**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

# 21-314

# Medical Review/Statistical(s)

22 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

# Clinical and Statistical Review for New Drug Application # 21-314

**Drug:** $^{13}$C-urea (75 mg tablets), as a component of the IDkit-hp™
**Device:** BreathID™ System

**Applicant's Intended Use:**
"The intended use of the Oridion BreathID™ system is to continually and non-invasively measure changes in the $^{13}CO2/^{12}CO2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori (H. pylori)* infection in the stomach. The Oridion BreathID System is to be used as an aid for initial diagnosis and post treatment monitoring of *H. pylori* infection."

**General Information:**

| | |
|---|---|
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**Submission/Review Dates:**

| | |
|---|---|
| Dates of Submission: | February 2, 2001; May 30,2001 |
| Date Review Begun: | March 29, 2001 |
| Date Review Completed: | November 9, 2001 |

**Drug Identification:**

| | |
|---|---|
| Generic Name: | $^{13}$C-urea |
| Proposed Trade Name: | IDkit-hp™, for use with the BreathID™ System |
| Chemical Name: | $^{13}$C-urea |
| Dosage Form: | 75 mg tablet |
| Route of Administration: | Oral |

**Related NDAs and 510(k)s:**
Meretek UBT
- NDA 20-586: approval September 17, 1996.
- Post-treatment monitoring indication: October 29, 1997
  - NDA 20-586, Supplement 002
  - CDRH 510(k) K972352

BreathTek UBT (previously known as Meretek UBT Lite)
- CDRH 510(k) K000316: clearance February 24, 2000
- NDA (20-586, Supplement 004): approval May 10, 2001

## TABLE OF CONTENTS


EXECUTIVE SUMMARY ..... 3
Summary of Clinical Findings ..... 3
A. Efficacy – Phase III Trial ..... 3
B. Safety – Phase III Trial ..... 5
C. Special Populations ..... 5
Recommendations ..... 6
CLINICAL REVIEW ..... 7
I. Introduction/Background ..... 7
A. Principle of the Test ..... 7
B. Procedure ..... 7
C. Related Drug/Devices ..... 8
D. Overview of Clinical Development Program ..... 8
E. Rationale for Dose Selection ..... 10
F. Regulatory Background ..... 10
II. Summary of Clinically Relevant Findings from Other Review Disciplines ..... 10
A. Chemistry ..... 10
B. Clinical Pharmacology ..... 11
C. OPDRA Consult ..... 12
D. Description of Clinical Data and Sources ..... 12
E. Phase III Clinical Data ..... 12
III. Clinical Review Methods ..... 12
A. Structure of the Review ..... 12
B. DSI Audit ..... 12
C. Financial Disclosure ..... 13
IV. Review of Controlled Clinical Study - Study 5266 ..... 13
V. Supportive Phase III Trials ..... 36
A. Hadassah Medical Center – Feasibility Study ..... 36
B. Wolfson Medical Center Beta Site Study ..... 37
C. University of Medicine and Dentistry (New Jersey) Clinical Trial ..... 38
D. Medical University of Luebeck (Germany) Clinical Trial ..... 38
VI. Integrated Summary of Safety (ISS) ..... 40
VII. Dosing and Administration Issues ..... 40
VIII. Use in Special Populations ..... 40
IX. Conclusions and Recommendations ..... 40
Appendix 1 – Additional Tables ..... 42
Appendix 2 – Recommended Label ..... 44

## EXECUTIVE SUMMARY
## Summary of Clinical Findings

Overview

| | |
|---|---|
| Generic Name: | $^{13}$C-urea |
| Proposed Drug Trade Name: | IDkit-hp™ |
| Proposed Device Trade Name: | BreathID™ System |
| Dosage Form: | 75 mg tablet |
| Route of Administration: | Oral |

**Applicant's Proposed Intended Use**

The intended use of the Oridion BreathID™ system is to continually and non-invasively measure changes in the $^{13}CO2/^{12}CO2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori (H. pylori)* infection in the stomach. The Oridion BreathID System is to be used as an aid for initial diagnosis and post treatment monitoring of *H. pylori* infection.

**A Efficacy – Phase III Trial**

Data to support the effectiveness of this new drug/device (BreathID) are obtained from a single multi-center, open-label pivotal study designed to assess the sensitivity and specificity of the BreathID system in determining the status of gastrointestinal infection with *H. pylori* (Pre-Therapy group), and to evaluate the ability of the BreathID system to monitor the efficacy of treatment for *H. pylori* (Post-Therapy group) by comparing the results of endoscopy-based methods with those of the BreathID test.

In the Pre-Therapy group, a total of 315 patients were enrolled at both sites, and of these, 312 (99.0%) comprised the efficacy population. In the Post-Therapy group, a total of 77 patients, 19 (24.7%) with pre-therapy assessment, and 58 (75.3%) without pre-therapy assessment were enrolled. The efficacy population comprised 73 patients, 19 (26.0%) with pre-therapy and 54 (74.0%) without pre-therapy.

Patients were eligible if they were referred to endoscopy because of dyspeptic symptoms, active peptic ulcer disease, or past history of documented peptic ulcer. All patients originated from Brigham and Women's Hospital or Massachusetts General Hospital, both located in Boston, Massachussets.

The performance data for all evaluable patients are summarized in the tables below.

**Pre-Therapy**
**Comparison of BreathID™ test to Congruent Endoscopic Tests**

| 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 (RUT) and positive histology; *H. pylori* negative is defined as negative RUT and negative histology.

**Sensitivity**: 100% [95% CI (92.5, 100)]**
**Specificity**: 99.2% [95% CI (97.2, 99.9)]**

**These calculations of sensitivity and specificity do not include 15 patients. In five of these patients results obtains from the RUT and histology did not match and in 10 of these patients, at least one of the 3 tests was missing.

**Pre-Therapy**
**Comparison of BreathID™ test to RUT (CLOtest®)***

| CLOtest® | BreathID™ Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 50 | 0 | 50 |
| Negative | 2 | 259 | 261 |
| Total | 52 | 259 | 311 |

* Four patients were missing RUT or BreathID™ test results

**Relative sensitivity: 100% [95% CI (94.2, 100)]**
**Relative specificity: 99.2% [95% CI (97.3, 99.9)]**

**Pre-Therapy**
**Comparison of BreathID™ test to Histology***

| Histology | BreathID™ Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 47 | 2 | 49 |
| Negative | 6 | 251 | 257 |
| Total | 53 | 253 | 306 |

* Nine patients were missing histology or BreathID™ test results

**Relative sensitivity: 95.9% [95% CI (86.0, 99.5)]**
**Relative specificity: 97.7% [95% CI (95.0, 99.1)]**

**Post-Therapy**
**Comparison of BreathID™ Test to Endoscopic Tests or Meretek UBT**

| Endoscopic Tests or Meretek UBT* | BreathID™ Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 21 | 1 | 22 |
| Negative | 0 | 50 | 50 |
| Total | 21 | 51 | 72 |

**H. pylori* positive is defined as at least one positive on either of the endoscopic tests or Meretek UBT

**Percent Agreement with positive subjects:** 95.5%
**Percent Agreement with negative subjects:** 100%

**B. Safety – Phase III Trial**

Of the 392 patients enrolled in the Phase III trial (315 enrolled in the Pre-Therapy and 77 additional patients in the post-Therapy portions of the study), only two patients reported one adverse event each. These adverse events are summarized as follows:

- One patient vomited the test solution. The adverse event was mild and judged not to be related to the device (BreathID), and possibly related to the endoscopy procedure. The patient recovered without treatment.

- One patient reported nausea and vomited repeatedly after completion of the endoscopy; the patient reported history of sensitivity to different sedative agents. The adverse event was mild and judged possibly related to the device (BreathID) and possibly related to the endoscopy. The patient recovered without treatment.

**C. Special Populations**

Pediatric patients (< 18 years) and patients with serious concomitant disease, which can be interpreted as including those with renal or hepatic impairment, were excluded from the clinical development program. Therefore, it is not possible to comment on the efficacy or adverse event profile in these populations.

**Efficacy**
The relative sensitivity and specificity of the BreathID test (Pre-Therapy) does not appear to be affected by age (<65 years versus ≥ 65 years), sex, or ethnic group (Caucasian, African-American, Asian-Pacific, Hispanic), although the analysis of some of these subgroups is limited by a small sample size. The relative sensitivity was 100% and specificity ranged from 98.2% to 100% for these various subgroups.

There were not enough patients in the Post-Therapy group to do similar subgroup analyses.

**Safety**
There have been only two adverse events reported in clinical trials conducted with the BreathID. Therefore, differences in age, gender, or ethnic group do not appear to influence the safety profile of this test.

**Recommendations**

The use of $^{13}$C-urea (75 mg tablets), as a component of the IDkit-hp™ to be used with the BreathID™ System is safe and effective to continually and non-invasively measure changes in the $^{13}CO2/^{12}CO2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori (H. pylori)* infection in the stomach. The Oridion BreathID System is to be used as an aid for initial diagnosis and post treatment monitoring of *H. pylori* infection.

Although the clinical data supports a recommendation for approval of $^{13}$C-urea (75 mg tablets) for this indication, unresolved CMC and Biopharmaceutics issues will result in an Approvable action. Before the product may be approved, it will be necessary for the applicant to:

- Demonstrate that the FD&C Yellow No. 6 used in this component conforms in identity and specification to the requirements of 21 CFR 74.706(a)(1) and (b). Document that the FD&C Yellow No. 6 is certified in accordance with 21 CFR 80. Obtain documentation that the dye conforms to 21 CFR 74.706(a)(1) and (b), and has been certified in accordance with 21 CFR 80. Alternatively, certified FD&C Yellow No. 6 may be obtained from a different supplier or the product may be reformulated without the dye.
- Provide documentation that will allow verification of the suitability of the components of [ ]
- Revise the specification for Citrica. Please add a specific identity test for citric acid. In addition, the acceptance criteria for : [ ] should be revised.
- Explain the cause of the observed failures of the submitted stability samples at both stability storage conditions.
- Provide new stability data from 3 batches justifying the proposed labeled storage condition of 15-30°C, given the multiple stability failures at both storage conditions. If the stability of the product cannot be demonstrated to support the labeled storage condition, propose a markedly reduced expiration dating period or, if appropriate, a different packaging system.
- Provide additional dissolution data to allow a more therapeutically relevant dissolution specification to be set. We request data from three tablet batches in water using sampling time points of 5, 10, 15, and 30 minutes.

Recommended wording for the label can be found in Appendix 2.

**CLINICAL REVIEW**

## I. Introduction/Background

| | |
|---|---|
| Generic Name: | $^{13}$C-urea and citric acid |
| Proposed Drug Trade Name: | IDkit-hp™ |
| Proposed Device Trade Name: | BreathID™ System |
| Dosage Form: | 75 mg tablets and Citrica powder for reconstitution |
| Route of Administration: | Oral |

**Applicant's Intended Use:**
"The intended use of the Oridion BreathID™ system is to continually and non-invasively measure changes in the $^{13}CO2/^{12}CO2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori (H. pylori)* infection in the stomach. The Oridion BreathID System is to be used as an aid for initial diagnosis and post treatment monitoring of *H. pylori* infection."

### A. Principle of the Test

The BreathID™ system is intended for use as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult humans. The system includes: the BreathID™ device, the IDcircuit™ or nasal cannula, a 75 mg $^{13}$C-urea tablet, a packet of 4.5 g of powdered Citrica (flavored citric acid) and a straw. The BreathID system continuously measures exhaled $^{13}CO2$ and $^{12}CO2$ concentrations from the patient's breath and then establishes a $^{13}CO2/^{12}CO2$ ratio using Molecular Correlation Spectrometry (MCS), Oridion's proprietary gas measuring technology. The IDcircuit continuously transports the exhaled breath from the patient to the BreathID Device. The $^{13}$C-urea and Citrica are used as a test solution. Results are displayed in real time on a computer screen and are printed after completing the test. The system is intended for use under the supervision of trained physicians, nurses, or other health care professionals.

### B. Procedure

The BreathID system is comprised the following components:
- 75 mg $^{13}$C-urea (tablet)
- One 4.4 gram packet of Citrica powder (flavored citric acid)
- One straw
- IDcircuit – nasal cannula (sampling device)
- BreathID device – analysis and printout of results

The patient is connected to the BreathID system and the patient's $^{13}CO2/^{12}CO2$ ratio in exhaled breath is monitored before and after a test solution is ingested. The test solution consists of 75 mg of $^{13}$C-urea and 4.5 g of Citrica dissolved in 200 mL of tap water. If *H. pylori* infection is present, urease splits the urea to produce $^{13}CO2$ and ammonia ($NH_3$). The $^{13}CO2$ then diffuses into the bloodstream and is excreted by the lungs into exhaled air. The increased ratio of $^{13}CO2/^{12}CO2$ in the exhaled breath is measured and detected by the BreathID system. In the absence of *H. pylori* infection, the entire dose of ingested urea is absorbed in the gastrointestinal tract and appears unchanged in the urine. The BreathID device software has a predictive algorithm that continually analyzes the trend of measured results and determines if

the measurements will be positive or negative. Following the ingestion of the test solution, results are available within 20 to 30 minutes.

**C. Related Drug/Devices**

There are currently marketed two other $^{13}$C-Urea Breath Tests (UBT). However, they require off-site equipment to analyze breath samples, which can delay the availability of results and may delay the initiation of therapy. The BreathID system non-invasively detects *H. pylori* infection in real-time, on-site. This provides a real-time diagnosis of *H. pylori* infection and will allow the physician to immediately initiate therapy, if needed.

**D. Overview of Clinical Development Program**

The clinical development program of the BreathID system includes the following studies:

1. A completed alpha feasibility study to get feedback from patients on the operation of the BreathID system (Hadassah Medical Center, Israel).

2. A completed beta site study to determine the practicality of the BreathID system when used by practitioners in the field (Wolfson Medical Center, Israel).

3. An ongoing study to evaluate the sensitivity and specificity of the BreathID system to detect *H. pylori* using a "20 minute" and "variable time" procedure, and to establish optimal parameters for the test (Luebeck Medical Center, Germany).

4. An ongoing study to determine whether the patient knowledge that a follow-up BreathID system to prove *H. pylori* eradication will be performed improves medical compliance and treatment related outcomes (various centers in New York and New Jersey).

5. A completed Phase III study (Study #5266) to evaluate the sensitivity and specificity of the BreathID system to detect *H. pylori* with a "20 minute" and "variable time" test procedure. The objectives of the study were also to monitor the efficacy of treatment for eradication of *H. pylori*, to optimize the cut-off for the discrimination of *H. pylori* positive and negative patients, and to determine the time required for the detection of *H. pylori* using the BreathID™ system, and to establish the criteria for the completion of the test (Massachusetts General Hospital, and Brigham and Women's Hospital, Boston, MA).

The final study (#5266) was considered pivotal and reviewed in detail. The remaining studies (#1-4) were considered supportive. The pivotal trial was a Phase III clinical efficacy and safety study conducted in the US and which enrolled 315 patients in the Pre-Therapy group and 77 in the Post-Therapy group.

| Study # | Status | Location | Design | N | Notes |
|---|---|---|---|---|---|
| -- | Completed (July to October 1998) | Israel (Hadassah Medical Center) | Pilot; determine precision in relation to commercially available IRMS* | 186 completed | Sens=100% Spec=97.7% |
| -- | Completed (March 1999 to Jan 10, 2000) | Israel (Wolfson Medical Center) | Pilot; determine precision in relation to "gold standard" (histology and rapid urease test) | 115 enrolled 97 evaluable | Sens=97.8% Spec=96.1% |
| 5266 | Completed (Sept 9, 1999 to June 22, 2000) | Massachusetts General Hospital, and Brigham and Women's Hospital, Boston, MA | Pivotal; "20 minute" and "variable time" assessment, monitor the efficacy of treatment, optimize the cut-off, determine optimal time, and completion criteria | 315 pre-therapy; 77 post-therapy | Pre- and Post-Treatment Phases |
| -- | Ongoing (Sept 1999 to present) | Germany (Luebeck Medical Center) | "20 minute" versus "variable time" procedure, optimize parameters | 169 enrolled (as of 12/21/00) | |
| -- | Ongoing (Sept 2000 to present) | US sites in NY and NJ | Effect on medical compliance and treatment related outcomes | 120 enrolled (as of 1/29/01) | |

* IRMS = isotope ratio mass spectrometry

## E. Rationale for Dose Selection

In the original Meretek UBT, approved in 1996, a 125 mg dose of $^{13}$C-urea was administered with a mixed-nutrient test meal (Ensure pudding). The test meal slowed gastric emptying and maximized the distribution of $^{13}$C-urea in the stomach, which increases the area and time of contact between the bacteria and the substrate. However, it has been subsequently shown, in the literature and by other applicants (i.e., Meretek's BreathTek UBT), that by including citric acid in the drug component of the test, the dose of 75 mg of $^{13}$C-urea can be reduced from 125 mg to 75 mg without reducing the diagnostic signal generated by the test. The mechanism by which citric acid influences the amount of $^{13}CO_2$ appearing in the breath is thought to be a delay in gastric emptying and enhanced intragastric distribution of urea.

The applicant has chosen a 75 mg dose of $^{13}$C-urea formulated as a tablet to be dissolved with citric acid powder in water prior to ingestion.

## F. Regulatory Background

The applicant met with the Division and CDRH on March 11, 1999. At that time it was agreed that the NDA would contain one clinical trial conducted by Oridion at two sites in the United States. Additional data would be provided in the NDA from 4 other trials (3 in Israel and 1 in Germany) to support the application.

The pivotal clinical trial was amended on September 29, 1999 to allow administration of proton pump inhibitors (PPIs) within one week before the date of entry into the study. This amendment was prompted by the hospital IRB shared by both clinical trial sites. There was concern that a large percentage of potential study participants on PPIs would be excluded. The applicant discussed the protocol with Dr. Dubois from CDRH in October 1999.

A pre-NDA/510(k) meeting was held with the Division and CDRH on March 16, 2000. At that time agreement was reached on the overall format and content of the NDA and 510(k) submissions.

# II. Summary of Clinically Relevant Findings from Other Review Disciplines

## A Chemistry

**Composition (per applicant)**

Urea: Each soluble 75mg tablet contains:
Active ingredients: $^{13}$C-enriched urea (99%)
Excipients: [redacted]

Citrica: Each 4.5 grams packet contains 4 grams citric acid, [redacted] mg aspartame, [redacted] FD&C yellow #6.

Several outstanding issues were identified in the chemistry review. Before the product may be approved, it will be necessary for the applicant to:

1. Demonstrate that the FD&C Yellow No. 6 used in this component conforms in identity and specification to the requirements of 21 CFR 74.706(a)(1) and (b). Document that the FD&C Yellow No. 6 is certified in accordance with 21 CFR 80. The documentation from [redacted] does not assure compliance with these regulations. Obtain documentation that the dye

conforms to 21 CFR 74.706(a)(1) and (b), and has been certified in accordance with 21 CFR 80. Alternatively, certified FD&C Yellow No. 6 may be obtained from a different supplier or the product may be reformulated without the dye.

2. Provide documentation that will allow verification of the suitability of the components of [ ] For example, a list of individual components and their regulatory references could be obtained from the supplier and submitted to your NDA. Alternatively, the supplier may submit this information in a Drug Master File. The product can also be reformulated without this flavor.
3. Revise the specification for Citrica. Please add a specific identity test for citric acid. In addition, the acceptance criteria for [ ] should be revised. Neither the proposed — limit for [ ] nor the proposed — limit for [ ] is supported by the available stability data. Please tighten the acceptance criteria accordingly or provide further justification for their retention.
4. Explain the cause of the observed failures of the submitted stability samples at both stability storage conditions. Address, for example, issues such as the variability of the data, and pouch integrity. Explain the following finding for batch 235.3 stored at 25°C/60% RH: [ ] and could not be tested."
5. Provide new stability data from 3 batches justifying the proposed labeled storage condition of 15-30°C, given the multiple stability failures at both storage conditions. For example, in batch 235.1 at 30°C, — RH ( — months) the following were observed:
   - [
   - 
   - 
   - 
   - ]

   If the stability of the product cannot be demonstrated to support the labeled storage condition, propose a markedly reduced expiration dating period or, if appropriate, a different packaging system.

*Clinical Reviewer's Comment: These deficiencies resulted in an Approvable action. For complete details, please see Dr. Seggel's review.*

**B. Clinical Pharmacology**

Urea is a naturally occurring substance present in many foods and in man. Urea is "generally recognized as safe" for use in food (21 CFR 184.1923). It is water-soluble and the endogenous end product of protein metabolism. It functions in the removal of ammonia from the body. The daily production of urea in man is approximately 25 to 30 gm, depending on the protein content in the diet. Essentially all urea formed in the human body is synthesized by the liver and diffuses from the liver to the body fluids where it is then excreted by the kidneys. The normal plasma concentration of urea is approximately 100 to 500 mg/L. The total body urea pool ranges from 700 to 2000 mg in normal healthy patients.

The physical and chemical properties of $^{12}C$-urea and $^{13}C$-urea are virtually identical. The $^{13}C$-isotope of carbon represents about 1% of all carbons. Calculations show that the endogenous $^{13}C$-urea pool ranges from 7 to 22 mg in a 70 kg adult. The addition of 75 mg of $^{13}C$-urea, equivalent to approximately 16 mg of $^{13}C$, is not considered to have any biological consequences.

One outstanding issue was identified. Before the product may be approved, it will be necessary for the applicant to:

Provide additional dissolution data from three tablet batches in water using sampling time points of 5, 10, 15, and 30 minutes. These data will allow us to determine a more therapeutically relevant dissolution specification.

*Clinical Reviewer's Comment: This deficiency resulted in an Approvable action. For complete details, please see Dr. Meyer's review.*

**C. OPDRA Consult**

OPRDA has no objections to the use of the proprietary name "IDkit-hp™." (Consult 01-0185, October 15, 2001).

**D. Description of Clinical Data and Sources**

| | |
|---|---|
| Material Submitted: | 21 volumes<br>Electronic data, including SAS transport files |
| Material Reviewed: | Volumes 1.2, 1.10-1.14; 1.20-1.21<br>Electronic data, including SAS transport files |

**E. Phase III Clinical Data**

One Phase III study (#5266) was considered pivotal and reviewed in detail to determine the safety and effectiveness of the $^{13}$C-urea tablet of the IDkit-hp when used in conjunction with the BreathID system for *H. pylori* by demonstrating similar diagnostic performance when compared to approved endoscopic methods and/or the Meretek UBT.

**III. Clinical Review Methods**

**A. Structure of the Review**

For the purpose of determining the safety and effectiveness of the $^{13}$C-urea tablet of the IDkit-hp when used in conjunction with the BreathID system for *H. pylori*, one US Phase III study was considered pivotal.

**B. DSI Audit**

A DSI audit was not requested for this study. The principal investigators for the study were:

- Dr. David L. Carr-Locke, Brigham and Women's Hospital, Boston, MA.
- Dr. William R. Brugge, Massachusetts General Hospital, Boston, MA.

*Clinical Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since $^{13}$C-urea and Citrica powder are not NMEs and have been used in combination for the same indications in other NDA/510k applications. Both compounds have well-characterized safety profiles. In addition, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.*

### C. Financial Disclosure

As per the applicant's certification, Drs. Carr-Locke and Brugge both had no financial conflicts of interest that would preclude them from participating in Study #5266.

## IV. Review of Controlled Clinical Study - Study 5266

Study Dates: September 9, 1999 to June 22, 2000.

### Study Design

This was a multi-center, open-label pivotal study designed to assess the sensitivity and specificity of the BreathID in determining the status of gastrointestinal infection with *H. pylori* (Pre-Therapy group), and to evaluate the ability of the BreathID system to monitor the efficacy of treatment for *H. pylori* (Post-Therapy group). Pre-Therapy the results of the BreathID system were compared to endoscopy-based methods (histology and CLOtest®). Post-Therapy the results of the BreathID system were compared to endoscopy-based methods or urea breath test (Meretek UBT) results.

### Objectives

- To evaluate the sensitivity and specificity of the BreathID system to detect the presence of *H. pylori* with a "20 minute" breath test procedure.
- To evaluate the sensitivity and specificity of the BreathID system to detect the presence of *H. pylori* with a "variable time" breath test procedure.
- To evaluate the ability of the BreathID system to monitor the efficacy of *H. pylori* eradication treatment.

### Patients

Patients referred to endoscopy because of dyspeptic symptoms, active peptic ulcer disease, or past history of documented peptic ulcer were enrolled in the study.

### Inclusion Criteria

To be eligible to participate in the Pre-Therapy part of the study, patients must have met the following inclusion criteria:

- Be over 18 years of age.
- Be referred to endoscopy because of dyspeptic symptoms, active peptic ulcer disease or past history of documented peptic ulcer.
- Be able and willing to sign the informed consent form.

*Clinical Reviewer's Comment: Amendment 2 (approval date: December 30, 1999) changed the inclusion criterion "Referred to endoscopy because of dyspeptic symptoms, active peptic ulcer disease or past history of documented peptic ulcer" to "Referred to endoscopy." This change eliminates the requirement for a patient to have active (or past history) of ulcer disease and is acceptable. Other sponsors have been granted approval for drug/device products by studying similar populations.*

To be eligible to participate in the Post-Therapy evaluation, patients who were not enrolled at baseline must have met the following inclusion criteria:

- Be over 18 years of age.
- Be positive for *H. pylori* by any other *H. pylori* test.
- Be undergoing treatment for the eradication of *H. pylori.*
- Be referred to monitor the efficacy of treatment.
- Be able and willing to sign the informed consent form.

**Exclusion Criteria**

Patients meeting any of the following exclusion criteria were not eligible to participate in the study:

- Have any concomitant disease(s), condition(s), or treatment(s) that would interfere with the evaluation of *H. pylori* status. Such treatment would include:
  - Treatment for the eradication of *H. pylori* taken during the 4 weeks immediately prior to participating in the study.
  - Treatment with an antibiotic(s) and/or bismuth preparation(s) within 4 weeks before entering into the study.
- Have any safety or ethical reason for not participating, such as:
  - Concomitant serious disease.
  - Pregnant and/or breast-feeding.
  - Known or suspected allergy to the study test solution.
  - Contraindication to endoscopy and/or biopsy.
  - Participation in another clinical trial while participating in the current study.

*Clinical Reviewer's Comment: Amendment 1 (Approval date: September 29, 1999) allowed deletions of the exclusion criterion "Administration of PPI (proton pump inhibitor) medications within 1 week before the date of entry to the study." This protocol change was not submitted to the Division for comment.*

**Sample Size**

A minimum of 250 patients was to be enrolled in the study for the pre-therapy (baseline) evaluation. The sample size was determined by requiring the width of the left part of a one-sided 95% confidence interval (CI) to be at most 5%. Assuming both sensitivity and specificity to be 95%, a sample size that would result in 100 positive (by the gold standard) evaluable patients and 100 negative (by the gold standard) evaluable patients would give rise to a 95% confidence interval of (90%, 100%). Assuming *H. pylori* prevalence in the study population to be about 60%, the sample size would have to be 250 in order to ensure 100 negative patients. For the post-therapy evaluation, up to 100 patients were to be evaluated.

**Study Design**

Pre-Therapy Phase

Patients evaluated by the Gastroenterology Division, from self-admission to the hospital, or by referral from a nearby institution or physician, and meeting the inclusion/exclusion criteria, were eligible to be enrolled in the pre-therapy evaluation. All patients underwent gastric biopsies during diagnostic endoscopy. The biopsy specimens were histologically examined for *H. pylori* and direct detection of urease activity using the CLOtest for verification of the presence of *H. pylori*. Patients were also evaluated using the BreathID™ system and the results collected from this test were compared to the results obtained from the invasive collection methods. In cases where the CLOtest and histology test results were both positive, patients were diagnosed as

infected with *H. pylori* and underwent therapy for the treatment of *H. pylori* infection. Patients whose CLOtest and histology test results were discrepant were considered non-evaluable.

Post-Therapy Phase

Any person testing positive for infection could have been included in the post-therapy evaluation for monitoring of *H. pylori* eradication. Additionally, any person undergoing treatment for the eradication of the bacterium or referred to monitor the efficacy of the treatment could have been enrolled in the study at this stage, irrespective of whether they participated in the pre-therapy evaluation. The post-therapy evaluation was conducted 4 to 6 weeks following the end of treatment for *H. pylori* eradication. At this time, patients were tested with Meretek's Urea Breath Test and/or endoscopy based methods as well as the BreathID system. These results were compared to the results derived from invasive collection methods. In cases where there was no indication for endoscopy, either the Meretek UBT or BreathID test was performed at the first visit, and the converse test was performed 24 to 96 hours after the first visit.

A 75 mg dose of $^{13}$C-urea was given to patients. [redacted] manufactured the $^{13}$C-urea tablet used in this study.

The patients enrolled in the study were evaluated according to the following schedule:

**Pre-Therapy Evaluation – Initial Visit**

During the same day, either before or after the BreathID test, patients underwent endoscopy with three biopsies taken from the antrum. Endoscopy was performed and biopsy specimens were taken.

*Clinical Reviewer's Comments:*

1. *Amendment 2 (approval date: December 30, 1999) changed the timing of endoscopy and BreathID testing. The original protocol stated: "During the same day, either before or after the BreathID test, subjects will undergo endoscopy..." Protocol Amendment 2 amended the text to read: "During the same week, either before or after the BreathID test, subjects will undergo endoscopy..."*
2. *Patients were instructed to fast one hour prior to administration of the BreathID test. Patients who had an endoscopy performed on the same day as the BreathID test were fasting for a longer period of time, as dictated by the endoscopic procedure.*

One antral biopsy specimen was assayed with the CLOtest and two antral specimens were assayed using histological examination. Based on these results, the patient status was classified as *H. pylori* Positive, *H. pylori* Negative, or Not Evaluable (in those cases where histology and CLOtest results were discrepant). See table below.

**Classification of Infection and Evaluability Based on Endoscopic Tests Pre-Therapy**

| Histology | CLOtest | Patient Status |
|---|---|---|
| Positive | Positive | *H. pylori* Positive (Infected) |
| Positive | Negative | Not Evaluable |
| Negative | Positive | Not Evaluable |
| Negative | Negative | *H. pylori* Negative (Not Infected) |

Non-evaluable patients were excluded from statistical analysis. Only patients with *H. pylori* positive or negative status and who completed the BreathID test were included in the pre-therapy sensitivity and specificity analysis.

*Clinical and Statistical Reviewers' Comment: The applicant classified patients with incongruent results by endoscopy as non-evaluable. Depending on the performance of BreathID, there may or may not be bias introduced in the sensitivity and specificity analyses by excluding these patients with incongruent results from the analyses. In our review, analyses will be conducted to assess the impact of the incongruent results on sensitivity and specificity. See Results section.*

Patients determined to be Positive, were offered treatment for the eradication of *H. pylori*. These patients came to a Post-Therapy visit 4 to 6 weeks after the end of treatment.

**Post-Therapy Evaluation - 1st Visit**

The first Post-Therapy evaluation visit was scheduled 4 to 6 weeks after the end of treatment for *H. pylori* eradication. Post Therapy visits were not required in patients testing negative for *H. pylori* or in patients not receiving treatment for any other reason.

**Post-Therapy Evaluation - 2nd Visit**

The second Post-Therapy evaluation visit was scheduled 24 to 96 hours after the first Post-Therapy visit. This 2nd visit was required only in cases in which there was no indication for endoscopy in the Post-Therapy 1st Visit.

Any person who tested positive for the infection in both CLOtest and histology was eligible to be included in a follow-up evaluation for the monitoring of *H. pylori* eradication following treatment. Additionally, any person undergoing treatment for the eradication of the bacterium or referred to monitor the efficacy of the treatment was eligible to be enrolled in the study at this stage, irrespective of participation in the study in the Pre-Therapy evaluation. The patients treated for the eradication of *H. pylori* had a BreathID test performed and were assayed by at least one of the following methods:

- Meretek UBT
- CLOtest + Histology

At the first Post-Therapy Visit, based on clinical findings, the physician was allowed to exercise clinical judgement as to whether or not an endoscopy was indicated. If the physician felt no endoscopy was indicated, the patient underwent either the BreathID test or Meretek's UBT. At the subsequent visit, the patient underwent the assay that was not previously performed.

If the physician elected to perform an endoscopy, the patient underwent endoscopy and BreathID test at the same visit (1st visit). Based on the endoscopic results, the patient was

classified as *H. pylori* Positive, or *H. pylori* Negative. If either test was positive, the patient was considered *H. pylori* Positive. See table below.

**Criteria of Infection and Evaluability Based on Endoscopic Tests Post-Therapy**

| Histology | CLOtest | Patient Status |
|---|---|---|
| Positive | Positive | *H. pylori* Positive (Infected) |
| Positive | Negative | *H. pylori* Positive (Infected) |
| Negative | Positive | *H. pylori* Positive (Infected) |
| Negative | Negative | *H. pylori* Negative (Eradicated) |

*Clinical and Statistical Reviewers' Comment: The applicant classified patients with incongruent results by endoscopy as H. pylori positive. This is acceptable to the reviewers since those patients were originally diagnosed with the infection before treatment.*

**Blinding Procedures**

**Baseline**

In order to ensure unbiased interpretation of assay results, the following steps for blinding were taken:

- The operator performing the BreathID Test was blinded to clinical information, endoscopic information, and all other *H. pylori* diagnostic information.
- The endoscopist was blinded to clinical information and breath tests results.
- The physician performing the urease test (CLOtest) was blinded to clinical information, breath tests results, endoscopic information, and all other *H. pylori* diagnostic information.
- The pathologist was blinded to clinical information, endoscopic information, and results of all *H. pylori* diagnostic information other than histology.
- The principal investigator or co-investigator(s) was blinded to the BreathID results.
- The principal investigator or co-investigator(s) remained unblinded for the results of histological examination and CLOtest, in order to evaluate the eligibility of the patient for the follow-up.

**Post-Therapy Visit(s)**

In order to ensure unbiased interpretation of assay results, the following steps for blinding were taken:

- The operator(s) performing the BreathID test and Meretek UBT were blinded to clinical information and all other *H. pylori* diagnostic information.
- The laboratory staff involved in the analysis of the $^{13}C$ breath samples was blinded to clinical information, BreathID results, and all other *H. pylori* diagnostic information.
- If endoscopy was performed, the same blinding procedures described for Baseline applied.

**Efficacy Analysis**

The Pre-Therapy efficacy population was defined as all patients with results available for comparison from the BreathID test and from at least one of the two endoscopic tests (CLOtest and histology).

Based on the efficacy population for Pre-Therapy evaluation, sensitivity and specificity, as well as their corresponding one-sided 95% Confidence Intervals are reported for the 20 minute procedure. Confidence intervals were calculated using exact methods.

*Statistical Reviewer's Comment: Since two-sided 95% Confidence Intervals are the Agency standard, two-sided 95% CIs will be calculated in this review and presented in the label.*

To evaluate the ability of the BreathID test to monitor the eradication treatment Post-Therapy, results of CLOtest + Histology or Meretek UBT test and BreathID test were compared for patients who completed both sets of tests (defined as Post-Therapy efficacy population). Comparing the BreathID test to another predicate device was done by calculating agreement parameters such as Kappa measure and the McNemar test.

**Evaluation Criteria**

20 Minute Procedure

For the "20 Minute Procedure", the number of positive, negative, false positive and false negative results obtained using the BreathID System were determined according to the following criteria:

- Positive Test Result = last two consecutive values at 18 minute and 20 minute timepoints > 6 DOB.
- Negative = last two consecutive values at 18 minute and 20 minute timepoints were ≤ 3 DOB.
- Indeterminate = when 18 minute and 20 minute timepoints were between 3 DOB to 6 DOB. If the result was still indeterminate after 20 minutes, the test was continued for another 10 minutes in order to evaluate the prolongation of the test in borderline cases. In these cases, the following applied:
  - Positive = after another 10 minutes, two consecutive values were > 6 DOB or when at 30 minute timepoint > 5 DOB.
  - Negative = after another 10 minutes, two consecutive values were < 3 DOB or when at 30 minute timepoint < 5 DOB.

Variable Time Procedure

*Clinical Reviewer's Comment: The Variable Time Procedure results were analyzed independently of [ ] and the applicant is not seeking approval at this time for this procedure. The procedure and the applicant's summary of results are provided only for completeness of the review.*

For the "Variable Time" procedure, the number of positive, negative, false positive and false negative results obtained using the BreathID™ Test was determined. Results were discriminated based on the following criteria:

- Positive Test Result = after the five minute timepoint, two consecutive values > 6 delta over baseline (DOB).
- Negative Test Result = after the five-minute timepoint, two consecutive values ≤ 3 DOB.
- Indeterminate Test Result = values are between 3 DOB to 6 DOB and/or after the 5 minute timepoint there are no two consecutive values above 6 DOB or below 3 DOB. If after 20 minutes the result continued to be indeterminate, the test was continued for another 10 minutes in order to evaluate the prolongation of the test in borderline cases. In these cases, the following applied:

- Positive = two consecutive values > 6 DOB or when the 30 minute timepoint > 5 DOB.
- Negative = two consecutive values < 3 DOB or when 30 minute timepoint < 5 DOB.

The applicant indicated that the Variable Time results demonstrated the equivalence of the standard 20 minute test to the varying time tests (both the 5 minute and the 4 minute) regarding the diagnostic results. The time required for this test is on average half that required for the standard test, 10 instead of 20 minutes, for the 5 minute rule and less than 8 minutes for the 4 minute rule. These results did not depend on clinical stage or on the specific medical center. Their conclusion was to prefer the variable time procedure over 20 minute procedure.

**Results**

*Clinical Reviewer's Comment: All the following tables in this review are reproductions from the applicant's submission, unless otherwise noted.*

A total of 315 patients were enrolled in the Pre-Therapy group and 77 in the Post-Therapy group at two sites (Sites 4 and 5). Some patients enrolled in both treatment phases, so there were only 373 individuals contributing data to the study. A summary of patients by site in the Pre-Therapy and Post-Therapy groups can be found in Table 1 below.

**Table 1**
**Summary of Patients**

| Category | Site 4 N (%) | Site 5 N (%) | Total N (%) |
|---|---|---|---|
| **Pre-Therapy** | | | |
| Enrolled population | 266 (100.0) | 49 (100.0) | 315 (100.0) |
| Efficacy population* | 264 (99.2) | 48 (98.0) | 312 (99.0) |
| **Post-Therapy** | | | |
| Enrolled population | | | |
| With Pre-Therapy | 18 (27.3) | 1 (9.1) | 19 (24.7) |
| Without Pre-Therapy | 48 (72.7) | 10 (90.9) | 58 (75.3) |
| Total | 66 | 11 | 77 |
| Efficacy population** | | | |
| With Pre-Therapy | 15 (28.6) | 1 (10.0) | 19 (26.0) |
| Without Pre-Therapy | 45 (71.4) | 9 (90.0) | 54 (74.0) |
| Total | 63 | 10 | 73 |

* All patients with results available for comparison from Breath ID test and from at least one of the two endoscopic tests (CLOtest and histology)
** All patients with results available for comparison from Breath ID test and from at least one of the three other tests (CLOtest, histology, and Meretek breath test)
Site 4 = Dr. David L. Carr-Locke, Brigham and Women's Hospital, 10, Boston, MA.
Site 5 = Dr. William R. Brugge, Massachusetts General Hospital, Boston, MA.

A summary of patient disposition in the Pre-Therapy and Post-Therapy groups by site is shown in Table 2 below. In the Pre-Therapy group, 9 (2.9%) patients did not complete the study. Of the patients that discontinued the trial, one (11.1%) patient terminated early due to an adverse event, and 8 (88.9%) due to other reasons. In the Post-Therapy group, 5 (6.5%) patients did not complete the study. Of these patients that discontinued the trial, two (40.0%) patients were lost to follow-up, 2 (40%) terminated their participation due to other reasons, and 1 (20.0%) terminated voluntarily.

**Table 2**
**Summary of Patient Disposition**

| Category | Site 4 N (%) | Site 5 N (%) | Total N (%) |
|---|---|---|---|
| **Pre-Therapy** | | | |
| Subjects completed | | | |
| Yes | 261 (98.1) | 45 (91.8) | 306 (97.1) |
| No | 5 (1.9) | 4 (8.2) | 9 (2.9) |
| Total | 266 | 49 | 315 |
| Reasons for early termination | | | |
| Death | - | - | - |
| Adverse event | | 1 (25.0) | 1 (11.1) |
| Procedure/protocol violation | - | - | - |
| Non-compliance | - | - | - |
| Voluntary withdrawal | - | - | - |
| Investigator withdrew | - | - | - |
| Lost to follow-up | - | - | - |
| Other reason | 5 (100.0) | 3 (75.0) | 8 (88.9) |
| Total | 5 | 4 | 9 |
| **Post-Therapy** | | | |
| Subjects completed | | | |
| Yes | 62 (93.9) | 10 (90.9) | 72 (93.5) |
| No | 4 (6.1) | 1 (9.1) | 5 (6.5) |
| Total | 66 | 11 | 77 |
| Reasons for early termination | | | |
| Death | - | - | - |
| Adverse event | - | - | - |
| Procedure/protocol violation | - | - | - |
| Non-compliance | - | - | - |
| Voluntary withdrawal | 1 (25.0) | | 1 (20.0) |
| Investigator withdrew | - | - | - |
| Lost to follow-up | 2 (50.0) | | 2 (40.0) |
| Other reason | 1 (25.0) | 1 (100.0) | 2 (40.0) |
| Total | 4 | 1 | 5 |

**Demographics**

Summaries of patient demographic and medical history information in the Pre-Therapy and Post-Therapy groups by site are summarized in Table 3 below. In the Pre-Therapy group, the mean age was 52.4 years, with a predominance of male (59.4%) Caucasian (66.3%) patients. There were 270/315 (85.7%) patients with a history of gastrointestinal disease. There were 227/315 (72.1%) patients who had used PPI or H2 medications within 6 weeks prior to enrollment.

In the Post-Therapy group that received treatment for *H. pylori* eradication, 18 (23.4%) received Pre-Therapy evaluation and 59 (76.6%) did not receive Pre-Therapy evaluation. The mean duration of treatment was 12.2 days (range: 8 to 14 days), and the mean time since the end of treatment was 5.6 weeks (range: 3.5 to 26.0 weeks). There were 29 (37.7%) patients selected for endoscopy to confirm eradication.

**Table 3**
**Summary of Patient Demographic and Medical History Information**

| Category | Site 4 | Site 5 | Total |
|---|---|---|---|
| **Pre-Therapy** | | | |
| Age | | | |
| N | 266 | 49 | 315 |
| Mean (Std) | 52.5 (14.93) | 52.0 (12.89) | 52.4 (14.61) |
| Gender | | | |
| Male | 159 (59.8%) | 28 (57.1%) | 187 (59.4%) |
| Female | 107 (40.2%) | 21 (42.9%) | 128 (40.6%) |
| Total | 266 | 49 | 315 |
| Race | | | |
| Caucasian | 174 (65.4%) | 35 (71.4%) | 209 (66.3%) |
| African-American | 27 (10.2%) | 4 (8.2%) | 31 (9.8%) |
| Native-American | 1 (0.4%) | - | 1 (0.3%) |
| Asian-Pacific | 16 (6.0%) | 2 (4.1%) | 18 (5.7%) |
| Hispanic | 42 (15.8%) | 8 (16.3%) | 50 (15.9%) |
| Other | 6 (2.3%) | - | 6 (1.9%) |
| Total | 266 | 49 | 315 |
| Past History* | | | |
| Gastroesophageal reflux | 203 (90.6%) | 14 (30.4%) | 217 (80.4%) |
| Active peptic ulcer | 14 (6.3%) | 6 (13.0%) | 20 (7.4%) |
| Non-ulcer dyspepsia | 11 (4.9%) | 36 (78.3%) | 47 (17.4%) |
| Non-active peptic ulcer | 5 (2.2%) | 0 (0.0%) | 5 (1.9%) |
| Total | 224 | 46 | 270 |
| Used H2/PPI medications within last 6 weeks | | | |
| Yes | 196 (73.7%) | 31 (63.3%) | 227 (72.1%) |
| No | 70 (26.3%) | 18 (36.7%) | 88 (27.9%) |
| Total | 266 | 49 | 315 |
| **Post-Therapy** | | | |
| Age | | | |
| N | 66 | 11 | 77 |
| Mean (Std) | 50.2 (14.07) | 47.4 (14.55) | 49.8 (14.08) |

* Categories are not mutually exclusive

**Table 3 (continued)**
**Summary of Patient Demographic and Medical History Information**

| Category | Site 4 | Site 5 | Total |
|---|---|---|---|
| Gender | | | |
| Male | 39 (59.1%) | 8 (72.7%) | 47 (61.0%) |
| Female | 27 (40.9%) | 3 (27.3%) | 30 (39.0%) |
| Total | 66 | 11 | 77 |
| Race | | | |
| Caucasian | 43 (65.2%) | 6 (54.5%) | 49 (63.6%) |
| African-American | 13 (19.7%) | 1 (9.1%) | 14 (18.2%) |
| Native-American | - | - | - |
| Asian-Pacific | 2 (3.0%) | 2 (18.2%) | 4 (5.2%) |
| Hispanic | 6 (9.1%) | 2 (18.2%) | 8 (10.4%) |
| Other | 2 (3.0%) | - | 2 (2.6%) |
| Total | 66 | 11 | 77 |
| Past History* | | | |
| Gastroesophageal reflux | 40 (83.3%) | 2 (18.2%) | 42 (71.2%) |
| Active peptic ulcer | 6 (12.5%) | - | 6 (10.2%) |
| Non ulcer dyspepsia | 2 (4.2%) | 10 (90.9%) | 12 (20.3%) |
| Non-active peptic ulcer | - | - | - |
| Total | 48 | 11 | 59 |
| Used H2/PPI medications within last 6 weeks | | | |
| Yes | 36 (75.0%) | 9 (90.0%) | 45 (77.6%) |
| No | 12 (25.0%) | 1 (10.0%) | 13 (22.4%) |
| Total | 48 | 10 | 58 |

* Categories are not mutually exclusive

**Summary of Treatment for *H. pylori* Eradication**

A summary of treatment for *H. pylori* eradication in the Post-Treatment group is summarized in Table 4 below.

**Table 4**
**Summary of Treatment for *H. pylori* Eradication**
**Post-Therapy**

| Category | Site 4 | Site 5 | Total |
|---|---|---|---|
| With Pre-Therapy Evaluation | | | |
| Yes | 17 (25.8%) | 1 (9.1%) | 18 (23.4%) |
| No | 49 (74.2%) | 10 (90.9%) | 59 (76.6%) |
| Total | 66 | 11 | 77 |
| Duration of Treatment (days) | | | |
| N | 66 | 11 | 77 |
| Mean (Std) | 12.4 (1.78) | 11.1 (1.67) | 12.2 (1.84) |
| Time Since End of Treatment (weeks) | | | |
| N | 66 | 11 | 77 |
| Mean (Std) | 5.6 (2.98) | 5.7 (2.93) | 5.6 (2.95) |
| Selected for Endoscopy to Confirm Eradication | | | |
| Yes | 27 (40.9%) | 2 (18.2%) | 29 (37.7%) |
| No | 39 (59.1%) | 9 (81.8%) | 48 (62.3%) |
| Total | 66 | 11 | 77 |

**Results – Pre-Therapy (20 Minute Procedure)**

*Clinical Reviewer's Data Validation Methods*
*Validation of the efficacy data was performed by reviewing the electronic and line listing raw data for 10% of the evaluable population (N=31 Pre-Therapy and 7 Post-Therapy). The patients were randomly selected. The reviewer's assessment of evaluability was the same as the applicant's for all patients in this sample. Also, all the patients with incongruent or missing results were evaluated by the reviewer.*

A comparison of the BreathID test results to two endoscopic test results (CLOtest and histology) is summarized in Table 5 below. The mean delta time for the BreathID test using "20 Minute" procedure in the total patient population tested was 21.0 min ranging from 11 to 32 minutes. Patients with incongruent test results were classified as non-evaluable. Those with no endoscopic test results were classified as missing.

**Table 5**
**Comparison of BreathID Test Results to Endoscopic Tests**
**Pre-Therapy**

| *H. pylori* status according to endoscopic tests* | BreathID™ Test | | | |
|---|---|---|---|---|
| | Positive | Negative | Missing | Total |
| Positive | 47 | 0 | 1 | 48 |
| Negative | 2 | 251 | 0 | 253 |
| Non-evaluable/missing | 5 | 9 | 0 | 14 |
| Total | 54 | 260 | 1 | 315 |
| | | | | |
| Sensitivity: 100% | 95% CI** | [93.8, 100] | | |
| Specificity: 99.2% | 95% CI** | [97.5, 100] | | |
| Positive predictive value: 95.9% | 95% CI** | [87.7, 100] | | |
| Negative predictive value: 100.0% | 95% CI** | [98.8, 100] | | |
| Accuracy: 99.3% | 95% CI** | [97.9, 100] | | |

Data Source: Table 3.1 (Section 14.0)

* *H. pylori* positive is defined as positive CLOtest® and positive histology; *H. pylori* negative is defined as negative CLOtest® and negative histology; Non-evaluable/missing includes all other cases. 24-hr CLOtest® results were used to evaluate efficacy.

** The lower limits of the one-sided confidence intervals are calculated using exact methods

*Statistical Reviewer's Comment: The sensitivity and specificity were recalculated for the 300 evaluable patients using two-sided 95% Confidence Intervals. The sensitivity was 100% with two-sided 95% CI [92.5%, 100%] and the specificity was 99.2% with two-sided 95% CI [97.2%, 99.9%]).*

In the Pre-Therapy population, five patients had incongruent endoscopic results and 10 patients had at least one test missing. We constructed the following table to report the results for these patients. In addition, we included information on whether or not the patient was taking PPI/H2 therapy and the time of their last dose in relation to the time of diagnostic tests.

**Non-Evaluable Patients (Pre-Therapy)**

| Reason for non-evaluability | Pt./Site No. | Histology | CLOtest | BreathID | Last date of PPI/H2 | Date of diagnostic tests | |
|---|---|---|---|---|---|---|---|
| | | | | | | Hx/CLO | BreathID |
| Histology and CLO test did not agree | 116/004 | - | + | + | 10/18/99 | 10/18/99 | 10/18/99 |
| | 133/004 | - | + | + | - | ? | 11/1/99 |
| | 209/004 | - | + | + | - | ? | 10/10/99 |
| | 282/004 | + | - | - | 1/24/00 | ? | 1/25/00 |
| | 109/005 | + | - | - | 8/11/99 | 9/11/99 | 9/11/99 |
| At least one test was not observed | 120/004 | - | NA | + | 10/14/99 | 12/13/99 | 12/13/99 |
| | 164/004 | NA | - | - | 11/16/99 | 11/17/99 | 11/17/99 |
| | 379/004 | NA | - | [redacted] | 4/25/00 | 4/26/00 | 4/26/00 |
| | 380/004 | NA | - | - | 4/26/00 | 4/27/00 | 4/27/00 |
| | 115/005 | NA | - | - | - | ? | 12/14/99 |
| | 123/005 | NA | - | - | 1/11/00 | 1/12/00 | 1/12/00 |
| | 159/005 | NA | - | - | - | ? | 5/30/00 |
| | 104/005 | NA | NA | + | 9/15/99 | - | 10/1/99 |
| | 411/004 | NA | NA | - | - | - | 6/1/00 |
| | 137/004 | + | + | NA | - | ? | - |

*Clinical and Statistical Reviewers' Comment: Seven (7) out of 15 (47%) non-evaluable patients were taking PPI/H2 therapy within two weeks of testing. This is similar or slightly less than the percentage of patients taking these therapies in the overall Pre-Therapy population (66% [209/315]).*

The comparison of BreathID test to CLOtest alone is summarized in Table 6.

**Table 6**
**Comparison of BreathID Test Results to CLOtest®**
**Pre-Therapy**

| CLOtest® | BreathID Test | | | |
|---|---|---|---|---|
| | Positive | Negative | Missing | Total |
| Positive | 50 | 0 | 1 | 51 |
| Negative | 2 | 259 | 0 | 261 |
| Non-evaluable/missing | 2 | 1 | 0 | 3 |
| Total | 54 | 260 | 1 | 315 |
| | | | | |
| Sensitivity: 100% | 95% CI* | [94.2, 100] | | |
| Specificity: 99.2% | 95% CI* | [97.6 100] | | |
| Positive predictive value: 96.2% | 95% CI* | [88.4, 100] | | |
| Negative predictive value: 100.0% | 95% CI* | [98.9, 100] | | |
| Accuracy: 99.4% | 95% CI* | [98.0, 100] | | |

Data Source: Table 3.2 (Section 14.0)
* The lower limits of the one-sided confidence intervals are calculated using exact methods

*Statistical Reviewer's Comment: The sensitivity and specificity were recalculated for the 311 evaluable patients using two-sided 95% Confidence Intervals. The sensitivity was 100% with two-sided 95% CI [92.9%, 100%] and the specificity was 99.2% with two-sided 95% CI [97.2%, 99.9%]).*

The comparison of BreathID test to histology was summarized in Table 7.

**Table 7**
**Comparison of BreathID Test Results to Histology**
**Pre-Therapy**

| Histology | BreathID Test | | | |
|---|---|---|---|---|
| | Positive | Negative | Missing | Total |
| Positive | 47 | 2 | 1 | 50 |
| Negative | 6 | 251 | 0 | 257 |
| Non-evaluable/missing | 1 | 7 | 0 | 8 |
| Total | 54 | 260 | 1 | 315 |
| Sensitivity: 95.9% | 95% CI* | [87.7, 100] | | |
| Specificity: 97.7% | 95% CI* | [95.4, 100] | | |
| Positive predictive value: 88.7% | 95% CI* | [78.9, 100] | | |
| Negative predictive value: 99.2% | 95% CI* | [97.5, 100] | | |
| Accuracy: 97.4% | 95% CI* | [95.3, 100] | | |

Data Source: Table 3.3 (Section 14.0)
* The lower limits of the one-sided confidence intervals are calculated using exact methods

*Statistical Reviewer's Comment: The sensitivity and specificity were recalculated for the 306 evaluable patients using two-sided 95% Confidence Intervals. The sensitivity was 97.7% with two-sided 95% CI [86.0%, 99.5%] and the specificity was 88.7% with two-sided 95% CI [95.0%, 99.1%]).*

*As can be seen from the tables above, only about 16% of the enrolled patients were diagnosed positive by endoscopic tests in the recruited population. This was much lower than 60%, the predicted disease prevalence. As a result, the two-sided 95% CIs for sensitivity were wider than expected.*

**Sensitivity Analyses**

*Statistical Reviewer's Comments: As mentioned before, sensitivity analyses are performed to assess the impact of the non-evaluable (i.e., incongruent and missing) test results on the sensitivity and specificity analyses. Three types of sensitivity analyses were performed for the comparison of BreathID to endoscopic test results. In all the sensitivity analyses, all the 15 non-evaluable cases were included. Patient #137 had BreathID test result missing, to include this patient in the analyses, this patient's BreathID test result was imputed to be negative.*

1. *Worst Case: If the BreathID was negative then the endoscopic test results were imputed as positive. If the BreathID was positive then the endoscopic test results were imputed as negative.*
2. *Non-Evaluable Patients Assigned a Negative Endoscopic Test Result: regardless of the BreathID result*
3. *Non-Evaluable Patients Assigned a Positive Endoscopic Test Result: regardless of the BreathID result.*

*For the worst case analysis, the results of the analysis are summarized in the table below. The imputed sensitivity was shown to be 83.9% with two-sided 95% CI [70.1%,91.3% ] and the imputed specificity was 97.3% with two-sided 95% CI [94.0%, 98.7%]. As expected, the sensitivity decreased as more patients in the non-evaluable subgroup had negative results from BreathID tests. Caution should exercised in interpreting these results. The purpose of performing this analysis is to see how much the sensitivity and specificity could be affected*

*under worst case conditions. However, the assumption behind this analysis is not necessarily reasonable, especially as the observed disease prevalence is low in this study.*

*Sensitivity Analysis #1*
***Worst Case***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *47* | *10* | *57* |
| *Negative* | *7* | *251* | *258* |
| *Total* | *54* | *261* | *315* |
| *Imputed Sensitivity: 82.5% , two sided 95% CI [70.1%, 91.3%]* | | | |
| *Imputed Specificity: 97.3%, two sided 95% CI [94.0, 98.7%]* | | | |

*The table below shows the results of the analysis where all non-evaluable patients were assigned a negative endoscopic test result. The sensitivity was unchanged compared to the applicant's analysis because all the non-evaluable patients were imputed to have no disease. The imputed specificity was 97.4% with two-sided 95% CI [94.7%,98.9%].*

*Sensitivity Analysis #2*
***Non-Evaluable Patients Assigned a Negative Endoscopic Test Result***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *47* | *0* | *47* |
| *Negative* | *7* | *261* | *268* |
| *Total* | *54* | *261* | *315* |
| *Sensitivity: 100% , two sided 95% CI [92.5%, 100%]* | | | |
| *Imputed Specificity: 97.4%, two sided 95% CI [94.7%,98.9%]* | | | |

*The table below shows the results of the analysis where all non-evaluable patients were assigned a positive endoscopic test result. The specificity was unchanged compared to the applicant's analysis because all the non-evaluable patients were imputed to have disease. The imputed sensitivity was 83.9%* with two-sided 95% CI [75.9%,93.1%].

*Sensitivity Analysis #3*
***Non-Evaluable Patients Assigned a Positive Endoscopic Test Result***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *52* | *10* | *62* |
| *Negative* | *2* | *251* | *253* |
| *Total* | *54* | *261* | *315* |
| *Imputed Sensitivity: 83.9% , two sided 95% CI [75.9%,93.1%]* | | | |
| *Specificity: 99.2%, two sided 95% CI [97.2%, 99.9%]* | | | |

**Subgroup Analyses**

*Clinical and Statistical Reviewers' Comments: The sponsor did not provide subgroup analyses in special populations. Therefore, we performed analyses comparing the BreathID to endoscopic methods for the Pre-Therapy group based on:*

1. *Age (< 65 and ≥ 65 years)*
2. *Sex (male and female)*

3. *Ethnicity (Caucasian, African-American, Asian-Pacific, Hispanic, and others).*

*There were not enough patients in the Post-Therapy group to do similar subgroup analyses.*

*Subgroup Analysis #1a*
***Age < 65 Years***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *41* | *0* | *41* |
| *Negative* | *1* | *197* | *198* |
| *Total* | *42* | *197* | *239* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 99.5%* | | | |

*Subgroup Analysis #1b*
***Age ≥ 65 Years***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *6* | *0* | *6* |
| *Negative* | *1* | *54* | *55* |
| *Total* | *7* | *54* | *61* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 98.2%* | | | |

*Subgroup Analysis #2a*
***Females***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *28* | *0* | *28* |
| *Negative* | *1* | *151* | *152* |
| *Total* | *29* | *151* | *180* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 99.3%* | | | |

*Subgroup Analysis #2b*
***Males***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *19* | *0* | *19* |
| *Negative* | *1* | *100* | *101* |
| *Total* | *20* | *100* | *120* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 99.0%* | | | |

*Subgroup Analysis #3a*
***Caucasians***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *18* | *0* | *18* |
| *Negative* | *2* | *180* | *182* |
| *Total* | *20* | *180* | *200* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 98.9%* | | | |

*Subgroup Analysis #3b*
***African-Americans***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *7* | *0* | *7* |
| *Negative* | *0* | *22* | *22* |
| *Total* | *7* | *22* | *29* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 100%* | | | |

*Subgroup Analysis #3c*
***Asian-Pacific Persons***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *3* | *0* | *3* |
| *Negative* | *0* | *15* | *15* |
| *Total* | *3* | *15* | *18* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 100%* | | | |

*Subgroup analysis #3d*
***Hispanics***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *17* | *0* | *17* |
| *Negative* | *0* | *29* | *29* |
| *Total* | *17* | *29* | *46* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 100%* | | | |

*Subgroup analysis #3e*
***Other including 1 Native American***

| *Endoscopic tests* | *BreathID Test* | | |
|---|---|---|---|
| | *Positive* | *Negative* | *Total* |
| *Positive* | *2* | *0* | *2* |
| *Negative* | *0* | *5* | *5* |
| *Total* | *2* | *5* | *7* |
| *Relative Sensitivity: 100%* | | | |
| *Relative Specificity: 100%* | | | |

**Effect of Acid Suppression Therapies – Pre-Therapy**

In order to determine if proton pump inhibitors (PPIs) and/or $H_2$-receptor antagonists (H2s) had any effect on the BreathID test, the data were analyzed by subsets of patients taking or not taking PPI and/or H2 medications on the day of the test and within 2 days or 2 weeks of the test. The BreathID test was compared to two endoscopic test results (CLOtest and histology) and the results are presented in Table 8.

**Table 8**
**Comparison of BreathID Test to Endoscopic Tests:**
**Effect of PPI and H2 Medications**
**Pre-Therapy**

| Category (total) | BreathID Test | | | | |
|---|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Accuracy (%) |
| All patients (315) | 100.0 | 99.2 | 95.9 | 100.0 | 99.3 |
| Taking PPI and/or H2 within 2 weeks (209) | 100.0 | 98.9 | 92.9 | 100.0 | 99.0 |
| Taking PPI but not H2 within 2 weeks (170) | 100.0 | 98.6 | 89.5 | 100.0 | 98.8 |
| Not taking PPI and/or H2 within 2 weeks (105) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 within 2 days (167) | 100.0 | 98.6 | 91.7 | 100.0 | 98.8 |
| Taking PPI but not H2 within 2 days (135) | 100.0 | 98.2 | 88.2 | 100.0 | 98.4 |
| Not taking PPI and/or H2 within 2 days (147) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 on day of the test (24) | 100.0 | 95.5 | 50.0 | 100.0 | 95.7 |

A comparison of BreathID to CLOtest® and Histology separately are presented in Tables 9 and 10 in Appendix 1.

*Clinical and Statistical Reviewers' Comment: It has been shown in the literature that PPIs decrease antral H. pylori colonization. The mechanism is postulated to be either migration of the organism from the antrum to the fundus (Logan et al. Gut 1995;36:12-6) or a decrease in bacterial burden (Graham et al. Am J Gastroenterol 1996;91:2120-4). In either case, the result is the development of false-negative results when testing is done by histology or urea breath test. UBT results have been shown to cause false negatives for two weeks after discontinuation of a PPI (Laine et al. Ann Intern Med 1998;129:547-50). Although not specifically studied, it is anticipated that there would also be false-negative results obtained by rapid urease testing since the mechanism of the test is similar to the UBT.*

*In our opinion, the data collected by the applicant does not adequately address the question of how well the BreathID test performs in the presence of PPIs since the "gold standard" (i.e., endoscopic tests) may be also affected, resulting in false negative results.*

**Results – Post-Therapy (20 Minute Procedure)**

In the Post-Therapy group, a total of 77 patients, 19 (24.7%) with Pre-therapy assessment, and 58 (75.3%) without Pre-therapy assessment were enrolled. The efficacy population comprised 73 patients, 19 (26.0%) with Pre-therapy and 54 (74.0%) without Pre-therapy.

*Clinical Reviewer's Comment: For the 54 patients enrolled without a Pre-Therapy assessment, there is no specific information on how the initial H. pylori diagnosis was made. However, this information is not necessary to characterize the performance of the test since the test is being compared to other diagnostic tests obtained at the same point in time.*

The mean delta time for the BreathID test in the total subject population tested was 21.2 min ranging from 20 to 32 minutes.

A comparison of the BreathID test results to the two endoscopic tests (CLOtest and histology) and Meretek UBT test results are presented in Table 11 below.

**Table 11**
**Comparison of BreathID System to Endoscopic or Meretek UBT**
**Post-Therapy**

| Endoscopic tests and Meretek test* | BreathID Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 21 | 1 | 22 |
| Negative | 0 | 50 | 50 |
| Non-evaluable/missing | 1 | 4 | 5 |
| Total | 22 | 55 | 77 |
| | | | |
| Exact p-value of McNemar test | 1.000 | | |
| Kappa coefficient | 0.967 | | |

Data Source: Table 3.5 (Section 14.0)

* *H. pylori* positive is defined as positive CLOtest and positive histology, or positive CLOtest and negative histology, or negative CLOtest and positive histology, or positive Meretek; *H. pylori* negative is defined as negative CLOtest and negative histology, or negative Meretek, indeterminate includes all other cases

*Clinical and Statistical Reviewers' Comment: The patients with incongruent endoscopic test results were considered positive in the protocol by the applicant. The percent agreement with positive subjects based on the post-therapy population was 95.5% with two-sided 95%CI [77.2%, 99.9%]. The percent agreement with negative subjects was 100% with two-sided 95% CI [92.9%, 100%].*

There were five patients with non-evaluable or missing data. We constructed the following table to report the results for these patients. In addition, we included information on whether or not the patient was taking PPI/H2 therapy and the time of their last dose in relation to the time of diagnostic tests.

**Non-Evaluable Patients (Post-Therapy)**

| Reason for non-evaluability | Pt./Site No. | Histology | Meretek | CLO-test | BreathID | Last Date of PPI/H2 | Dates of diagnostic tests | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Hx/CLO | BreathID |
| At least one test was not performed | 138/004 | NA | NA | - | - | 11/2/99 | 11/3/99 | 11/3/99 |
| | 274/004 | NA | NA | NA | + | - | - | 1/19/00 |
| | 231/004 | NA | NA | NA | - | 11/20/99 | - | 12/27/99 |
| | 352/004 | NA | NA | NA | - | 4/5/00 | - | 4/6/00 |
| | 130/005 | NA | NA | NA | - | 2/16/00 | | 2/17/00 |
| | 218/004 | - | NA | - | + | 12/15/99 | 12/16/99 | 12/16/99 |

A comparison of BreathID to CLOtest®, Histology, and Meretek UBT separately are presented in Tables 12-14 in Appendix 1.

**Effect of Acid Suppression Therapies – Post-Therapy**

In order to determine if proton pump inhibitors (PPIs) and/or $H_2$-receptor antagonists (H2s) had any effect on the BreathID test, the data were analyzed by subsets of patients taking or not taking PPI and/or H2 medications within 2 days or 2 weeks of the test. The BreathID test was compared to two endoscopic test results (CLOtest and histology) and the results are presented in Table 15 below.

**Table 15**
**Comparison of BreathID Test to Endoscopic Tests:**
**Effect of PPI and H2 Medications**
**Post-Therapy**

| Category (total) | BreathID Test | | | | |
|---|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Accuracy (%) |
| All patients (28) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 within 2 weeks (21) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI but not H2 within 2 weeks (19) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Not taking PPI and/or H2 within 2 weeks (7) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 within 2 days (16) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI but not H2 within 2 days (14) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Not taking PPI and/or H2 within 2 days (12) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

*Clinical and Statistical Reviewers' Comment: As discussed previously, the data collected by the applicant are not considered sufficient*

**Summary**

The results of the Pre-Therapy analysis of the BreathID system utilizing the "20 Minute" procedure demonstrated a sensitivity of 100% with two-sided 95% CI [92.5%,100%] and specificity of 99.2% with two-sided 95% CI [97.2%, 99.9%]) when compared to the endoscopic tests (CLOtest and histology). When the BreathID test was compared to CLOtest alone the sensitivity was 100% with two-sided 95% CI [92.9%, 100%] and the specificity was 99.2% with two-sided 95% CI [97.2%, 99.9%]). The analysis of BreathID compared to histology alone resulted in a sensitivity of 97.7% with two-sided 95% CI [86.0%, 99.5%] and a specificity of 88.7% with two-sided 95% CI [95.0%, 99.1%]). Sensitivity analyses, which included the non-evaluable patients, demonstrated similar sensitivity and specificity results compared to those obtained in the evaluable population.

The relative sensitivity and specificity of the BreathID test (Pre-Therapy) does not appear to be effected by age (<65 years versus ≥ 65 years), sex, or ethnic group (Caucasian, African-American, Asian-Pacific, Hispanic), although the analysis of some of these subgroups is limited by a small sample size. The relative sensitivity was 100% and specificity ranged from 98.2% to 100% for these various subgroups.

In the Post-Therapy group, a comparison of the Breath ID test with endoscopic tests (CLOtest and histology) or Meretek UBT resulted in a sensitivity of 95.5% with two-sided 95%CI [77.2%, 99.9%]. The specificity was 100% with two-sided 95% CI [92.9%, 100%].

There were not enough patients in the Post-Therapy group to do subgroup analyses in special populations as was done in the Pre-Therapy group.

The data gathered in patients taking proton pump inhibitors (PPIs) and/or $H_2$-receptor antagonists (H2s) (Pre-Therapy and Post-Therapy) was considered insufficient

## V. Supportive Phase III Trials

### A. Hadassah Medical Center – Feasibility Study

**Objective**

To prove the efficacy of Oridion's Breath ID system by comparing its precision to that received when using any commercially available Isotope Ratio Mass Spectrometry (IRMS) for breath analysis.

**Study Design**

Six groups of patients were enrolled in the study: healthy patients, and those with peptic disease, dyspepsia, gastroesophageal reflux disease, post-eradication of *H. pylori*, and patients with miscellaneous gastrointestinal symptoms. All patients fulfilling inclusion criteria underwent both the BreathID system and any commercially available IRMS. The isotope ratios measured were compared.

**Results**

There were 191 patients who were tested for *H. pylori*. Five (5) patients were withdrawn from the study due to data quality control considerations. Data obtained with the BreathID system when compared to mass spectrometer measurements of the identical samples are summarized in the table below. No adverse events were reported.

Comparison of BreathID Test to IRMS

| ***H. pylori* status by IRMS** | BreathID | | |
|---|---|---|---|
| | **Positive** | **Negative** | **Total** |
| Positive | 101 | 0 | 101 |
| Negative | 2 | 83 | 85 |
| Total | 103 | 83 | 186 |

Relative Sensitivity: 100% 95% Confidence Interval [96.4, 100]
Relative Specificity: 97.6% 95% Confidence Interval [91.8, 99.7]

**B. Wolfson Medical Center Beta Site Study**
Evaluation of a Novel Continuous Real Time $^{13}$C-urea Breath Analyzer for *Helicobacter pylori*

**Objective**

To determine the diagnostic value of a new $^{13}$C-urea breath test, BreathID system, for the diagnosis of *H. pylori* in patients with upper gastrointestinal symptoms.

**Study Design**

Consecutive patients, referred for upper endoscopy because of upper gastrointestinal symptoms and signs, were enrolled in the study. Results obtained using BreathID system were compared to the results derived from rapid urease testing and histological examination.

**Results**

Of the 115 patients enrolled, complete test data were available for 97 patients (41 men and 56 women) who were classified as either positive or negative for *H. pylori* by the gold standard tests (histological analysis of biopsies from endoscopy and rapid urease test). The gold standard identified *H. pylori* in 46 patients (47.4%). The sensitivity of the BreathID system was 97.8% and the specificity was 96.1%.

*Clinical Reviewer's Comment: The results of this study have been published:*

> Shirin H, Kenet G, Shevah O, et al. Evaluation of a novel continuous real time $^{13}$C urea breath analyser for *Helicobacter pylori*. Aliment Pharmacol Ther 2001;15:389-94.

*The following information was obtained from the article.*

Comparison of BreathID Test to Endoscopic Results

| ***H. pylori* status by Endoscopic tests** | BreathID | | |
|---|---|---|---|
| | **Positive** | **Negative** | **Total** |
| Positive | 45 | 1 | 46 |
| Negative | 2 | 49 | 51 |
| Non-evaluable | 6 | 8 | 14 |
| Total | 53 | 58 | 97 |

*Of the 115 enrolled, 18 were excluded from the analysis. In four patients the rapid urease test was missing and 14 patients were considered not evaluable because of a discrepancy between the rapid urease test and histology. A summary of the 14 non-evaluable patients can be found in the table below.*

| Rapid Urease Test | Histology | BreathID | Number of Patients |
|---|---|---|---|
| - | + | - | 8 |
| - | + | + | 5 |
| + | - | + | 1 |

*In addition, to the Pre-Therapy phase of the study, the applicant compared the BreathID results to isotope ratio mass spectrometry (Analytical Precision, AP 2003, UK). Forty (40) patients*

*testing positive for H. pylori were included in a follow-up evaluation 4-6 weeks after the end of antimicrobial treatment (clarithromycin, amoxicillin, and a PPI for 7 days). The eradication rate was 82.5%. The correlation between BreathID and isotope ratio mass spectrometry breath tests was 100%.*

**C. University of Medicine and Dentistry (New Jersey) Clinical Trial**
Factors Influencing the Success of Treatment for *H. pylori* Infection

**Objective**
To determine whether the patient knowledge that a follow-up test to prove *H. pylori* eradication will be performed improves medical compliance and treatment related outcomes.

**Study Design**
Patients referred for upper endoscopy because of upper gastrointestinal symptoms and signs, were enrolled in the study. If found to be H. pylori positive, patients were given eradication therapy and asked to return in 4 to 6 weeks and which time the BreathID test was performed to document eradication. Patients randomized to the Control group were not informed of plans to perform the BreathID test while patients in the Experimental group were told about the follow-up test. Patients returned medication bottles for an assessment of compliance and were given a survey to assess clinical symptoms and satisfaction with the test.

**Results**
At the time of NDA submission, the study was still ongoing. However, the data from 35 patients who had both BreathID and CLOtest results are shown below.

**Comparison of BreathID Test to Rapid Urease Test (RUT) Results**

| ***H. pylori* status by RUT** | **BreathID** | | |
|---|---|---|---|
| | **Positive** | **Negative** | **Total** |
| Positive | 19 | 1 | 20 |
| Negative | 0 | 15 | 15 |
| Total | 19 | 16 | 35 |

Relative Sensitivity: 95% 95% Confidence Interval [75.1, 99.9]
Relative Specificity: 100% 95% Confidence Interval [78.2, 100]

**D. Medical University of Luebeck (Germany) Clinical Trial**

**Objectives**
- How the concentration of $^{13}CO_2$ measured in the breath with the BreathID system correlates with the degree of gastritis
- Which biopsy specimen in the stomach provides the highest degree of sensitivity and specificity for the execution of the rapid urease test
- The rate of infection among symptomatic and asymptomatic household members of pediatric patients infected with *H. pylori*
- The performance of the BreathID in pediatrics

**Study Design**

Adult patients underwent EGD with biopsies for histology and rapid urease test and the results were compared to the BreathID test. Pediatric patients underwent a commercially available urea breath test and the results were compared to the BreathID test.

**Results**

At the time of NDA submission, the study was still ongoing. However, the data from 114 patients who had both BreathID and congruent endoscopic (histology and CLOtest) results are shown below.

**Comparison of BreathID Test to Endoscopic Results**

| *H. pylori* status by Endoscopic tests | BreathID | | |
|---|---|---|---|
| | **Positive** | **Negative** | **Total** |
| Positive | 16 | 1 | 17 |
| Negative | 1 | 91 | 92 |
| Total | 17 | 92 | 109 |

Relative Sensitivity: 94.1% 95% Confidence Interval [71.3, 99.9]
Relative Specificity: 98.9% 95% Confidence Interval [94.1, 100]

## VI. Integrated Summary of Safety (ISS)

Of the 373 patients in the pivotal Phase III Study (Pre- and Post-Therapy groups combined), only two patients reported one adverse event each. These adverse events are summarized as follows:

- One patient vomited the test solution. The adverse event was mild and judged not to be related to the device (BreathID), and possibly related to the EGD procedure. The patient recovered without treatment.

- One patient reported nausea and vomited repeatedly after completion of the endoscopy; the patient reported history of sensitivity to different sedative agents. The adverse event was mild and judged possibly related to the device (BreathID) and possibly related to the endoscopy. The patient recovered without treatment.

No deaths or serious adverse events were reported in this trial or in supportive trials, both completed and ongoing, as of January 29, 2001.

## VII. Dosing and Administration Issues

The applicant has demonstrated that use of a 75mg $^{13}$C-urea tablet and citric acid powder as part of the IDkit-hp and when used in conjunction with the BreathID system for *H. pylori* demonstrates substantially equivalent diagnostic performance when compared to approved endoscopic methods and/or the Meretek UBT.

## VIII. Use in Special Populations

Pediatric patients (< 18 years) and patients with serious concomitant disease, which can be interpreted as including those with renal or hepatic impairment, were excluded from the clinical development program. Therefore, it is not possible to comment on the efficacy of the BreathID test in these populations.

The relative sensitivity and specificity of the BreathID test (Pre-Therapy) does not appear to be effected by age (<65 years versus ≥ 65 years), sex, or ethnic group (Caucasian, African-American, Asian-Pacific, Hispanic), although the analysis of some of these subgroups is limited by a small sample size. The relative sensitivity was 100% and specificity ranged from 98.2% to 100% for these various subgroups. See Results section for corresponding data tables.

There were not enough patients in the Post-Therapy group to do subgroup analyses in special populations as was done with the Pre-Therapy group.

## IX. Conclusions and Recommendations

The use of $^{13}$C-urea (75 mg tablets), as a component of the IDkit-hp™ to be used with the BreathID™ System is safe and effective to continually and non-invasively measure changes in the $^{13}CO2/^{12}CO2$ ratio of exhaled breath, which may be indicative of increased urease production associated with active *Helicobacter pylori (H. pylori)* infection in the stomach. The Oridion BreathID System is to be used as an aid for initial diagnosis and post treatment monitoring of *H. pylori* infection.

Although the clinical data supports a recommendation for approval of $^{13}$C-urea (75 mg tablets) for this indication, unresolved CMC and Biopharmaceutics issues will result in an Approvable action. Before the product may be approved, it will be necessary for the applicant to:

- Demonstrate that the FD&C Yellow No. 6 used in this component conforms in identity and specification to the requirements of 21 CFR 74.706(a)(1) and (b). Document that the FD&C Yellow No. 6 is certified in accordance with 21 CFR 80. Obtain documentation that the dye conforms to 21 CFR 74.706(a)(1) and (b), and has been certified in accordance with 21 CFR 80. Alternatively, certified FD&C Yellow No. 6 may be obtained from a different supplier or the product may be reformulated without the dye.
- Provide documentation that will allow verification of the suitability of the components of [ ]
- Revise the specification for Citrica. Please add a specific identity test for citric acid. In addition, the acceptance criteria for [ ] and [ ] should be revised.
- Explain the cause of the observed failures of the submitted stability samples at both stability storage conditions.
- Provide new stability data from 3 batches justifying the proposed labeled storage condition of 15-30°C, given the multiple stability failures at both storage conditions. If the stability of the product cannot be demonstrated to support the labeled storage condition, propose a markedly reduced expiration dating period or, if appropriate, a different packaging system.
- Provide additional dissolution data to allow a more therapeutically relevant dissolution specification to be set. We request data from three tablet batches in water using sampling time points of 5, 10, 15, and 30 minutes.

Recommended wording for the label can be found in Appendix 2.

/S/

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**Concurrence:**
HFD-590/TLMO/RocaR
HFD-725/TLStat/HigginsK
HFD-590/DivDir/AlbrechtR

**cc:**
HFD-590/Div File/NDA 21-314

## Appendix 1 – Additional Tables

### Table 9
### Comparison of BreathID Test to CLOtest Test: Effect of PPI and H2 Medications - Pre-Therapy

| Category (total) | BreathID Test | | | | |
|---|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Accuracy (%) |
| All patients (315) | 100.0 | 99.2 | 96.2 | 100.0 | 99.4 |
| Taking PPI and/or H2 within 2 weeks (209) | 100.0 | 98.9 | 93.1 | 100.0 | 99.0 |
| Taking PPI but not H2 within 2 weeks (170) | 100.0 | 98.7 | 89.5 | 100.0 | 98.8 |
| Not taking PPI and/or H2 within 2 weeks (105) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 within 2 days (167) | 100.0 | 98.6 | 92.0 | 100.0 | 98.8 |
| Taking PPI but not H2 within 2 days (135) | 100.0 | 98.3 | 86.2 | 100.0 | 98.5 |
| Not taking PPI and/or H2 within 2 days (147) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Taking PPI and/or H2 on day of test (24) | 100.0 | 95.5 | 66.7 | 100.0 | 95.8 |

### Table 10
### Comparison of BreathID Test to Histology Effect of PPI and H2 Medications - Pre-Therapy

| Category (total) | BreathID Test | | | | |
|---|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Accuracy (%) |
| All patients (315) | 95.9 | 97.7 | 88.7 | 99.2 | 97.4 |
| Taking PPI and/or H2 within 2 weeks (209) | 92.9 | 97.7 | 86.7 | 98.9 | 97.1 |
| Taking PPI but not H2 within 2 weeks (170) | 89.5 | 98.0 | 85.0 | 98.6 | 97.0 |
| Not taking PPI and/or H2 within 2 weeks (105) | 100.0 | 97.5 | 91.3 | 100.0 | 98.0 |
| Taking PPI and/or H2 within 2 days (167) | 91.7 | 97.8 | 88.0 | 98.6 | 96.9 |
| Taking PPI but not H2 within 2 days (135) | 88.2 | 98.2 | 88.2 | 98.2 | 96.9 |
| Not taking PPI and/or H2 within 2 days (147) | 100.0 | 97.4 | 89.3 | 100.0 | 97.9 |
| Taking PPI and/or H2 on day of test (24) | 100.0 | 91.3 | 33.3 | 100.0 | 91.7 |

## Table 12
## Comparison of BreathID™ Test Results to CLOtest
## Post-Therapy

| CLOtest® | BreathID™ Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 7 | 0 | 7 |
| Negative | 0 | 21 | 21 |
| Total | 7 | 21 | 28 |
| Exact p-value of McNemar test | NA | | |
| Kappa coefficient | 1.000 | | |

Sensitivity: 100% [95% Confidence Interval: 65.2, 100]
Specificity: 100% [95% Confidence Interval: 86.7, 100]

## Table 13
## Comparison of BreathID Test Results to Histology
## Post-Therapy

| Histology | BreathID Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 6 | 0 | 6 |
| Negative | 1 | 20 | 21 |
| Total | 7 | 20 | 27 |
| Exact p-value of McNemar test | 1.000 | | |
| Kappa coefficient | 0.899 | | |

Sensitivity: 100% [95% Confidence Interval: 60.7, 100]
Specificity: 100% [95% Confidence Interval: 76.2, 99.9]

## Table 14
## Comparison of BreathID Test Results to Meretek
## Post-Therapy

| Meretek's test | BreathID Test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Positive | 14 | 1 | 15 |
| Negative | 0 | 31 | 31 |
| Non-evaluable/missing | 0 | 1 | 1 |
| Total | 14 | 33 | 47 |
| | | | |
| Exact p-value of McNemar test | 1.000 | | |
| Kappa coefficient | 0.950 | | |
| | | | |
| Sensitivity: 93.3% | 95% CI* | [72.1, 100] | |
| Specificity: 100.0% | 95% CI* | [90.8, 100] | |
| Positive predictive value: 100.0% | 95% CI* | [80.7, 100] | |
| Negative predictive value: 96.9% | 95% CI* | [86.0, 100] | |
| Accuracy: 97.8% | 95% CI* | [90.1, 100] | |

Data Source: Table 3.8 (Section 14.0)
** The lower limits of the one-sided confidence intervals are calculated using exact methods.

**Appendix 2 – Recommended Label**

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22 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

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Joette Meyer
12/4/01 03:33:40 PM
BIOPHARMACEUTICS

Qian Li
12/6/01 04:09:01 PM
BIOMETRICS

Karen Higgins
12/6/01 04:10:23 PM
BIOMETRICS

Rigoberto Roca
12/17/01 10:25:03 AM
MEDICAL OFFICER

Renata Albrecht
12/18/01 05:38:45 PM
MEDICAL OFFICER

# Review Memo

**To:** File, K011668

**From:** Review Scientist, Bacteriology Devices Branch, Division of Clinical Laboratory Devices, Office of Device Evaluation, HFZ-440.

**Date:** July 2, 2001

**Re:** Oridion Medical Ltd. BreathID™ Test System

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## Background

Oridion Diagnostics, Ltd. submitted this premarket notification (510k) to obtain a substantial equivalent determination for the Breath ID™ Test system. The firm previously submitted the device as K003950 and a K9 (Cannot Respond in 30 days-Request for additional information) letter was issued to the firm on February 14, 2001. The firm then contacted the FDA and an interactive review process began on March 8, 2001 with a Teleconference.

The Breath ID™ Test system is the first urea breath test to measure in a continuous manner changes of $^{13}CO_2$ to $^{12}CO_2$ ratio of exhaled breath after drinking a test drink which includes $^{13}CO_2$ enriched urea. The system measures urease activity associated with *Helicobacter pylori* organisms colonizing the lining of the human stomach to aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients. The system uses an infrared gas-measuring instrument, molecular correlation spectroscopy (MCS), to measure the level of change in the $^{13}CO_2$ to $^{12}CO_2$ ratio which may be indicative of a physiological or metabolic change in the patients' condition. The test is administered by trained operators under the supervision of a health care professional.

The Breath ID™ Test system is a combination in vitro diagnostic device and drug. The device consists of the IDkit-hp™(the instrument), the IDcircuit™ (Oridion Nasal FilterLine™), a 75 mg $^{13}C$ -urea tablet (the drug component), a 4.5 gram package of powdered Citrica (citric acid), and a drinking straw. A baseline sample of exhaled breath is collected through the IDcircuit™ (a nasal cannula). The patient drinks, through the straw, 75 mg of $^{13}C$-urea dissolved in 200 ml of water. The patient continues to breathe normally as the Breath ID system continually measures his/her exhaled breath and records the changes in the $^{13}CO_2$ to $^{12}CO_2$ ratio. The instrument ends the measurement automatically when there is sufficient data to determine if the result is positive or negative. The Test Kit (IDkit-hp™) then performs the test for the presence of *H. pylori*. The system includes single-use Quality Control system check canisters, which contain known concentrations of CO2 and a Calibration system which consists of gases of known concentration and isotope ratios to adjust the $^{12}CO_2$ and $^{13}CO_2$ calibration curve. The firm recommends QC checks and calibrations after every 25 tests.

*Helicobacter pylori* are gram-negative microaerophilic spiral-shaped bacteria associated with chronic, diffuse, and superficial gastritis of the fundus and atrium, which produce large amounts of urease enzyme. The presence of urease enzyme is considered an indicator of *Helicobacter pylori* infection because few other bacteria survive in the stomach. *Proteus* spp. can survive but do not produce as much urea. It has been reported in numerous scientific journals that gastric carcinoma was preceded in many cases by a *Helicobacter pylori* infection. Because of its association with peptic ulcer disease, the NIH Consensus Development Panel on *H. pylori* developed guidelines for diagnosing and treating *H. pylori* infection.

CHRONOLOGY OF EVENTS: The submission was received in the Document Mail Center on May 17, 2001, in DCLD as an "Add-to-file. It was returned to DMC on May 30, and made into a new 510(k). Review of the submission began June 22 and was completed on July 2, 2001.

Because of the Drug Component, the firm submitted an NDA #21-314 to CDER. The FDA/CDER guidance document on H. pylori infection, the NIH consensus document and the CDC Case definition publications were referenced for this review.

CDER was also consulted about the Pre- and Post-Therapy studies. Kristen Meier, Ph.D. of the Office of Science and Biometrics, Division of Statistics, was consulted about the statistical data.

**Review Documentation**

ADMINISTRATIVE ITEMS: The submission contains all the necessary administrative items. The Indications for use statement, the Truth and Accuracy Statement, and a 510(k) Summary were included. A financial disclosure statement was also enclosed. The Meretek Diagnostic UBT® Breath Test was selected as the predicate device.

The firm submitted a copy of a letter from CDC stating that this device is not regulated by CLIA. A copy of the manufacturer's statement and the CDC letter were provided to the CLIA director.

SUMMARY ANALYSIS OF INFORMATION AND DATA:

1. **Clinical Data**

   The Protocol used for the study was submitted. The study was divided into a pre-therapy and a post-therapy arm. The patients were recruited from those referred to endoscopy for evaluation for H. pylori infection. Those patients testing positive were offered treatment after completion of the tests. Testing was again performed four to six weeks after the end of treatment to demonstrate the performance of the device for monitoring patients. The confirmatory test consisted of endoscopy followed by Breath ID or UBT® Breath Test and Breath ID Test. The study sites were Massachusetts General and Brigham and Women's Hospitals in Boston. The investigators were identified. The objectives of the study were clearly stated, the exclusion and inclusion criteria, risks and benefits of the device, and methods for procedures used.

The clinical data summary tables were presented. Definitions were provided for *H. pylori* positive and negative using CDER's guidance.

***Reviewer's comments**: The firm provided results from each site, line data for the studies, and the patient history forms. There were 315 subjects enrolled in the Pre-treatment study, 54 were positive, of these, five were not evaluable, 260 were negative, of these, nine were not evaluable. Only 77 were enrolled in the Post-treatment study, 22 were positive, one was non-evaluable, 55 were negative, and four were not evaluable. The firm presented data with and without the non-evaluables as recommended by our statistician.*

If the non-evaluable samples (5) are discarded the Oridion Post therapy sensitivity is 100% with a 95% CI (93.8-100) and a Specificity of 99.2% (97.2-99.9). The Post-Therapy results yielded a Sensitivity of 100% (95% CI 60.7-100) and a Specificity of 100% (95% CI 86.1-100). BreathID™ results were also presented for % Agreement positive and % Agreement Negative when compared to histology results alone and CLOtest™ alone. Favorable results were obtained.

## 2. Cut-off Studies

Cut-off Point Study data was provided which supported the firms interpretation that an increase of 5.0 delta per mil over baseline was considered a positive test. The data was generated during pre-clinical studies and validated in the multi-center clinical study.

## 3. Non-clinical Data

a. Interference Studies: The firm conducted studies to determine if external sources such as mouth wash, chewing gum, carbonated beverage, cigarette smoke, alcohol or acetone ingestion, would effect the outcome of the test. Twenty individuals had their breath measured 4 times before and 4 times after use of the particular substance. The smokers actually smoked before and during the breath collection procedure. The data showed little effect on the BreathID results even if acetone were injected through a breath stimulator. The most notable were alcohol and tobacco smoke ($p < 0.01$).

b. Reproducibility studies: Two separate studies were conducted, one for reproducibility of the instrument using different standard gas-bag mixtures, and one for repeatability. In the repeatability study, three patients, one H. pylori negative and two H. pylori positive were measured on three different days. The data showed stability over different batches for different operators and for the devices. The overall reproducibility standard deviation was 0.67 and the coefficient of variation was 13.4%. The patient study showed variation in time, but the disease classification remain unchanged.

4. **Software Components:**

The firm thoroughly presented software component information, including risk management, software requirements and calibration procedures, software development, validation, and qualification test procedures.

5. **Labeling**

The Operators Manual and the Package insert were submitted for review. The labeling now conforms to 21 CFR 809.10.

6. **CDER Consult**

Dr. Meyer in the Division of Anti-Infective Drugs provided recommendations for the Oridion Post Therapy study. Dr. Meyer stated that FDA we had advised Oridion to conduct a study similar to the Meretek study. However, we did not recommend how many samples the firm should analyze, but advised them that they should have sufficient samples to obtain similar sensitivity, specificity, and 95% confidence intervals to the Meretek's device. (Meretek evaluated 445 patients for their monitoring study, Meretec had a 95.5% sensitivity with a (93-97 )95% CI a specificity of 96% with a (93-98) 95% CI.) We also discussed the statistical methods used, and the definitions of *H. pylori* positive.

Dr. Meyer also informed us that they had received the NDA.

**Conclusions**

The data is complete and demonstrates safety and efficacy of the device. I recommend that a SE determination letter be sent to the firm.

REVIEWER ..... DATE.....
Freddie M. Poole

CONCUR .....DO NOT CONCUR.....DATE.....
Woody R. Dubois, Ph.D., Chief, Virology Branch