

Package Insert
IDkit Hp™ One for BreathID® Hp System
Breath Test for Detection of *H. pylori*

SECTION 1. PACKAGE INSERT

This package insert includes information for conducting the *H. pylori* test using **BreathID® Hp Breath Test System** for analysis with the Breath Test Kit, IDkit Hp™ One.

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SECTION 2. INTENDED USE

The BreathID® Hp System is intended for use to continually and non-invasively measure changes in the ¹³CO₂/¹²CO₂ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The 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 and pediatric patients ages 3-17 years old. The BreathID® Hp System consists of the appropriate IDkit Hp™ kit and the BreathID® Hp test device.

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

SECTION 3. SUMMARY AND EXPLANATION

Since the initial identification of *H. pylori* in the early 1980s [1], the management of upper gastrointestinal disease has changed dramatically. "*Helicobacter pylori* is now recognized as an important pathogen and a causal relationship between *H. pylori* and chronic active gastritis, duodenal ulcer, and gastric ulcer is well documented"[2].

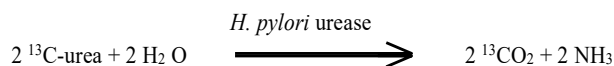
Currently there are numerous *H. pylori* detection technologies for upper gastrointestinal disease including biopsy and serum analysis. These technologies depend on two general approaches for obtaining a sample for testing: invasive and non-invasive. The first invasive test method requires an endoscopic gastric biopsy. The tissue collected from the biopsy is then examined in a laboratory by microbiological culture of the organism, direct detection of urease activity in the tissue, or by histological examination of stained tissue. Biopsy-based methods present an element of patient risk and discomfort and may provide false negative results due to sampling errors. The second invasive test is a serological test; this requires a blood sample which is used to detect serum antibodies to *H. pylori*. The disadvantage of this test is that it is difficult to distinguish between positive active infections and past exposure to infection, and therefore it is not a conclusive indicator of current *H. pylori* infection.

¹³C-urea breath tests provide a non-invasive and non-hazardous analysis of the exhaled breath. The BreathID® test (described in the next section) measures the ¹²CO₂ and ¹³CO₂ components of the exhaled breath before and after the oral ingestion of ¹³C-enriched urea. This establishes the baseline ratio of ¹³CO₂/¹²CO₂ and the post ingestion ratio of ¹³CO₂/¹²CO₂ in order to determine the Delta Over Baseline¹ (change in the ¹³CO₂/¹²CO₂ ratio).

SECTION 4. PRINCIPLES OF THE BREATHID® BREATH TEST

The BreathID® non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of ¹³C-enriched urea; it is used to identify those patients with *H. pylori* infection.

The BreathID® breath test is performed as follows: a 75 mg ¹³C-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*, ¹³C-urea is decomposed to ¹³CO₂ and NH₃ according to the following equation:



The ¹³CO₂ is absorbed into the blood and then exhaled in the breath. Absorption and distribution of ¹³CO₂ is fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the ¹³CO₂ occurs immediately after the solution is ingested and enables immediate detection of increased ¹³CO₂ in the exhaled breath of *H. pylori*-positive patients. In the case of *H. pylori*-negative patients, the ¹³C-urea does not produce ¹³CO₂ in the stomach because there are no human enzymes that can decompose the urea in the stomach.

4.1. DESCRIPTION OF THE MODE OF OPERATION OF THE BREATHID® Hp DEVICE

The test begins with the collection of a baseline breath sample. The patient breathes normally while the BreathID® Hp device collects samples through the IDcircuit™ nasal cannula. The IDcircuit™ extracts moisture and patient secretions from the breath samples to provide accurate CO₂ readings, and the device measures the ¹³CO₂/¹²CO₂ ratio of the baseline measurement. The patient then ingests a test drink consisting of ¹³C-urea tablet 75 mg and 4.3 g of Citrica Powder (4g citric acid).

¹ Delta Over Baseline is defined as: $\{ (^{13}\text{CO}_2^{(n)}) / (^{12}\text{CO}_2^{(n)}) - (^{13}\text{CO}_2^{(0)}) / (^{12}\text{CO}_2^{(0)}) \} * 1000 / \{ (^{13}\text{CO}_2^{(PDB)}) / (^{12}\text{CO}_2^{(PDB)}) \}$ where PDB is the standard ¹³C/¹²C isotope ratio (=1.1273%). (0) is the baseline measurement and (n) is the measurement of interest.

While the patient continues to breathe normally, the BreathID® Hp device continually and non-invasively samples the patient's breath (via the cannula) and measures the changes in the ¹³CO₂/¹²CO₂ 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 ¹³CO₂/¹²CO₂ ratio in response to the administered ¹³C-urea. Once the BreathID® Hp device 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.

SECTION 5. REAGENT

5.1. DESCRIPTION OF THE ¹³C-UREA DIAGNOSTIC COMPONENT

The diagnostic drug component of the kit is ¹³C-enriched urea prepared as a tablet. The tablet should be dissolved with Citrica Powder in a glass of water, providing a clear, colorless solution for oral administration.

The 75 mg ¹³C-urea component is supplied as a tablet in a sealed pouch. The 4.3 g of Citrica Powder (4 g citric acid [3,4,5], aspartame, and Tutti Frutti flavoring) is supplied in a separate sealed pouch.

An average adult body normally contains about 9.0 grams of urea, which is a product of protein metabolism. Urea in the body is referred to as a natural isotopic abundance urea since it is composed of 98.9% ¹²C-urea and 1.1% ¹³C-urea.

Greater than or equal to 99% of the carbon molecules in the supplied tablet are in the form of ¹³C; a stable, naturally occurring, non-radioactive isotope of carbon. ¹³C-urea is the diamide of ¹³C carbonic acid and is highly soluble in water (1 gram per ml at 25°C). It has the following chemical formula: ¹³CH₄N₂O.

5.2 WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic use only. The ¹³C-urea tablet and Citrica Powder are dissolved in a glass of water and the resulting solution is taken orally as part of the diagnostic procedure.
2. Phenylketonurics: Contains Phenylalanine, 84 mg per dosage unit of Citrica Powder.
3. In the case of accidental overdose – drink water and call the physician.
4. A negative result does not rule out the possibility of *H. pylori* infection. False negative results can occur with this procedure. If clinical signs suggest *H. pylori* infection, retest with a new sample or an alternate method.
5. A false positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmanni*.
6. A false positive test could occur in patients who have achlorhydria.
7. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori*. Ingesting these medications within two weeks prior to performing the breath test may produce false negative test results.
8. Tiny particles may remain visible in the reconstituted ¹³C-urea and Citrica solution after thorough mixing for up to five minutes. However, if more substantial particulate matter is still present after five minutes of mixing, the solution should not be used, and a new kit should be opened.
9. Safety and effectiveness has not been assessed in children below the age of 3 years.

5.3. MIXING THE ¹³C-UREA TABLET

1. Dissolve the Citrica and the ¹³C-enriched urea tablet in 150 to 200 ml (5.1 to 6.8 oz) of tap water in a single drinking cup of at least 236 ml (8 oz) in capacity.
2. Stir thoroughly with the provided straw for a few minutes, until the Citrica Powder and the urea tablet are completely dissolved.

Note: *Tiny particles may remain visible after thorough mixing. However, if more substantial particulate matter is still present after five minutes of stirring, discard the solution and repeat the procedure with a new kit.*

5.4. SHELF LIFE AND STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. The following components of the test kit have expiration dates: the ¹³C-urea tablet and the Citrica Powder. Do not use either of these components beyond the expiration date stated on the respective labels.

5.5. PURIFICATION OR TREATMENT

Purification or treatment for the ¹³C-urea tablet is not required prior to use.

5.6. INSTABILITY OR DETERIORATION

There are no known physical, biological, or chemical indications of instability or deterioration for the ¹³C-urea tablet.

SECTION 6. ADVERSE EVENTS

6.1 Following FDA clearance of the IDkit Hp™ One kits, the following adverse events have been identified: anaphylactic reaction, diarrhea and vomiting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

6.2 In two clinical studies conducted in 465 patients of at least 18 years-old and older to determine the initial diagnosis and post treatment monitoring of *H. pylori* infection using the IDkit Hp™ Two kits (using the identical ¹³C-urea tablet and Citrica powder), the following adverse events experienced by 1.5% of these patients were nausea (0.6%), throat burning (0.4%) and lightheadedness (0.4%). The last one was reported after blowing into the bags.

The potential adverse events were experienced by the patients within minutes of ingestion of the ¹³C-urea tablet and Citrica powder.

6.3 In a clinical study conducted in 53 pediatric patients, aged 3 to 17 years, using the IDkit Hp™ Two kit (using the identical ¹³C-urea tablet and Citrica powder) one adverse event of vomiting was experienced by one subject (1.89%). It resolved on the same day.

SECTION 7. INSTRUMENTS

For detailed information on the BreathID® Hp device, reference the Operator's Manual contained within the BreathID® Hp Package.

7.1 USE AND FUNCTION OF BREATHID® HP SYSTEM

The BreathID® Hp System is intended for use to continually and non-invasively measure changes in the ¹³CO₂/¹²CO₂ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori* (*H. pylori*) infection in the stomach. The 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 and pediatric patients ages 3-17 years old. The BreathID® Hp System consists of the IDkit Hp™ One and the BreathID® Hp test device.

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

7.2 INSTALLATION PROCEDURES

The BreathID® Hp software is installed in the BreathID® Hp device upon delivery. To setup the BreathID® Hp:

1. Make sure the power on/off switch is OFF
2. Connect the power cable to the AC socket located on the back panel of the device.
3. Connect the power cable to a properly grounded outlet. It is recommended that you connect the power cable to an uninterrupted power supply (UPS) that supports 100-240 VAC, 50/60 Hz, 750VA
4. Insert the printer paper as shown in the Operator's Manual.

For detailed set-up instructions, reference the Operator's Manual provided in the BreathID® Hp Package.

7.3 PRINCIPLE OF OPERATION

The BreathID® non-invasive breath test is a diagnostic test that analyzes a breath sample before and after ingestion of ¹³C-enriched urea; it is used to identify those patients with *H. pylori* infection.

The BreathID® breath test is performed as follows: a 75 mg ¹³C-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. The ¹³CO₂ is absorbed into the blood and then exhaled in the breath. Absorption and distribution of ¹³CO₂ is fast. Therefore, the cleavage of urea by the *H. pylori* urease that produces the ¹³CO₂ occurs immediately after the solution is ingested and enables immediate detection of increased ¹³CO₂ in the exhaled breath of *H. pylori*-positive patients.

For detailed information on the principle of operation of the BreathID® Hp device, refer to section 4.

7.4 PERFORMANCE CHARACTERISTICS

Adults

A single center, one-arm, blinded, comparative study was conducted to demonstrate the clinical equivalence of the modified BreathID® Hp System compared to the original BreathID® System. The study included a total of 79 consecutive evaluable adult subjects. The breath test was performed according to the standard procedure and routine clinical practice while the subject was connected simultaneously to both the original BreathID® device and the modified BreathID® Hp device via two standard cannulae. The outcome measures of both devices were used for the comparison. The following percent agreements were determined:

- Percent agreement with positive patients: 100% x 17/17 = 100% [95% CI (81.6, 100)]
- Percent agreement with negative patients: 100% x 60/62 = 96.8% [95% CI (89.0, 99.1)]

Pediatrics

A multi-center, non-randomized, open label study was conducted with the primary goal of confirming the safety of the ¹³C-urea substrate in pediatric subjects, and a secondary goal of evaluating performance of the BreathID® Hp System in pediatric subjects with breath collection using IDkit Hp™ One in this population, compared to stool antigen testing. Supported by existing clinical performance in the adult population, device performance was assessed in a limited clinical study in a pediatric population as described below. The study was not powered to assess efficacy in pediatric subjects and the standard reference method (i.e. composite results based on samples from endoscopy) was not used as the comparator method. The study included a total of 53 consecutive pediatric subjects with 41 evaluable for efficacy. The positive percent agreement between the breath test and the stool antigen test results was 93.3% [95% CI:68.05;99.83] and the negative percent agreement was 100% [95% CI: 86.77%;100%].

A detailed description of the performance characteristics of the modified BreathID® Hp device in adult and pediatric patients is provided in section 13.

7.5 OPERATING INSTRUCTIONS

Detailed instructions on the operation of the BreathID® Hp device are provided below in section 9 and in the Operator's Manual provided in the BreathID® Hp Package.

7.6 CALIBRATION PROCEDURE

Calibration is performed 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 Meridian for repair or replacement.

For a detailed description of the calibration procedure, refer to section 9.3 or the Operator's Manual.

7.7 OPERATIONAL PRECAUTIONS AND LIMITATIONS

The following precautions and limitations are applicable to the BreathID® Hp device:

1. A negative result does not rule out the possibility of *H. pylori* infection. False negative results can occur with this procedure. If clinical signs suggest *H. pylori* infection, retest with a new sample or an alternate method.
2. A false positive test may (rarely) occur due to urease associated with other gastric spiral organisms observed in humans such as *Helicobacter heilmanni*.
3. A false positive test could occur in patients who have achlorhydria.
4. Antimicrobials, proton pump inhibitors, and bismuth preparations are known to suppress *H. pylori*. Ingesting these medications within two weeks prior to performing the breath test may produce false negative test results.
5. To ensure accurate performance and prevent device failure, do not expose the BreathID® Hp device to conditions beyond those specified in the Operator's Manual.
6. To avoid entanglement, carefully attach the IDcircuit to the patient.
7. To ensure patient safety, place the device on a stable, flat surface such as a table or desk.
8. Place the device in a location with ample room for ventilation.
9. Do not open or tamper with the device.
10. The operator is required to follow all on-screen instructions.
11. Do not tamper with device software
12. Do not use in the presence of flammable gases or anesthetics.
13. Do not pull on the IDcircuit.
14. Do not clean or sterilize the IDcircuit. The IDcircuit is intended for single patient use only. Dispose of the IDcircuit according to standard operating procedures or local regulations regarding the disposal of contaminated medical waste.
15. Do not spray or pour any liquid on the device or its components.
16. Do not use any caustic or abrasive cleaners on the device.
17. Do not place any object or material anywhere on the device.
18. U.S. Federal Law restricts this device to sale by, or on the order of, a physician or healthcare provider.

The above precautions and limitations are also provided in the Operator's Manual supplied with the BreathID® Hp Package.

7.8 HAZARDS

The following hazards are applicable to the BreathID® Hp device:

1. Do not open the cover panels. There are no user-serviceable parts inside. There is a risk of electrical shock.
2. The BreathID® Hp is to be serviced by qualified personnel, certified by Meridian.
3. The device is not suitable for use in the presence of a flammable anesthetic mixture together with air, oxygen or nitrous oxide.

The above hazards are also provided in the Operator's Manual provided in the BreathID® Hp Package.

7.9 SERVICE AND MAINTENANCE

Service and maintenance information is provided in the Operator's Manual.

SECTION 8. SPECIMEN COLLECTION AND PREPARATION

8.1. PATIENT PREPARATION

Remind the patient that the Citrica contains 84 mg of phenylalanine per packet of Citrica Powder. Phenylketonurics restrict dietary phenylalanine.

The patient should have fasted at least one hour before administering the solution. The patient should not have taken antimicrobials, proton pump inhibitors or bismuth preparations within two weeks prior to administering the test.

8.2. ADDITIVES AND PRESERVATIVES

The BreathID® Hp System does not require any additives, preservatives, etc. to maintain the integrity of the breath sample.

8.3. INTERFERING SUBSTANCES

Potentially interfering substances typically found in a patient's breath were tested using the original BreathID® System to determine their effect on the test results. The potential sources tested were:

- Mouthwash
- Chewing gum
- Carbonated beverages
- Cigarette smoke
- Acetone (to simulate the effect of ketone production that may result from some diets)
- Alcohol

There was no observation that these substances had any significant influence on the outcome of the test.

8.4. BREATH SAMPLE HANDLING INSTRUCTIONS

The analysis of the breath sample is conducted in real-time; therefore, there are no instructions for the storage, handling or shipping for the breath sample.

SECTION 9. PROCEDURE

9.1. MATERIALS

A single BreathID® IDkit Hp™ One is provided to perform the Breath Test.

Each IDkit Hp™ One for the BreathID® Hp Breath Test System contains:

- One tablet of 13C-enriched urea, 75 mg.
- One packet of 4.3 g (4 g citric acid, aspartame, Tutti Frutti flavoring) of Citrica Powder.
- One IDcircuit™ nasal cannula.
- One straw for stirring and drinking.

Materials Needed But Not Provided:

- A drinking cup with a capacity of eight ounces (236 ml) or greater.
- Tap water.

9.2. STEP-BY-STEP PROCEDURE

For more detailed information regarding the step-by-step procedure, on screen instructions and device operation, refer to the BreathID® Hp Operator's Manual.

For performing the BreathID® H. pylori test, use the IDkit Hp™ One single-use kit.

1. Before opening the kit, verify that the entire package is intact.
2. Ensure that the BreathID® Hp device is activated and the status is **Ready**. The status appears on the top right of the screen.
3. Follow the screen instructions.
4. Connecting the IDcircuit™:
 - I. Take the IDcircuit™ out of its bag and slide the tubing sleeve down as far as it will go. Gently place the cannula tips into the patient's nostrils, and place the cannula tubing over the ears, as shown in Figure 1.
 - II. Slide the tubing sleeve up towards the neck to fit comfortably under the chin.
 - III. Connect the IDcircuit™ to the BreathID® Hp device by twisting the orange connector at the free end of the cannula clockwise until it is secured into the dedicated socket of the BreathID® Hp device.
 - IV. Verify that the IDcircuit™ is not twisted or kinked and that the cannula tips are in the nostrils. Ensure that the IDcircuit™ cannula tips moldings are positioned inwards.
 - V. Press on the START button on the touch screen to proceed. The baseline values will be measured by the BreathID® Hp device and the results will be shown on the screen.
5. Preparing the test drink:

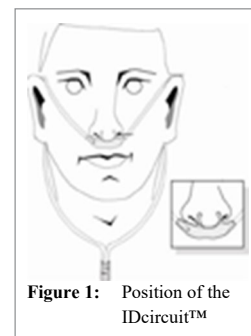


Figure 1: Position of the IDcircuit™

Note: Administer the test drink within two hours of preparation, as this is the maximal time for maintaining solution stability.

- I. Dissolve the Citrica Powder and the ¹³C -enriched urea tablet in 5.1 to 6.8 oz (150 to 200 ml) of tap water in a single drinking cup of at least eight ounces (236 ml) in capacity.
- II. Stir thoroughly with the provided straw for a few minutes, until the Citrica Powder and the ¹³C-urea tablet are completely dissolved.

Note: Tiny particles may remain visible after thorough mixing. However, if more substantial particulate matter is still present after five minutes of stirring, discard the solution and repeat the procedure with a new kit.

6. Administering the test drink and starting measurement:

Note: Do not administer the drink until prompted by the screen instructions on the device (this makes certain that the baseline sample has been collected properly).

- I. Ensure that the patient drinks the solution through the straw.
- II. The patient, including pediatric patients aged 3-17 regardless of age and bodyweight, must drink the solution within two minutes and consume the entire amount.
- III. After the patient finishes drinking the solution, press the **Continue** button on the touch screen to proceed.

7. Measurement:

The BreathID® Hp device continually analyzes the trend of measured results. When the device determines that the final value will be positive or negative, i.e. greater or less than 5 Delta Over Baseline, it will automatically end the test and print out the results. The breath sample is analyzed in real-time by the BreathID® Hp device, therefore the stability of the final breath sample will not affect the outcome of the results.

8. Removing and discarding the IDcircuit™:

When the measurement is complete, disconnect the IDcircuit™ from both the patient and the device. Dispose of the IDcircuit™ and all other used components of the kit, according to standard operating procedures or local regulations for the disposal of used medical waste.

Note: If you do not disconnect the IDcircuit™, instructions will appear on the device screen reminding you to do so. The device will not proceed to the next screen until the IDcircuit™ is disconnected.

9. Printing Results:

- I. After the measurement is complete, the device will automatically print the test results. The printout contains the graph as seen on the screen, including the Patient ID (if entered), date, time, test number and Delta Over Baseline value of the last point measured.
- II. Tear off the printed results and fill in additional patient data as required.

9.3. CALIBRATION

The calibration stability of the BreathID® Hp system is ensured by the Meridian proprietary ¹²CO₂ and ¹³CO₂ Isotope Specific Infrared (ISIR) lamps. The physical process underlying gas discharge emissions supports this stability. The emissions are caused by molecular rotation-vibration transitions, each generating a spectral line at a specific wavelength, uniquely defined to an accuracy of better than 0.01 Å (Angstrom). Five gas samples of known concentration and isotope ratio are used to adjust the absorption cell calibration curves, aiming to attain identical isotope ratios over the collection range of CO₂ concentrations. This will ensure accurate readings in both negative and positive samples.

In addition, quality checks as described below in section 9.4 are performed by the BreathID® Hp device after every 25 tests in order to ensure that the system performs within established limits, and calibration is performed if required.

Refer to the BreathID® Hp Operator’s Manual for a complete description of the calibration procedure.

9.4. QUALITY CONTROL

The BreathID® Hp device is an instrument for measuring changes in the ratio of ¹³CO₂ to ¹²CO₂ in the patient’s exhalation. Since the BreathID® Hp is not a laboratory device, no field laboratory quality control procedures are required. The BreathID® Hp device undergoes rigorous quality assurance procedures before leaving the manufacturer.

However, to ensure correct functioning of the BreathID® Hp in the field, a self-test is required once every 25 breath tests. BreathID® Hp 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 system is functional and is performing within specifications.

Complete operating information including appropriate quality control activities is provided in the BreathID® Hp Operator’s Manual.

SECTION 10. TEST RESULTS

10.1. THE TEST METHOD

The ratio of ¹³CO₂ to ¹²CO₂ in breath samples is determined by Molecular Correlation Spectrometry (MCS™), which is utilized by the BreathID® Hp device software.

10.2. CALCULATION OF RESULTS

The results are provided as Delta Over Baseline. Delta Over Baseline is the difference between the Delta value (based on a ratio of ¹³CO₂/¹²CO₂) in the test specimen and the corresponding baseline sample. There are no calculations required by the user.

10.3. DETERMINATION OF THE CUTOFF POINT

The cutoff point is the level (threshold) used to discriminate between *H. pylori*-infected and uninfected individuals.

The Delta Over Baseline cutoff point was determined to be five in a controlled study of 186 adult asymptomatic and symptomatic patients (101 infected and 85 uninfected). The study was conducted in Israel using a local reference standard called the Isotope Ratio Mass Spectrometer (IRMS). The cutoff point was evaluated by determining the original BreathID® test result (DOB) threshold at which positive and negative patients, as determined by the Isotope Ratio Mass Spectrometer, were best distinguished. Figure 2 shows the BreathID® test cutoff point graphically, which distinguishes *H. pylori*-positive and negative patients.

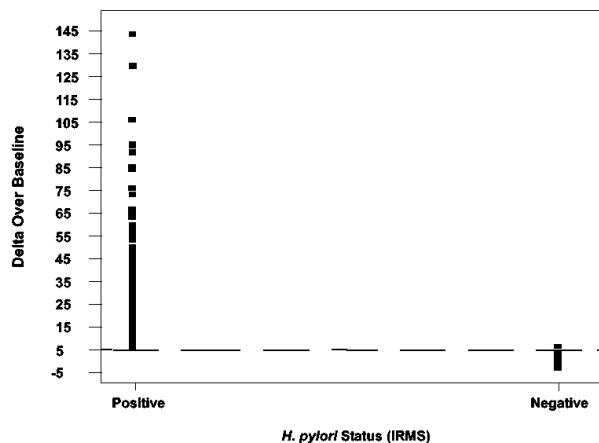


Figure 2: Cutoff for BreathID® Test as Determined in an Initial Clinical Study

The cutoff point was confirmed in a controlled pivotal clinical study where 300 subjects were enrolled. The study consisted of a

pre-therapy and post-therapy phase. Patients enrolled in the pre-therapy phase had dyspeptic symptoms, active peptic ulcer disease, or a past history of peptic ulcer disease. To be eligible for the post-therapy phase, *H. pylori*-positive patients had to be treated for infection four weeks prior to enrollment (some patients participated in both the pre-therapy and post-therapy phases). In the pre-therapy phase, 47 patients were found to be infected and 253 were found to be uninfected. Congruent results obtained by rapid urease test and histological examination of biopsy tissue were used as the reference standard. In the post-therapy phase, 22 patients were infected and 50 were uninfected. The reference standard was a positive finding by endoscopic test (rapid urease or histology) or urea breath test (UBT). For more details, refer to section 13.

Figure 3 below shows the original BreathID® Delta Over Baseline results.

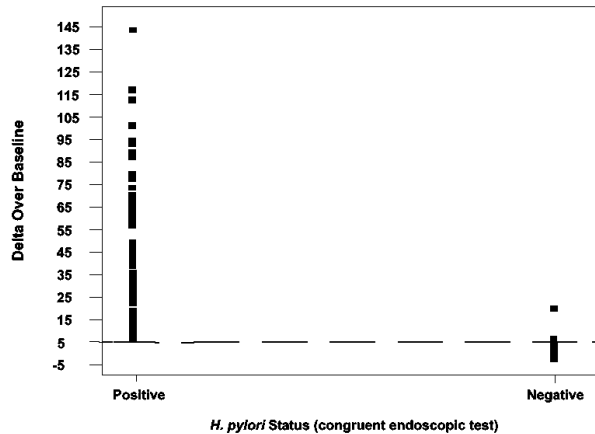


Figure 3: Cutoff Point for BreathID® Test as Determined for Pre-Therapy Patients in the Pivotal Clinical Study

10.4. INTERPRETATION OF RESULTS

A BreathID® test result of greater than 5 Delta Over Baseline is interpreted as diagnostically positive, indicating the presence of urease associated with *H. pylori*. A BreathID® test result of less than or equal to 5 Delta Over Baseline is interpreted as diagnostically negative, indicating the absence of urease associated with *H. pylori*.

The 5 Delta Over Baseline cutoff point applies to both initial diagnosis and post treatment monitoring of *H. pylori* infection in adult and pediatric patients. For more details, refer to section 13.

SECTION 11. LIMITATIONS OF THE TEST

1. Post treatment monitoring of *H. pylori* should be performed after at least four weeks of treatment for *H. pylori* infection. Earlier assessment may give false results.
2. Safety and effectiveness in patients under the age of 3 years have not been established.
3. Data is insufficient for recommending the use of this test on patients with total or partial gastrectomy.
4. Data is insufficient to recommend the use of this test on pregnant and lactating women.
5. A correlation between the number of *H. pylori* organisms in the stomach and the BreathID® test results has not been established.

SECTION 12. EXPECTED VALUES

Delta Over Baseline values for the original BreathID® test were determined in a controlled clinical study of 186 adult asymptomatic and symptomatic patients (101 infected and 85 uninfected) in Israel, using a known reference standard called the Isotope Ratio Mass Spectrometer (IRMS) and performed in a local Israeli laboratory. The range of Delta Over Baseline values for the uninfected patients was determined to be between -1 and 8. A histogram of the distribution of Delta Over Baseline values from uninfected patients is shown in Figure 4 below.

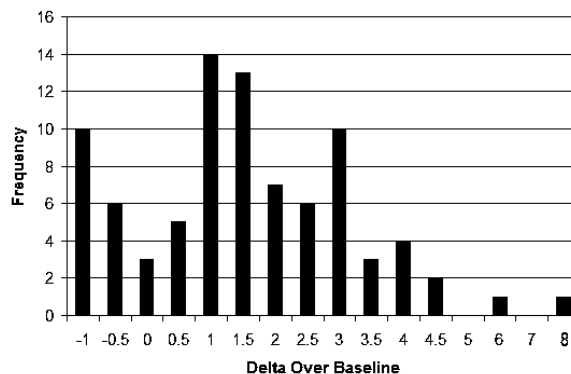


Figure 4: Distribution of Data for Uninfected Patients as Determined in an Initial Clinical Study

Delta Over Baseline values, as determined by the original BreathID® in a pivotal clinical study, were used to confirm the initial clinical data.

In the pre-therapy phase, there were 47 infected and 253 uninfected patients. Congruent results obtained by rapid urease test and histological examinations of biopsy tissue were used as the reference standard and were confirmed by the original BreathID® in the 47 infected patients. In the post therapy phase, 22 patients were infected and 50 were uninfected. The reference standard in this phase was at least one positive finding from either an endoscopic test (rapid urease or histology) or by a UBT.

The following values were obtained for the data from the pivotal study:

Upper 97.5% percentile of the Negative patients: 2.245

Lower 2.5% percentile of the Positive patients: 7.212

A histogram of the distribution of Delta Over Baseline values from pre- therapy uninfected (first phase) patients is shown in Figure 5 below.

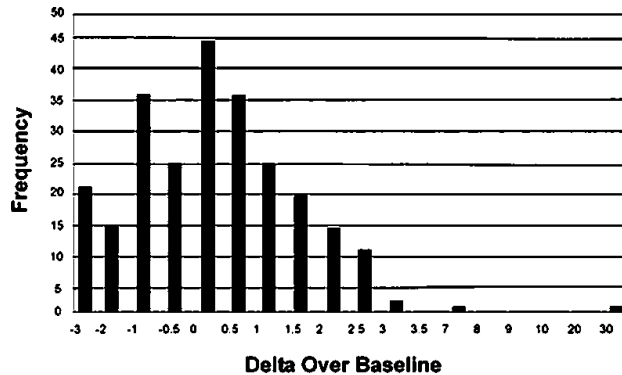


Figure 5: Distribution of Data for Pre-Therapy Uninfected Patients as Determined in the Pivotal Study

SECTION 13. PERFORMANCE CHARACTERISTICS

13.1. ORIGINAL BREATHID® CLINICAL PERFORMANCE RESULTS

13.1.1. PATIENT RESULTS

The relationship between pre- and post-therapy with the original BreathID® test results in patients enrolled in the clinical study was examined. Of the 13 patients who were positive pre-therapy and negative post-therapy and the three patients who were positive pre- and post-therapy, none had a borderline result post-therapy. The post-therapy negative patients were close to 0 Delta Over Baseline and the post-therapy positive patients were well above the 5 Delta Over Baseline threshold, again supporting the system coherency.

13.1.2 DIAGNOSTIC METHODS COMPARISON IN ADULTS IN CLINICAL TRIAL

Experimental Design

The data presented here was collected from a prospective, open-label clinical trial, designed to assess the sensitivity and specificity of the original BreathID® test compared to other methods in determining the status of gastrointestinal infection with *H. pylori* (pre-therapy phase). In addition, the clinical trial was designed to evaluate the ability of the original BreathID® system to monitor the efficacy of therapy for *H. pylori* (post-therapy phase).

There were 315 adult pre-therapy patients at two United States hospitals in the study. There were 77 post-therapy patients who were positive for infection and who had undergone eradication therapy at least four weeks previously. Nineteen of these post-therapy patients participated in the pre-therapy phase as well.

Patients were evaluated by at least two of four diagnostic methods:

1. Histopathology: Biopsy specimens, fixed with 10% buffered formalin, were cut into 4 mm sections stained with Giemsa stain, and examined by an experienced pathologist.
2. Rapid Urease Test: Biopsy specimens were tested for urease activity with a FDA-cleared test according to the instructions in its package insert.
3. Urea breath test (UBT) for *H. pylori* (post-therapy only): A FDA-cleared UBT test was performed according to the instructions in its package insert.
4. BreathID® test: The BreathID® test was performed in accordance with the procedures described in its package insert.

Results

The results are presented in two-way contingency tables. The exact binomial distribution was used to calculate the lower and upper limits of the 95% confidence intervals of the performance statistic.

Pre-Therapy

Table 2 and Table 3 compare the original BreathID® to rapid urease tests and histological exams, respectively. In Table 1, the original BreathID® outcome is compared to congruent results from the two endoscopy biopsy-based methods (rapid urease test and histological exam).

Table 1: Comparison of the Original BreathID® Test to Congruent Endoscopic Tests (RUT and histological exam) Pre-Therapy

Congruent Endoscopic Tests*	BreathID® Test		
	Positive	Negative	Total
Positive	47	0	47
Negative	2	251	253
Total	49	251	300

**H. pylori* positive is defined as positive rapid urea test and positive histology.
H. pylori negative is defined as negative rapid urea test and negative histology.
 Sensitivity: 100% [95% CI (92.5, 100)]
 Specificity: 99.2% [95% CI (97.2, 99.9)]

Table 2: Comparison of the Original BreathID® Test to Rapid Urease Test (RUT) Pre-Therapy

RUT	BreathID® Test		
	Positive	Negative	Total
Positive	50	0	50
Negative	2	259	261
Total	52	259	311

% positive agreement: 100% [95% CI (94.2, 100)]
 % negative agreement: 99.2% [95% CI (97.3, 99.9)]

Table 3: Comparison of the Original BreathID® Test to Histology Pre-Therapy

Histology	BreathID® Test		
	Positive	Negative	Total
Positive	47	2	49
Negative	6	251	257
Total	53	253	306

% positive agreement: 95.9% [95% CI (86.0, 99.5)]
 % negative agreement: 97.7% [95% CI (95.0, 99.1)]

Post Therapy

Table 4 compares the results from the original BreathID® to the results from endoscopic tests.

Table 4: Comparison of Original BreathID® test to Endoscopic Tests Post-Therapy

Endoscopic	BreathID® Test		
	Positive	Negative	Total
Positive	6	0	6
Negative	0	20	20
Total	6	20	26

* *H. pylori* positive is defined as positive RUT and positive Histology
H. pylori negative is defined as negative RUT and negative Histology
 % positive agreement: 100% [95% CI (60.7, 100)]
 % negative agreement: 100% [95% CI (86.1, 100)]

Table 5 compares the results from the original BreathID® to the results from a rapid urease test (RUT).

Table 5: Comparison of the Original BreathID® test to RUT Post-Therapy

RUT	BreathID® Test		
	Positive	Negative	Total
Positive	7	0	7
Negative	0	21	21
Total	7	21	28

% positive agreement: 100% [95% CI (65.2, 100)]
 % negative agreement: 100% [95% CI (86.7, 100)]

Table 6 compares the results from the original BreathID® to the results from a histological exam.

Table 6: Comparison of the Original BreathID® test to Histology Post-Therapy

Histology	BreathID® Test		
	Positive	Negative	Total
Positive	6	0	6
Negative	1	20	21
Total	7	20	27

% positive agreement: 100% [95% CI (60.7, 100)]

% negative agreement: 95.2% [95% CI (76.2, 99.9)]

Table 7 compares the results from the original BreathID® to the results from a UBT.

Table 7: Comparison of the Original BreathID® test to UBT Post-Therapy

UBT	BreathID® Test		
	Positive	Negative	Total
Positive	14	1	15
Negative	0	31	31
Total	14	32	46

% positive agreement: 93.3% [95% CI (68.1, 99.8)]

% negative agreement: 100% [95% CI (90.8, 100)]

Table 8 compares the original BreathID® to congruent results from the two biopsy- based methods (rapid urease test and histological exam) or urea breath test.

Table 8: Comparison of the Original BreathID® Test to Endoscopic Tests and/ or UBT Post-Therapy

Endoscopic Tests and UBT*	BreathID® Test		
	Positive	Negative	Total
Positive	20	1	21
Negative	0	50	50
Total	20	51	71

**H. pylori* positive is defined as either positive RUT and positive Histology, or positive UBT.

H. pylori negative is defined as either negative RUT and negative Histology, or negative UBT.

% positive agreement: 95.2% [95% CI (76.2, 99.9)]

% negative agreement: 100% [95% CI (94.2, 100)]

13.2. ORIGINAL BREATHID® AND BREATHID® HP COMPARATIVE CLINICAL DATA

Comparison of BreathID® Hp Test to BreathID® Test

A single center, one-arm, blinded, comparative study was conducted to demonstrate the clinical equivalence of the modified BreathID® Hp System compared to the original BreathID® System. The Study included a total of 79 consecutive evaluable adult subjects. The breath test was performed according to the standard procedure and routine clinical practice while the subject was connected simultaneously to both the original BreathID® device and the modified BreathID® Hp device via two standard cannulae. The outcome measures of both devices were used for the comparison.

Table 9 compares the modified BreathID® Hp System results to the original BreathID® results for each subject.

Table 9: Comparison of the Modified BreathID® Hp Test to the Original BreathID® Test

BreathID® Hp	BreathID® Test		
	Positive	Negative	Total
Positive	17	2	19
Negative	0	60	60
Total	17	62	79

**H. pylori* positive is defined as positive on the original BreathID® System.

% positive agreement: 100% [95% CI (81.6, 100)]

% negative agreement: 96.8% [95% CI (89.0, 99.1)]

13.3. CONFIRMATORY STUDY OF IDKIT HP™ ONE IN THE PEDIATRIC POPULATION

Experimental Design

A multi-center, non-randomized, open label study was conducted with the primary goal of confirming the safety of the ¹³C-urea substrate in pediatric subjects, and a secondary goal of evaluating performance of the BreathID® Hp System with IDkit Hp™ One in pediatric subjects aged 3-17 years using and the same 5 DOB diagnostic cut-off, in this population compared to stool antigen testing. A central lab analyzed the stool specimens.

The study was conducted at 6 clinical sites where the sites were geographically diverse, differing in size and diverse in experience. Local site personnel were trained on administering the breath test.

Results

A total of 54 subjects were screened, 1 subject was a screening failure prior to any study related procedure. Fifty-three subjects were enrolled and followed for safety assessment, 41 of which completed the full study protocol requirements with evaluable endpoints. There were no reportable major safety concerns due to adverse events.

Table 10 presents the diagnosis as assessed by the BreathID® Hp System using IDkit Hp™ One compared to the assessment by an FDA cleared *H. pylori* stool antigen test.

Table 10: Comparison of the BreathID® Hp Test using IDkit Hp™ One to an FDA-cleared *H. pylori* stool antigen test

Stool antigen results	BreathID® Hp test using IDkit Hp™ One		
	Positive	Negative	Total
Positive	14	1	15
Negative	0	26	26
Total	14	27	41

% positive agreement: 93.3% [95% CI (68.05, 99.83)]

% negative agreement: 100% [95% CI (86.77, 100)]

13.4. REPRODUCIBILITY AND REPEATABILITY RESULTS

Analytical studies were conducted to evaluate the reproducibility and precision (repeatability) of results when measurements are made by different technicians and/or using different BreathID® Hp devices, or when testing is done on different days and at different sites.

13.5. REPRODUCIBILITY ANALYTICAL STUDY

Three different accurate gas isotope pairs were used with Delta Over Baseline (DOB) values of 4.5, 5.9, and 15.5 in a bench study. Three operators were asked to operate each of three BreathID® Hp devices in three different sites for five days, in order to measure the DOB values for samples from each of the three batches. The results demonstrated that the standard deviation and overall reproducibility were stable over different batches for both the operator, the devices and between days. The reproducibility standard deviation was less than 0.57 for all batches and the between days and operators standard deviation was less than 0.70, which is less than the natural variability of the DOB measurement. Table 11 summarizes the results of the Reproducibility Analytical Study.

Table 11: Results of Reproducibility Analytical Study

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%

13.6. PRECISION ANALYTICAL STUDY (REPEATABILITY)

Three different accurate gas isotope pairs were used with Delta Over Baseline (DOB) values of 4.3, 5.9, and 15.5 in a bench study. The DOB values for samples from each of the three batches were measured on the BreathID® Hp device twice a day for 12 days. The results demonstrated that the standard deviation and overall repeatability were stable over different batches and different days. The repeatability standard deviation was less than 0.69, and the overall between days standard deviation was less than 0.74, which is less than the natural variability of the DOB measurement. Table 12 summarizes the results of the Precision Analytical Study.

Table 12: Results of the Precision Analytical Study

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%

SECTION 14. BIBLIOGRAPHY

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