510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K130524

B. Purpose for Submission:

Clearance for modification of a cleared instrument (K011668)

C. Manufacturer and Instrument Name:

Exalenz Bioscience BreathID Hp System

D. Type of Test or Tests Performed:

H. pylori ^{13}C-urea Breath Test

E. System Descriptions:

1. Device Description:
   The modified BreathID® Hp System is a non-invasive breath test system for detecting the presence of *Helicobacter pylori* (*H. pylori*). The system consists of an electro-optical medical device with embedded software designed to measure and compute the changes in ratio between $^{13}CO_2$ and $^{12}CO_2$ concentrations in the patient's exhalation and a test kit. The test kit consists of:
   - IDcircuit™ - Oridion Nasal FilterLine™ (nasal cannula) (K980325)
   - A 75mg ^{13}C-urea tablet
   - A 4.3g package of powdered Citrica (citric acid)
   - Drinking straw
   - Package Insert (Instructions for Use)

   The modified BreathID® Hp System measures and computes the ratio between $^{13}CO_2$ and $^{12}CO_2$ in the patient's exhalation before and after the ingestion of ^{13}C-urea. The change in the $^{13}CO_2$ / $^{12}CO_2$ ratio before and after ingestion of ^{13}C-urea is referred to as the Delta over Baseline (DOB).

   The basis of the ^{13}C measurement method for both the modified and unmodified versions of the BreathID® System is a technology called Molecular Correlation Spectroscopy™ (MCS™). MCS™ is based on the concept of optical absorption of specific radiation emitted from CO_2 discharge lamps.

2. Principles of Operation:

The Exalenz BreathID® Hp System non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of ^{13}C-enriched urea; it is used to identify those patients with *H. pylori* infection. The Exalenz BreathID® Hp System breath test is performed as follows: a 75 mg ^{13}C-urea tablet and 4.3 g Citrica Powder are dissolved in water, and the resulting solution is ingested by the patient. The presence of the Citrica creates an acidic environment in the stomach and also delays the transfer of the ingested solution to the duodenum. These two characteristics facilitate the decomposition of the urea by *H. pylori*, if present. Thus, in the presence of urease associated with gastric *H. pylori*, ^{13}C-urea is decomposed to $^{13}CO_2$ and NH_3 according to the following equation:

$$2\ {}^{13}\text{C-urea} + 2\ H_2O \xrightarrow{\text{H. pylori urease}} 2\ {}^{13}CO_2 + 2\ NH_3$$

The $^{13}CO_2$ is absorbed into the blood and then exhaled in the breath. Absorption and distribution of $^{13}CO_2$ is fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the $^{13}CO_2$ occurs immediately after the solution is ingested and enables immediate detection of increased $^{13}CO_2$ in the exhaled breath of *H. pylori*-positive patients.

In the case of *H. pylori*-negative patients, the ^{13}C-urea does not produce $^{13}CO_2$ in the stomach because there are no human enzymes that can decompose the urea in the stomach.

The test begins with the collection of a baseline breath sample. The patient breathes normally while the BreathID® Hp System collects samples through the IDcircuit™ nasal cannula. The IDcircuit™ extracts moisture and patient secretions from the breath samples to provide accurate CO_2 readings, and the device measures the $^{13}CO_2$ / $^{12}CO_2$ ratio of the baseline measurement. The patient then ingests a test drink consisting of ^{13}C-urea tablet 75 mg and 4.3 g of citric Powder (4g citric acid). While the patient continues to breathe normally, the BreathID® Hp System continually and non-invasively samples the patient's breath (via the cannula) and measures the changes in the $^{13}CO_2$ / $^{12}CO_2$ ratio versus the original baseline sample. These changes are displayed as a graph on the display screen while the test continues. The graph shows multiple points that allow the physician to identify the change in the DOB of the $^{13}CO_2$ / $^{12}CO_2$ ratio in response to the administered ^{13}C-urea. Once the BreathID® Hp System has collected enough data to determine whether or not a patient is *H. pylori*-positive, (i.e. the graph passes the threshold unambiguously), it automatically ends the test and prints out the results.

3. Modes of Operation:

Single sample

4. Specimen Identification:

   Manual

5. Specimen Sampling and Handling:

   Specimen acquired through nasal cannula

6. Calibration:

   Calibration is performed by the instrument by diluting pre-dose patient breath or operator breath into five different concentrations within an absolute maximum concentration range. The device uses these five concentrations to determine the systematic error of the system and to ensure that the estimated systematic error is below a specified value. If the systematic error is not below the specified value, the device prompts the user to contact Exalenz for repair or replacement.

7. Quality Control:

   To ensure correct functioning of the BreathID® Hp System in the field, a self test is required every 25 breath tests. BreathID® Hp System will automatically perform a self test after 25 tests are completed, during the baseline measurement phase of the next patient test. This procedure confirms that the BreathID® Hp System is functional and is performing within specifications.

8. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes___X_____ or No_____

   The sponsor provided all software documentation in Section 18 of the submission. They followed the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices and provided adequate documentation. The current BreathID Hp System software version is 2.1.7.

F. Regulatory Information:

1. Regulation section:

   21 CFR 866.3110 Campylobacter fetus serological agents

2. Classification:

   Class I

3 Product code:

MSQ

4. Panel:

83 Microbiology

G. Intended Use:

1. Indication(s) for Use:
The Exalenz BreathID® Hp System is intended for use to continually and non-invasively measure changes in the $^{13}CO_2$ / $^{12}CO_2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The Exalenz BreathID® Hp System is indicated for use as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. The Exalenz BreathID® Hp System consists of the IDkit:Hp™ and the BreathID® Hp test device.

The device is for use by trained health care professionals. To be administered under a physician's supervision.

2. Special Conditions for Use Statement(s):

For prescription use only

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

BreathID® System, Exalenz Bioscience Ltd., K011668

2. Comparison with Predicate Device:

Similarities		
Item	**Exalenz Modified BreathID® Hp System**	**Exalenz BreathID® System (K011668)**
Product Code	MSQ – Test, Urea (Breath or Blood)	MSQ – Test, Urea (Breath or Blood)
Regulation Number	21 CFR 866.3110 *Campylobacter fetus* serological reagents	21 CFR 866.3110 *Campylobacter fetus* serological reagents
Regulatory Class	Class I	Class I
Intended Use / Indications for Use	The Exalenz BreathID® Hp System is intended for use to continually and non-	The Exalenz BreathID® Hp System is intended for use to continually and non-

Similarities		
Item	**Exalenz Modified BreathID® Hp System**	**Exalenz BreathID® System (K011668)**
	invasively measure changes in the $^{13}CO_2$ / $^{12}CO_2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The Exalenz BreathID® Hp System is indicated for use as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. The Exalenz BreathID® Hp System consists of the IDkit:Hp™ and the BreathID® Hp test device. The device is for use by trained health care professionals. To be administered under a physician's supervision.	invasively measure changes in the $^{13}CO_2$ / $^{12}CO_2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The Exalenz BreathID® Hp System is indicated for use as an aid in the initial diagnosis and post treatment monitoring of *H. pylori* infection in adult patients. The Exalenz BreathID® Hp System consists of the IDkit:Hp™ and the BreathID® Hp test device. The device is for use by trained health care professionals. To be administered under a physician's supervision.
Use Environment	By healthcare professionals in the clinical setting	By healthcare professionals in the clinical setting
Test Sample	Gas Sample continually transported to test measurement device by Exalenz (formerly Oridion) nasal cannula FilterLine™ (K980325)	Gas Sample continually transported to test measurement device by Exalenz (formerly Oridion) nasal cannula FilterLine™ (K980325)
^{13}C Urea	75mg tablet dissolved in water (NDA 21-314)	75mg tablet dissolved in water (NDA 21-314)
Applicable pre- and post-treatment	Yes	Yes
Test Meal	4.3g Citrica (citric acid) dissolved in water	4.3g Citrica (citric acid) dissolved in water
Test Duration	10-30 minutes	10-30 minutes
Breath Collection	Continually over test duration	Continually over test duration
Cut-off Point	5.0 DOB per mil (post dose	5.0 DOB per mil (post dose

Similarities		
Item	**Exalenz Modified BreathID® Hp System**	**Exalenz BreathID® System (K011668)**
	minus pre dose)	minus pre dose)
Organism	*Helicobacter pylori* in vivo	*Helicobacter pylori* in vivo
Reagent	^{13}C Urea	^{13}C Urea
Result	$^{13}CO_2/^{12}CO_2$ ratio – Molecular Correlation Spectroscopy™ (MCS™)	$^{13}CO_2/^{12}CO_2$ ratio – Molecular Correlation Spectroscopy™ (MCS™)

Differences		
Item	**Exalenz Modified BreathID® Hp System**	**Exalenz BreathID® System (K011668)**
Operating System	Windows® CE	Windows® 95
Software Development Language / Environment	C# within Microsoft Visual Studio	LabView™ and its associated code generation functions
User Interface	Touchscreen monitor	Mechanical push button for operation
Footprint	Small footprint for desktop use with an integrated touchscreen monitor	Standalone device with wheels, including a monitor on an extendable arm
Data Acquisition Board	A custom data acquisition card	An off-the-shelf data acquisition card
Pneumatic Unit	1 pump	2 pumps
CO_2 sensor	$^{12}CO_2$ cell in $^{13}CO_2$ / $^{12}CO_2$ measurement subsystem	Capnograph
System Check (Quality Control)	Utilizes operator breath or pre-dose patient breath	Utilizes a supplied gas canister containing approximately 100% CO_2
In-Measurement Variability Reduction	Performed by the $^{13}CO_2$ / $^{12}CO_2$ measurement subsystem	Performed by the sealed reference cell, fibers, shutter and second detector

I. Special Control/Guidance Document Referenced (if applicable):

FDA Draft Guidance "Establishing Performance Characteristics of *In Vitro* Diagnostic Devices for the Detection of *Helicobacter pylori*," September 23, 2010

J. Performance Characteristics*:*

1. Analytical Performance:

a. Accuracy:

See Precision study

b. Precision/Reproducibility:

Precision

The Precision study was performed in accordance with the following standards:

- Clinical and Laboratory Standards Institute EP05-A2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline* – Second Edition, 2004
- Clinical and Laboratory Standards Institute EP15-A2 *User Verification of Performance for Precision and Trueness; Approved Guideline* – Second Edition, 2005

The Precision study was performed with three *H. pylori* samples that included a high positive, low positive and moderate positive, as defined in the FDA Draft Guidance "Establishing Performance Characteristics of In Vitro Diagnostic Devices for the Detection of *Helicobacter pylori*," September 23, 2010. The Precision validation was performed using one modified BreathID® Hp System for twelve days, executing two runs per day. Each test run included three different combinations of baseline / post-ingestion combinations, and each combination of baseline / post-ingestion gases was consecutively tested twice. Calibration was performed on the first and seventh days of the Precision study. The tabulated accuracy results and the tabulated repeatability results are provided in the tables below, respectively.

Precision Study DOB Accuracy Results

Expected DOB	Accuracy (Mean)	95% CI
DOB: 4.3‰	4.67	[4.5 – 4.85]
DOB: 5.9‰	5.85	[5.52 – 6.17]
DOB: 15.5‰	15.78	[15.57 – 15.99]

DOB Repeatability and Between-Day Precision

Expected DOB	Parameter	SD Value	95% CI	CV
DOB: 4.3‰	Repeatability	0.559	[0.499 – 0.635]	12.0%
	Between-Days Precision	0.603	[0.525 – 0.681]	12.9%
DOB: 5.9‰	Repeatability	0.479	[0.427 – 0.544]	8.2%
	Between-Days Precision	0.691	[0.621 – 0.760]	11.8%
DOB: 15.5‰	Repeatability	0.689	[0.615 – 0.784]	4.4%
	Between Days Precision	0.738	[0.664 – 0.811]	4.7%

Reproducibility

The Reproducibility study was performed in accordance with the following standards:

- Clinical and Laboratory Standards Institute EP05-A2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline* – Second Edition, 2004

- Clinical and Laboratory Standards Institute EP15-A2 *User Verification of Performance for Precision and Trueness; Approved Guideline* – Second Edition, 2005

The Reproducibility study was performed with three *H. pylori* samples that included a high positive, low positive and moderate positive, as defined in the FDA Draft Guidance "Establishing Performance Characteristics of *In Vitro* Diagnostic Devices for the Detection of *Helicobacter pylori*," September 23, 2010. The Reproducibility study was performed using three devices in three different sites for five days. Two test runs were executed per day by different operators. Each test run utilized three different combinations of baseline / post-ingestion gases and each combination of baseline / post-ingestion gases was consecutively tested three times. Calibration was performed on the first day of the Reproducibility study. The tabulated accuracy results and the tabulated reproducibility results are provided in the tables below, respectively.

Reproducibility Study DOB Accuracy Results

Expected DOB	Accuracy (Mean)	95% CI
DOB: 4.5‰	4.82	4.60 – 5.05
DOB: 5.9‰	6.18	4.97 – 7.40
DOB: 15.5‰	15.69	15.41 – 15.98

DOB Reproducibility, Between-Day Reproducibility and Between-Operator Reproducibility

Expected DOB	Parameter	SD Value	95% CI	CV
DOB: 4.5‰	Reproducibility	0.524	0.483 – 0.573	10.9%
	Between-Days Reproducibility	0.533	0.455 – 0.624	11.0%
	Between-Operators Reproducibility	0.524	0.444 – 0.619	10.9%
DOB: 5.9‰	Reproducibility	0.563	0.518 – 0.615	9.2%
	Between-Days Reproducibility	0.648	0.576 – 0.712	10.6%
	Between-Operators Reproducibility	0.697	0.612 – 0.780	11.4%
DOB: 15.5‰	Reproducibility	0.536	0.494 – 0.586	3.4%
	Between-Days Reproducibility	0.536	0.479 – 0.585	3.4%
	Between-Operators Reproducibility	0.538	0.485 – 0.591	3.4%

c. Linearity:

Not applicable

d. Carryover:

Not applicable

e. Interfering Substances:

Not applicable

2. Other Supportive Instrument Performance Data Not Covered Above:

BreathID® Hp System
The modified BreathID® Hp System has the same fundamental scientific technology and principle of operation utilized in the unmodified BreathID® System. The technological modifications of the BreathID® Hp System are modifications to the configuration of the system and software revisions as a result of the modified hardware configuration.

This modified BreathID® Hp System is designed to be more compact, less expensive and easier to maintain than the unmodified system. In addition, the modified BreathID® Hp System either eliminates or consolidates components that have become redundant or obsolete.

Analytical studies
Gas Collection Verification

A Gas Collection Verification was performed to verify that the $^{12}CO_2$ cell of the $^{13}CO_2$ and $^{12}CO_2$ measurement subsystem of the BreathID® Hp System could adequately replace the Capnograph of the unmodified BreathID® System for measuring the CO_2 concentration in incoming gases. Twenty (20) tests were performed with breath samples that were not ^{13}C enriched from ten (10) different subjects. Each of the twenty (20) tests also included seven (7) DOB measurements from the measurement phase (MP) in various calibration ranges. The results of the Gas Collection Verification demonstrated that the DOB standard deviation of all measurement phase (MP) test results were within the specifications, all MP test sample concentrations were within the calibration range, and that all MP sample concentrations had a standard deviation of less than 0.2. Therefore, the $^{12}CO_2$ cell of the $^{13}CO_2$ and $^{12}CO_2$ measurement subsystem of the BreathID® Hp System has been verified to adequately replace the Capnograph of the unmodified BreathID® System for measuring the CO_2 concentration in incoming gases.

System Check Verification

A System Check Verification was performed to verify that operator breath or pre-dose

patient breath could adequately replace the gas canister containing approximately 100% CO_2 for the purposes of the System Check, one of the Quality Control functions of the BreathID® Hp System and the unmodified BreathID® System. Twenty (20) tests were performed with breath samples from eleven (11) different subjects. Each of the twenty (20) tests also included seven (7) DOB measurements. The results of the System Check Verification demonstrated that in all cases where the ^{12}C curves were randomly changed and a calibration was then required, the situation was correctly identified by the BreathID® Hp System and a calibration was performed. In all cases where the ^{12}C curves were unchanged and the calibration process was unable to expand the calibration range, the BreathID® Hp System correctly identified the situation and did not perform a calibration. In the case where the ^{12}C curve was unchanged, but the calibration range was expanded and a calibration was then required the BreathID® Hp System correctly identified the situation and performed a calibration. All test results following a System Check and calibration were within the specifications of the BreathID® Hp System. Additionally, all test results following a System Check that did not require calibration were within the specifications of the BreathID® Hp System. Therefore, the System Check Verification not only demonstrated that operator breath or pre-dose patient breath could be adequately used for the System Check procedure, but it also demonstrated that the calibration process was effective.

Software Verification and Validation

Software Verification evaluated all system functionality and consisted of evaluations of the software through unit, integration and system level testing, as well as code reviews. Software Validation consisted of various test cases to qualitatively test the software system of the BreathID® Hp System. The test case categories that were utilized for the software validation of the BreathID® Hp System were:

- H. Pylori Patient Mode Tests
- System Test
- Utilities, and
- System Failures

All test cases were implemented with a known input and an expected output. The expected output was visually compared against the actual output. All test cases were verified to have passing results.

Comparative Validation

A Comparative Validation was performed to evaluate the agreement of the modified BreathID® Hp System DOB measurements to its predicate device, the unmodified BreathID® System. The Comparative Validation was performed in accordance with the following standard:

- Clinical and Laboratory Standards Institute EP09-A2 *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline* – Second Edition

The Comparative Validation was performed with three *H. pylori* samples that included a high positive, low positive and moderate positive, as defined in the FDA Draft Guidance "Establishing Performance Characteristics of In Vitro Diagnostic Devices for the Detection of *Helicobacter pylori*," September 23, 2010. The Comparative Validation was performed with one modified BreathID® Hp System and one unmodified BreathID®

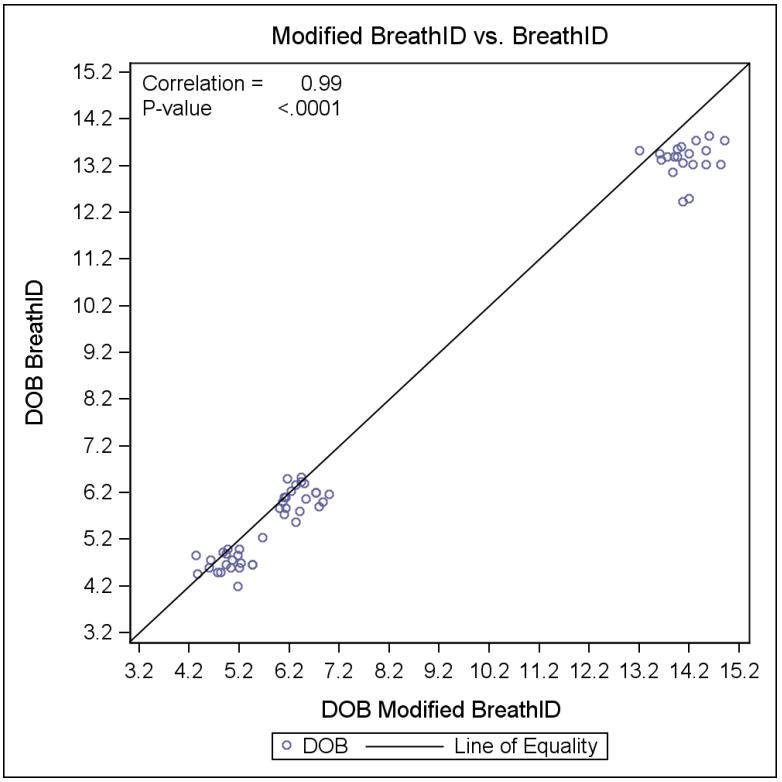
System, executing two runs per day for five days. Each test run included three different combinations of baseline / post-ingestion gases and each combination of baseline / post-ingestion gases was consecutively tested twice. The modified BreathID® Hp System and the unmodified BreathID® System were evaluated simultaneously by connecting the two devices with a Y-Connector. Calibration was performed on the first day of the Comparative Validation. The table below provides the results and analysis of the Comparative Validation.

Distribution of DOB Measurements Between Modified and Unmodified BreathID® Systems

Expected DOB	Parameter	N	Mean	SD	Min	Median	Max
DOB: 4.5‰	DOB Modified BreathID®	20	4.96	0.350	4.3	4.97	5.6
	DOB Unmodified BreathID®	20	4.69	0.233	4.2	4.65	5.2
	Difference in DOB Between Devices		0.27	0.368	-0.5	0.28	1.0
DOB: 5.8‰	DOB Modified BreathID®	20	6.37	0.297	6.0	6.33	7.0
	DOB Unmodified BreathID®	20	6.07	0.266	5.5	6.07	6.5
	Difference in DOB Between Devices		0.30	0.366	-0.3	0.20	0.9
DOB: 13‰	DOB Modified BreathID®	20	14.09	0.424	13.2	14.03	14.9
	DOB Unmodified BreathID®	20	13.32	0.358	12.4	13.37	13.8
	Difference in DOB Between Devices		0.78	0.526	-0.3	0.75	1.7

A Pearson's correlation coefficient was calculated between the DOB measurements from the unmodified and modified BreathID® Systems. A correlation plot of the DOB measurements from the modified and unmodified BreathID® Systems is provided in the figure below. The following values were calculated:

- $r = 0.9944$ (95% CI: [0.9904, 0.9966]
- $p < 0.0001$



Correlation Plot of DOB Measurements from Unmodified and Modified BreathID® Systems

The table below presents the slope and intercept of the Deming Regression, along with the respective 95% confidence interval (CI).

Deming Regression Slope and Intercept

Deming Slope [95% CI]	Deming Intercept [95% CI]
1.06 [1.029, 1.095]	-0.05 [-0.302, 0.197]

Clinical Study

A single center, non-randomized, blinded, comparative study was conducted to compare the modified BreathID® Hp System to the unmodified BreathID® System. The breath test was performed according to the standard procedure described in the device's instructions for use and routine clinical practice while the subject was connected simultaneously to both the BreathID® Hp System and the unmodified BreathID® System via two standard nasal cannulae. The outcome measures of both devices were used for the comparison.

In order to prevent a spectrum bias, the breath test was performed in addition to, and independent of the local clinical practice. In cases were a serum blood test was performed, these blood tests were the only means used to diagnose the presence of *H.*

pylori. In other cases, where the investigator did not feel a blood test was warranted (change in diet prescribed, or symptoms not specific to *H. pylori*), the patient was periodically followed up at the clinic as routine general practice with no eradication therapy prescribed. In these cases, only if symptoms persisted or became more related to *H. pylori* infection, was the patient sent for blood tests. The breath testing was performed by a site technician and not in the proximity of the Principal Investigator. The breath test results were made available to the treating physician (Principal Investigator) only once the patient's management protocol had been determined. Thus, the test results from both devices were masked from the treating physician and did not have an impact on the patient's treatment.

The clinical study was conducted in compliance with its protocol and in accordance with the ethical principles under Investigational Review Board (IRB) approval consistent with Good Clinical Practice (GCP) and with applicable regulatory requirements. The table below presents the subjects' accountability and the subjects' baseline characteristics per protocol (PP).

Subject Baseline Characteristics

Parameter		Statistic	PP
Age		N	79
		Mean (SD)	49.2 (16.54)
		Median [min-max]	50.5 [18.4 – 87.8]
Height		N	77
		Mean (SD)	164.0 (9.90)
		Median [min-max]	163.0 [142.0 – 185.0]
Weight		N	79
		Mean (SD)	69.5 (16.65)
		Median [min-max]	66.0 [43.0 – 117.0]
BMI		N	77
		Mean (SD)	25.7 (4.92)
		Median [min-max]	24.4 [17.4 – 44.4]
Sex	Male	% (n/N)	41.77% (33/79)
	Female	% (n/N)	58.23% (46/79)
Ethnicity	African-American	% (n/N)	1.27% (1/79)
	Asian-Pacific	% (n/N)	68.35% (54/79)
	Caucasian	% (n/N)	12.66% (10/79)
	Hispanic	% (n/N)	15.19% (12/79)
	Other	% (n/N)	2.53% (2/79)

PP Analysis Set

The PP analysis set consisted of all subjects enrolled in the study that did not have any major protocol deviations and had no other relevant *H. pylori* testing prior to enrollment

in the study, which was defined as no positive test results within 2012 and no negative test results within three months prior to enrollment. The cross tabulation of the diagnosis as assessed by both the modified and unmodified BreathID® Systems in the PP analysis set is provided in the table below. The PP analysis set included 79 valid subjects per the protocol.

PP Analysis Set Agreement

		Unmodified BreathID® System		Total
		Positive	**Negative**	
BreathID® Hp System	**Positive**	17	2	19
	Negative	---	60	60
Total		17	62	79

- Positive percent agreement = 100% [95% CI (81.6, 100)]
- Negative percent agreement = 97% [95% CI (89.0, 99.1)]

This result satisfied the acceptance criterion of ≥ 95% and therefore the study was successful in demonstrating equivalence of the two devices.

K. Proposed Labeling:

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

L. Conclusion:

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