematocrit ranges from 38 to 67% with an average of 50.3% Hct. The meter performed as well at high altitude as at lower elevations in the hands of a HCP.

4. Clinical cut-off**:**
Not applicable.

5. Expected values/Reference range:

The labeling states treatment goals according to the American Diabetes Association as follows:

Medical practice goals for non pregnant people with diabetes are: [1]

Before meal glucose: 90 to 130 mg/dL (5.0 to 7.2 mmol/L)

Bedtime glucose: 110 to 150 mg/dL (6.1 to 8.3 mmol/L)

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

[1] American Diabetes Association: Standards of Medical Care for Patients With Diabetes Mellitus (Position Statement). Diabetes Care 25 (Suppl. 1): S37, 2002.