CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-900

MEDICAL REVIEW & STATISTICAL REVIEW

DEC 1 1 1997

Medical and Statistical Review of NDA 20-900 and 510(k) K973000

Date Submitted:	August 6, 1997
Date Received:	August 8, 1997
Date of Consultation:	August 8, 1997
Date Review Completed:	November 18, 1997
Applicant:	Alimenterics Inc. 301 American Road Morris Plains, NJ 07950
Device:	Pylori-Chek Breath Test Kit
Drug:	^{13}C-Urea
Dose:	100 mg
Pharmaceutical Form:	White, crystalline powder

Material Reviewed:

- 5 volumes

Proposed Labeling:

The following sections of the label are important in evaluating the clinical use of the drug/device applications:

Intended Use

The following statement is stated in the **Intended Use** section of the label. "The [redacted] Pylori-Chek [redacted] Test [redacted] is intended for use with the LARA™ [redacted] for the qualitative detection of urease associated with *Helicobacter pylori* as an aid in the diagnosis of *H. pylori*-associated [redacted]

Warnings and Precautions

- For in vitro diagnostic use only. The Pylori-Chek solution is ingested as part of the diagnostic procedure.
- A negative Pylori-Chek breath test result alone does not rule out the possibility of *H. pylori* infection. Always evaluate the Pylori-Chek Breath Test results along with clinical signs and patient history when diagnosing *H. pylori* related disease. If clinical signs and patient history are suggestive of *H. pylori* infection and the Pylori-Chek Breath Test result is negative, retest with a new sample or an alternate method.
- [redacted]
- Failure of the patient to fast as directed may affect the results.
- Antibiotics, omeprazole, and bismuth preparations suppress *H. pylori*. Ingestion of these substances within four (4) weeks prior to performing the Alimenterics Pylori-Chek Breath Test may lead to false negative results.

- False positive results may occur in patients with achlorhydria or [redacted] gastric spiral organisms such as *Helicobacter hominis*.

[redacted]

Performance Characteristics: Clinical Trials

The data presented in this section were collected from a clinical trial conducted at seven sites in both Europe and the United States. Patients who were referred for upper gastrointestinal endoscopy were eligible to enter the study. Of the 432 patients who entered into the study, [redacted] Patients who entered the study were tested for *H. pylori* infection using the following four diagnostic methods:

Histopathology. Two biopsy specimens obtained from endoscopy were evaluated by an experienced pathologist using hematoxylin-eosin stain and the Warthin-Starry methods.

Bacterial Culture. Biopsy tissue was cultured using selective and nonselective media at 37 [redacted] C [redacted] Samples were examined every 3 days for 12 days. *H. pylori* were identified on the basis of gram morphology and production of cytochrome oxidase, catalase, and urease.

CLOtest®. A biopsy specimen obtained from endoscopy was tested for urease activity in accordance with the CLOtest® instructions.

Alimenterics Pylori-Chek Breath Test. The breath test was performed in accordance with the instructions described in this package insert.

Study Results

This section compares the results of the Alimenterics [redacted] Breath Test to the results obtained with other reference standards. Tables 2 [redacted] compare the Alimenterics Pylori-Chek Test results to [redacted] histology and CLOtest®, respectively. Table [redacted] compares the Alimenterics Pylori-Chek Breath Test results to the result determined by a combination of reference methods (i.e. a patient was considered positive if either the culture was positive or both the CLOtest and histology were positive). [redacted]

Medical Officer's Comments: The CDER reference standard should be used to define the combined reference standard since this is the standard used for the approved Meretek application (See below). The definition of "indeterminate" and "negative" should also be defined as outlined in Appendix #1.

Labeling Table
Comparison of Pylori-Chek Breath Test
to Histology

	Pylori-Chek Breath Test Results			
Histology Results	Positive	Negative	Indeterminate	Total
Positive	215	12	4	231
Negative	6	143	8	157
Total	221	155	12	388

Sensitivity: 94.7
Specificity:

Labeling Table
Comparison of Pylori-Chek Breath Test
to CLOtest®

	Pylori-Chek Breath Test Results			
CLOtest®	Positive	Negative	Indeterminate	Total
Positive				
Negative	6	146		
Total	225		12	

Sensitivity: 95.6 %
Specificity: 96.

Labeling Table
Comparison of Pylori-Chek Breath Test
to Combined Reference Methods

	Pylori-Chek Breath Test Results			
	Positive	Negative	Indeterminate	Total
Positive			4	
Negative	5		8	
Total		158	12	

Sensitivity:
Specificity: 96.7 %

Medical Officer's Comment: The reference standard referred to in Table 4 is the CDRH standard. The previously approved Meretek UBT label used the CDER reference standard to define the "combined reference methods". Using the CDER standard, Table should be presented as follows:

Labeling Table 4
Comparison of Pylori-Chek Breath Test
to Combined Reference Methods
(CDER Reference Standard)

	Pylori-Chek Breath Test Results			
	Positive	*Negative*	*Indeterminate*	*Total*
Positive	*221*	*14*	*4*	
Negative	*5*	*144*	*8*	
Total			*12*	

Sensitivity: *94.0 %*
Specificity: *96.6 %*

Limitations of the Test

1. A correlation between the number of *H. pylori* organisms in the stomach and the values has not been established.
2. The performance characteristics of the test have not been established for monitoring the efficacy of antimicrobial therapies for the treatment of *H. pylori* infection.
3. The performance characteristics of this test for persons under the age of 18 and over the age of 75 have not been established .
4. The breath specimen integrity due to storage of breath samples in breath collectors under ambient conditions has not been determined beyond 30 days.

Required Materials

- One vial containing 100 mg 13C-labeled urea (powder)
- One bottle containing 50 mL water for reconstituting the urea
- Three breath collectors, each with an affixed bar code label
- Three patient labels
- One reusable pouch (containing the three breath collectors and 3 patient labels)
- Package Insert
- A LARA Analyzer

Device Description

Pylori-Chek Breath Kit Components

- Each breath kit contains the following: 100mg 13C-urea, 50 ml [redacted] water, three breath collection devices with affixed bar code labels, three-part patient label, one re-sealable pouch, and a package insert.

The LARA™ System

- The LARA (Laser Assisted Ratio Analyzer) System is a laser-based analyzer that employs optogalvanic spectroscopy technology to analyze to ratio of $^{12}CO_2$ to $^{13}CO_2$ in breath samples.

Summary of Testing Procedure

- The patient exhales one breath into the breath collector.
- The patient consumes an entire 8 oz. Test meal (Ensure-vanilla flavored liquid).
- The 50 mL bottle of water is added to the ^{13}C-urea powder.
- The jar is closed and mixed until all the powder is dissolved.
- The patient consumes all of the Pylori-Chek Urea solution.
- After 30 minutes, the patient provides another sample
- After 30 additional minutes, the patient provides another sample
- The three breath samples are placed in the reusable pouch, they are sealed and delivered to the laboratory for analysis

Non-Clinical Studies

Seven non-clinical studies were conducted. The review of these studies was performed by Dr. Doria Dubois, Microbiology Officer, Center for Device and Radiologic Health. The titles of these studies are as follows:

- Storage of Breath Specimens
- Integrity of Breath Specimens During Transport
- Control Stability Study
- Control Stability Study Using Control Tests Packaged in Sealed Pouches
- Carryover Study (Analyzer Validation)
- Verification of Calibration Study (Control Frequency Study - Analyzer Validation)
- Intersystem Comparison Study

Summaries of Clinical Studies

Four clinical studies were conducted using the LARA Breath Test System:

- Phase 1 Study
- Specificity Study
- Pivotal Study
- Supplemental Study ("Cold Trap" Study)

A brief summary of these 4 clinical studies follows:

Phase 1 Study

The objective of this study was to evaluate the sensitivity and specificity of the Pylori-Chek Breath Test Kit using a preliminary value for the cut-off. Seventy-nine patients were enrolled at two sites. Of these, 67 (84.8%) were evaluable. Using five biopsy-based reference standards, a cutoff of 7.5 delta was calculated. Sensitivity ranged from [redacted] and specificity ranged from [redacted] depending on the reference standard. There were no adverse events reported in the study.

Specificity Study

The objective of this study was to determine the specificity of the LARA System in healthy, *H. pylori* seronegative subjects. One hundred seventy-one (171) subjects were enrolled at one clinical site. Of these, 142 (83%) were included in the specificity determination. The specificity was 93.5% using a cut off of 5.0 delta. When a cutoff of 7.8 delta with an intermediate zone between 7.01 and 8.60 was applied, a specificity of 98.5% (CI 94.8% to 99.8%) was obtained. There were no adverse events reported in the study.

Pivotal Study

The objectives of the study were to evaluate the ability of the LARA Breath Test System to detect the presence of *H. pylori* infection and evaluate the sensitivity and specificity of the System as compared with reference methods. One thousand forty eight subjects were enrolled at 10 sites. Of these 875 (85.9%) were included in the analysis. A diagnostic cutoff point of 7.8 delta was calculated with an intermediate zone between 7.01 delta and 8.6 delta. Five different reference standards were used (See protocol description below for definitions). The performance characteristics are outlined in Table 1.

Table 1 Performance Characteristics Based on Five Reference Standard (Pivotal Study)

Performance Characteristics	Range Based on Five Reference Standards
Sensitivity	[redacted]
Specificity	
Positive Predictive Value	
Negative Predictive Value	

Statistical differences were observed for sensitivity and specificity by site of breath collection between Europe and North America (sensitivity and specificity were lower in North America).

Some breath samples did not contain enough CO_2 to permit LARA System analysis. The Pylori-Chek breath collector used a desiccant to remove water vapor from the breath samples. The desiccant was found to absorb both water vapor and CO_2. The device was modified to improve water vapor removal without affecting CO_2 content. One-hundred

and twenty breath samples (3.9%) had low CO_2 content. Only five patients reported adverse events in the Pivotal Study who had received the breath test.

Supplemental ("Cold Trap") Study

The objectives of the study were to verify that the modified breath test system performed comparably to the device used in the Pivotal Study and to "challenge" the sensitivity and specificity calculated using the diagnostic cutoff and indeterminate zone determined in the Pivotal Study. 431 patients attempted to take the Pylori-Chek Breath Test and 397 were included in the analysis. There were 32 (2.5%) samples which were unusable due to low CO_2 content.

Statistical Reviewer's Comment: The reduction in samples which were unusable due to low CO_2 content from 3.9% in the Pivotal Study to 2.5% in the Cold Trap Study is statistically significant ($p=0.02$ using the test of equal proportions based on the normal approximation to the binomial distribution).

The performance characteristics were calculated using a diagnostic cutoff of 7.8 delta with an indeterminate zone of 7.01 to 8.60 delta (excluding 3.2% of patients). The performance characteristics are shown in Table 2.

Table 2 Performance Characteristics Based on Five Reference Standard (Cold Trap Study)

Performance Characteristics	Range Based on Five Reference Standards
Sensitivity	
Specificity	
Positive Predictive Value	
Negative Predictive Value	

Using the results in this study, an [redacted] analysis was performed to yield a cutoff to maximize total predictive value. Using these results, a cutoff of 6.1 delta was calculated with an indeterminate zone between 5.51 and 6.70 (which excluded 3% of the patients). The performance characteristics using this cutoff value and indeterminate zone are shown in Table 3.

Table 3 Performance Characteristics Based on Five Reference Standards Using a Cutoff Value of 6.1 and Indeterminate Zone Between 5.51 and 6.70 (Cold Trap Study)

Performance Characteristics	Range Based on Five Reference Standards
Sensitivity	
Specificity	
Positive Predictive Value	
Negative Predictive Value	

Statistical Reviewer's Comment: Since the cutoff point of 6.1 delta, with corresponding indeterminate zone of 5.51 to 6.70, was determined using results from the Cold Trap Study and then applied to the Cold Trap Study, it is impossible to know how representative the performance characteristics given in Table 3 are of the true performance characteristics of the Pylori-Chek Breath Test. The only way to answer this question would be to perform a validation study of the new cutoff point and indeterminate zone.

There were six patients who reported adverse events. These were thought to be due to the endoscopy procedure, or to ingestion of the test meal.

Review of "Pivotal" and "Cold Trap" Clinical Studies

Pivotal Study

The Pivotal Study was a multi-center study in North America and Europe which assessed the sensitivity and specificity of the Pylori-Chek Breath Test Kit and the LARA System as compared to traditional biopsy-based methods of *H. pylori* detection (central histology, bacterial culture, and rapid urease test).

Patients scheduled for esphagogastroduodenoscopy (EGD) were recruited into the study. Each subject underwent EGD and had the Pylori-Chek Breath Test Kit performed between one hour and 24 hours following endoscopy. Evaluators for each of the component tests for *H. pylori* detection were "blind" as to the endoscopy findings and the results of other tests.

The list of investigators are outlined in Table 4.

Table 4 Clinical Investigators
(Pivotal Study)

Investigator	Study Site
U.S. Investigators	
Dr. Charlene Prather	Mayo Clinic
Dr. David Cave	Boston, Mass
Dr. Loren Laine	Los Angeles, California
Dr. Sam Kline	St. Louis, Missouri
Dr. Enrique Carter	Pasco, Washington
Foreign Investigators	
Dr. GNJ Tytgat	Amsterdam, The Netherlands
Dr. Dino Vaira	Bologna, Italy
Dr. Francis Megraud Dr. Herve Lamouliatte	Bourdeaux, France
Dr. Roy Pounder	London, England
Dr. Sander van Zanten	Halifax, Canada

Exclusion Criteria

Patients were excluded if they were taking antibiotics active against *H. pylori* or omeprazole within four weeks prior to endoscopy. In an IDE Supplement dated November 14, 1995, Alimenterics proposed to broaden this exclusion criterion to also exclude patients taking any proton pump inhibitor.

- Were younger than 18 and older than 75 years of age
- Had ingested bismuth in the two weeks prior to endoscopy
- Had ingested antibiotics active against *H. pylori* or proton pump inhibitors within four weeks prior to endoscopy
- Had used in the seven days prior to endoscopy: (a) a non-steroidal anti-inflammatory drug ("NSAID") in any amount; or (b) aspirin in an amount exceeding 650 mg/day.
- Were pregnant or nursing
- Have had previous gastric surgery resulting in the removal of the antral area
- Had active gastric bleeding
- Had mental impairment or retardation
- Were unable to understand or failed to give a written informed consent
- Were unable to undergo the breath test within 24 hours after endoscopy
- Had reduced lung capacity and were unable to blow through the breath collector for the capture of alveolar breath.

Study Populations

- Safety Population: This population was comprised of all patients entered into the study who received the ^{13}C-urea solution.

- Intent-to-Treat Population: This population included those subjects with a valid breath test (i.e. not "unable to process") and valid determinations for at least 2 of 3 reference tests.

- Efficacy Population: This population included subjects who had a valid UBT and valid results for all reference tests applicable to the reference standard used. Any subjects with protocol violations affecting efficacy variables were excluded. Those who reported the following were excluded:
    - Ingestion of bismuth two weeks prior to UBT
    - Ingestion of PPI or antibiotics 4 weeks prior to UBT
    - Active gastric bleeding
    - UBT less than 1 hour or greater than 24 hours post endoscopy
    - Resection of antrum

- Withdrawals and Discontinuations: This population included patients who either withdrew consent or were withdrawn from the study by the investigator.

Assessment Criteria
The sensitivity, specificity, PPV, and NPV were determined through comparison with 5 reference standards. The criteria for each are outlined below:

- IDE Reference Standard: If either central histopathology or the bacterial culture result was positive from any sample, the patient was considered to be infected with *H. pylori*. A patient was considered negative if all bacterial culture and central pathology readings were negative for that patient, or if one result was missing or indeterminate and the other was negative.

- CDER Reference Standard: This was defined as follows by the sponsor: A patient was considered positive if either the bacterial culture was positive or both the central histopathology and CLOtest results were positive. A patient was considered negative if (1) all three reference standards were negative; or (2) the bacterial culture and any one other reference test was negative, regardless of the outcome of the third reference test.

Medical Officer's Comment: The reference standards are presented in the description of the Pivotal Study only. The CDER Standard should also consider patients with both a negative CLOtest and histopathology result with no culture result as H. pylori negative. This situation is not described in the sponsor's description (See Attachment 1). Nevertheless, validation of the primary data suggest that this scenario was classified as negative for the data in the pivotal study (See Attachment 2).

- CLOtest Reference Standard: A patient was considered positive or negative based on the result of the CLOtest alone. If an indeterminate result was obtained, that patient could not be included in the analysis of sensitivity and specificity.

- Central Histopathology Reference Standard: A patient was considered positive if the central histopathology result for either antrum or corpus was positive. A patient was considered negative for the presence of *H. pylori* if the central histopathology was negative. An indeterminate result in both antrum and corpus for a patient excluded the subject from analysis.

Evaluation of Urea Breath Test
Breath samples were analyzed using the LARA System to detect a change in $^{13}CO_2/^{12}CO_2$ ratios and if the baseline sample to the post-urea samples indicated an increase above a pre-determined level in either post-urea sample, the patient's breath test result was considered positive for *H. pylori*. If comparison of the baseline breath sample to the post-urea breath samples indicated an increase within the indeterminate zone, the patient's result was considered to be "indeterminate". The following categories were used for the purpose of statistical analysis:

- Positive: The difference between the delta values in either 30-minute or 60-minute breath samples and the baseline sample greater than the diagnostic cut-off and outside the indeterminate zone.

- Negative: The difference between the delta values between both the 30-minute and 60-minute breath samples and the baseline sample less than, or equal to, the diagnostic cut-off and outside the indeterminate zone.

- Missing: The value for both the 30 and 60-minute samples were not determined.

- Indeterminate: If the maximum delta value at either 30 or 60 minutes is in the indeterminate zone.

- Unable to process: Samples containing less than 50% of the CO_2 (low CO_2) concentrations in exhaled breath were considered unable to process samples. These were further characterizes as follows:
    - UAP1: When the baseline sample had low CO_2, no determination could be made even if the other two samples had sufficient CO_2;
    - UAP2: When both the 30 and the 60 minute samples were low in CO_2;
    - UAP3: When either the 30 or the 60-minute sample was low in CO_2 and the other was below or equal to the cutoff;
    - UAP4: When samples were processed incorrectly due to instrument malfunction or power failure

Testing sites
The study report does not state the number and location of sites used to test UBT samples in the Pivotal Study.

Sample Size
The estimated number of patients required to be positive by the reference standard needed for a 95% CI of sensitivity no wider than +/- 2.5% was 292. The estimated number of patients required to be negative by the reference standard needed for a 95% CI, with a specificity of no wider than +/- assuming a projected specificity of 90% was 553. A total of approximately 972 patients were needed for the study if 292 positive patients are required and 30% of the patients are expected to be positive. To further assure that a enough patients would be enrolled, a total of 1200 patients were initially intended to be enrolled.

Medical Officer's Validation of Primary Data
The Medical Officer requested data for the Pivotal Study to be submitted in tabular form as shown in Appendix #2. Using this table, the medical officer confirmed the sensitivity and specificity data as outlined in the sponsor's Table 7 (Pivotal Study Data Analysis (N. American and European Total) - ITT Population Analysis by Site of Breath Collection) for the CDER reference standard.

Results

Patient Disposition

A total of 1048 patients were enrolled (signed a consent form), of which 1019 received and attempted a UBT. Twenty-nine patients were withdrawn from the study prior to UBT administration:

- 9 did not want to stay
- 6 were unable to undergo endoscopy
- 2 were on antibiotics
- 1 was on omeprazole
- 1 was on aspirin
- 1 was on bismuth
- 3 were unable to consume Ensure
- 1 had a history of GI bleeding
- 1 had a low blood count and the endoscopy was abandoned.
- 1 had a resected antrum
- 1 developed pancreatitis following ERCP
- 2 did not attempt a UBT as the kit did not arrive within 24 hours of endoscopy

Among the 1019 patients attempting the UBT, 875 were included in the analysis as shown in Table 5 which presents patient disposition for the Pivotal Study.

Table 5: Disposition of Patients
(Pivotal Study)

	N	Percent
# of Patients Attempting UBT	1019	100%
# of Patients Withdrawn/disqualified	2	0.19%
# UBT unable to process (UAP)	142	13.93%
# Included in Analysis	875	85.86%

Two patients were disqualified: One because consent was withdrawn and the other because the UBT was not complete. Among the 142 patients who were categorizes as "unable to process", 30 patients from Halifax were UAP due to a single occurrence of instrument malfunction. One sample from Amsterdam was lost following a temporary power outage, and 111 did not contain sufficient levels of CO_2 in one or more breath collectors. Hence 111 of 1019 patients (11%) were not "evaluable" because they had samples that did not contain enough CO_2. The reasons for patients having UAP results are outlined in Table 6.

Table 6. Patients with Samples Classified as "Unable to Process"
(Pivotal Study)

Reason	Description	N
UAP1	Baseline sample with low CO_2	58 (40.8%)
UAP2	Both 30 and 60 minute samples were low in CO_2	9 (6.3%)
UAP 3	Either 30 or 60 minute samples were low in CO_2 and the other below or equal to cutoff	44 (31%)
UAP 4	Those samples that were processed incorrectly due to instrument malfunction or power failure	31 (21.8%)

Medical Officer and Statistical Reviewer's Comment:
Eleven percent of the patients (111/1019) were classified as "unable to process" due to one or more samples that contained "low CO_2". The proposed package insert states that "an unevaluable test result may be obtained when the $\%CO_2$ in a sample falls below 2%. Such a result would be indicated as "unable to process" on the report. These patients should be re-tested if possible, by obtaining fresh samples." It is recommended that UAP data with regard to the low CO_2 be included in the package insert. This will provide the user some idea of the likelihood of achieving a UAP result.

Patient Accountability:
Patient Accountability is presented in Table 7 for the ITT population.

Table 7: Patient Accountability
(Pivotal Study)

Investigator	Enrolled n (%)*	Withdrawn n (%)	UAP n (%)	Patients in Population n (%)
North America				
Boston	87 (100)	4 (5)	7 (8)	76 (87)
Halifax	103 (100)	5 (5)	38 (37)	60 (58)
Los Angeles	139 (100)	2 (1)	21 (15)	116 (83)
Pasco	34 (100)	5 (15)	10 (29)	19 (56)
Rochester	51 (100)	0 (0)	11 (22)	40 (78)
St. Louis	30 (100)	2 (7)	8 (27)	20 (67)
Total	**444 (100)**	**18 (4)**	**95 (21)**	**331 (75)**
Europe				
Amsterdam	209 (100)	1 (<1)	9 (4)	199 (95)
Bologna	190 (100)	0 (0)	20 (11)	170 (89)
Bordeaux	101 (100)	1 (1)	14 (14)	86 (85)
London	104 (100)	11 (11)	4 (4)	89 (86)
Total	**604 (100)**	**13 (2)**	**47 (8)**	**544 (90)**

*Percents are based on the number of subjects enrolled at each center.

Statistical Reviewer's Comment: Evaluability rates were generally lower in the North American centers than in the European centers. This was due mainly to the higher rate of UAP samples in North America.

Performance Characteristics:
Statistical tests for uniformity of sensitivity exhibited significant differences between European and North American sites for the IDE and central histology reference standards, with sensitivities in North America sites lower than in European sites. Specificity was significantly lower in North America compared to Europe for all five reference standards. Table 8 presents the results for all reference standards in North America and Europe.

Table 8 Analysis by Site of Breath Collection (Percent)
(Pivotal Study)*

	North America				Europe			
	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV
IDE	86.9	85.3	84.7	87.4	93.7	95.1	95.5	93.2
CDER	91.1	86.4	85.3	92.5	95.5	94.4	94.8	95.2
CDRH	91.7	86.5	85.3	92.5	95.5	94.4	94.8	95.1
CLO	91.0	86.0	84.7	91.2	94.7	94.0	94.4	94.3
Histo	88.4	84.9	84.7	89.2	95.0	94.0	94.4	94.8

* Sen = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value

Statistical Reviewer's Comment: Due to the various significant differences in sensitivity and specificity between the North American and European sites, along with the differences in evaluability and UAP rates, it does not appear advisable to pool results across geographic sites. This is not of great concern, however, as these numbers are not going to be included in the label.

The sensitivity and specificity in North America were lower than Europe. The European sites had microbiologist experienced in the culture and identification techniques for *H. pylori*. Similarly, the same sites had histopathology technicians trained in the orientation and preparation of gastric biopsies. In contrast, U.S. sites exhibited problems with the preparation and orientation of biopsies. The techniques for the preparation of histopathology slides in the U.S. often called for slicing blocks until almost no material was left in the block. This was found to be the case in several U.S. sites with the result that blocks were found to be inadequate for central evaluation. Also, contamination of tissue was a problem at two of the U.S. sites.

Analyses by Demographic and Medical Diagnosis Sub-populations:
There were no significant differences in sensitivity, specificity or indeterminate results based on age, gender, or race between or within continents. 57 patients (6.5%) were diagnosed with duodenal ulcers on endoscopy and the sensitivity and specificity was 93%

and 100%, respectively. A total of 44 (5%) patients were diagnosed with gastric ulcers and 854 had gastritis by histopathology. Only 73% and 64% of duodenal and gastric ulcer patients, respectively were infected with *H. pylori*.

Medical Officer's Comment: The large proportion of H. pylori negative ulcer patients has been seen in other clinical trials designed to evaluate the efficacy of therapeutic regimens on H. pylori eradication.

Cold Trap Study

This study was a supplement to the Pivotal Study and was conducted at 7 investigational sites in the U.S. and in Europe. During the course of the Pivotal Study a silica gel desiccant in the breath collectors was used to remove water vapor. The sponsor stated:

"It was noted that the ability of the desiccant to remove water vapor varied with age leading to varying amounts of water vapor in the discharge cells. In addition, it was found that some CO_2 was absorbed by the desiccant as well. Because the disassociation rates of $^{13}CO_2$ and $^{12}CO_2$ in discharges vary differently with gas composition, the precision and accuracy of the measurement were not optimal."

To address this issue, the desiccant was removed from the breath collector and instead, water vapor removal was achieved with a water vapor "cold trap" in the Analyzer. A qualification study confirmed that this modification consistently reduces water vapor content in breath samples to insignificant levels, thus eliminating the need for the desiccant in the breath collectors.

Study Objectives

- To verify that the modified breath test system performed comparably to, or better than, the system used for the Pivotal Study.
- To provide an independent test (challenge) of the sensitivity and specificity calculated using the diagnostic cutoff and indeterminate zones determined in the Pivotal Study.

Investigational Plan

The study protocol was similar to the Pivotal Study (see previous description)

Clinical Investigators

The study was conducted at a subset of investigational sites used during the Pivotal Study as shown in Table 9.

Table 9. Clinical Investigators
("Cold Trap" Study)

Investigator	Study Site
U.S. Investigators	
Dr. Enrique Carter	Pasco, Washington
Dr. David Cave	Boston, Mass
Dr. Loren Laine	Los Angeles, California
Dr. Charlene Prather*	Rochester, Minnesota
Foreign Investigators	
GNJ Tytgat	Amsterdam, The Netherlands
Dino Vaira	Bologna, Italy
Dr. Sander van Zanten	Halifax, Canada

* Contributed only one sample

Medical Officer and Statistical Reviewer's Comment: Note that these investigators are a subset of the investigators in the Pivotal Study. Hence, the results from this study should not be considered completely independent of those from the Pivotal Study since similar bias (due to characteristics of the study dependent on the clinical investigators) could have been present in both studies.

Testing Sites
Two testing sites were used to analyze samples collected in the study: one was located at the Amsterdam site and the other at Alimenterics. Samples were sent by air for analysis.

Sample Size Calculation
The projected sample size of 350 evaluable patients assumed 30% of the patients would be positive:

- The estimated number of patients to be positive was to be 73 assuming a 95% CI of sensitivity no wider than +/- 5% and a projected sensitivity of 95%.
- The estimated number of patients to be negative was to be 138 assuming a 95% CI of specificity no wider than +/- 5% and a projected specificity of 90%.
- 450 patients were to be recruited.

Study Populations, Assessment Criteria, and Inclusion and Exclusion Criteria
These were identical to those described for the Pivotal Study.

Medical Officer's Validation of Primary Data
The Medical Officer requested data for the Pivotal Study to be submitted in tabular form as shown in Appendix #2. Using this table, the medical officer confirmed the sensitivity and specificity data as outlined in the sponsor's Table 7 - Supplemental Study Data Analysis - Cutoff 6.1 delta (N. American and European Total) - ITT Population Analysis by Site of Breath Collection) for the CDER reference standard.

Results

Demographics

The study was balanced for gender. 292 of 397 patients were Caucasian, 31 were Black, 10 were Asian, and 55 were Hispanic. Fifty-four patients were < 30, 124 patients were 30 - 45 y/o, 121 were 45 - 60 y/o, and 121 were greater than 60. Most patients (392) had gastritis, 19 had gastric ulcers and 31 had duodenal ulcers. Thirty percent of patients were smokers, 50% were non-smokers, and 20% were ex-smokers.

Disposition

Among the 431 patients who attempted the UBT, 3 withdrew or were disqualified, and 31 (7.2%) had breath samples that were unable to process (UAP). Therefore, 397 patients were left in the ITT population. Among those with samples that were UAP, 14 tests were UAP due to lower than acceptable levels of CO_2 in the baseline sample. Two were due to low CO_2 levels in both the 30 and 60 minute samples. Fourteen were negative in one sample and had low CO_2 in the other, making it impossible to determine a result. One patient had one sample with CO_2 levels >6% (most likely due to smoking). No samples were lost due to instrument malfunction.

Table 10 compares the number of samples considered UAP for the Pivotal and Cold Trap studies.

Table 10. Comparison of Breath Samples Considered UAP
(Pivotal and Cold Trap Studies)

	No of Breath Samples Evaluated	No. of Breath Samples with Low CO2	% of Breath Samples with Low CO2
Pivotal Study	3051	120	3.9
Cold Trap Study	1284	32	2.5

This data suggests that the addition of the cold trap in the analyzer succeeded in reducing the number of UAP samples due to low CO_2 content.

Statistical Reviewer's Comment: The percent of breath samples with low CO_2 in the Cold Trap Study is, in fact, significantly lower than that found in the Pivotal Study (p=0.02 using the test of equal proportions based on the normal approximation to the binomial distribution).

Medical Officer and Statistical Reviewer's Comment: The observation that 7% of all enrolled patients had to be made "unevaluable" because of one or more samples were UAP related to low CO_2 is concerning. The proposed package insert states that "an unevaluable test result may be obtained when the %CO_2 in a sample falls below 2%. Such a result would be indicated as "unable to process" on the report. These patients should be re-tested if possible, by obtaining fresh samples."

It is recommended that UAP data with regard to the low CO_2 be included in the package insert. This will provide the consumer some idea as to the likelihood of achieving a UAP result.

Performance Characteristics: Cutoff = 7.8 delta
Table 11 provides the sensitivity and specificity data calculated in the cold trap study using a cut off of 7.8 delta.

Table 11: Performance Characteristics for All Sites Combined - Cutoff 7.8 delta (Cold Trap Study)

Reference	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
IDE Protocol	90 (85.5, 93.6)	98 (94.4, 99.6)	98.58	86.71
CDER Protocol	91 (86.7, 94.5)	98 (94.5, 99.6)	98.6	88.4
CDRH Protocol	92 (88.1, 95.5)	98 (94.6, 99.6)	98.6	90.2
CLOTest™	93 (89.1, 96.2)	98.1 (94.6, 99.6)	98.6	91.2
Central Histology	91.8 (87.4, 95.1)	98 (84.6, 99.6)	98.5	89.4

When comparing the results of the Pivotal Study to those in the Cold Trap Study using a cutoff of 7.8 delta, the range in sensitivities did not change using the 5 different reference standards (Pivotal study, [redacted] Cold Trap Study, [redacted]. However, the specificity increased by 7% for all reference standards in the Cold Trap Study (specificity range = [redacted] as compared with the Pivotal Study (specificity range = [redacted]

Analyses by Demographic and Medical Diagnosis Subpopulations
Table 12 presents analyses for the ITT populations using the CDER protocol according to various demographic and diagnostic groups.

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Table 12: Analyses by Demographic and Diagnostic Subpopulations Using the CDER Protocol as the Reverence Standard (Cold Trap Study)

Demographics		Positive Reference			Negative Reference						
	Eval	TP	Ind	FN	TN	Ind	FP	Sen	Spec	PPV	NPV
Male	129	78	1	12	37	0	1	86	97	98	75
Female	125	75	3	3	42	1	1	96	98	99	93
< 30 y/o	40	17	0	4	19	0	0	81	100	100	83
30-44 y/o	80	52	0	7	20	1	0	88	100	100	74
45-60 y/o	80	51	1	3	23	0	2	94	92	96	88
> 60 y/o	54	33	3	1	17	0	0	79	0	100	0
Caucasian	215	123	4	9	76	1	2	93	97	98	89
Black	24	19	0	5	0	0	0	79	0	100	0
Hispanic	2	1	0	0	1	0	0	100	100	100	100
Asian	4	3	0	0	1	0	0	100	100	100	100
Other	9	7	0	1	1	0	0	87	100	100	100
DU	30	27	0	0	3	0	0	100	100	100	100
GU	19	12	0	0	7	0	0	100	100	100	100
Gastritis	390	207	11	19	149	1	3	92	98	98	89
Smoker	117	70	2	7	37	0	1	91	97	99	84
Non-Smoker	201	94	8	9	88	0	2	91	98	98	91
Ex-Smoker	76	42	1	4	28	1	0	91	100	100	88

Ind = Indeterminate, Eval = Evaluable Population, Sen = Sensitivity, Spec = Specificity, TP = true positive, TN = true negative, FN = false negative, FP = false positive

Statistical Reviewer and Medical Officer's Comment: Sensitivity was significantly lower in males compared to females, and in blacks compared to Caucasians (p=0.03 in both cases using the test of equal proportions based on the normal approximation to the binomial distribution). Negative predictive value was also significantly lower in males compared to females, and in blacks compared to Caucasians (p=0.02 and p<0.001, respectively, using the same test as above). The clinical significance of these results is unknown.

Performance Characteristics: Cutoff = 6.1 delta

An ROC analysis of the Supplemental Study data was performed by the sponsor to maximize the total predictive value. This value yields a higher sensitivity but lower specificity than that obtained using a cutoff of 7.8 delta. The cutoff was chosen based on the average of cutoffs obtained by [redacted] analysis using the five reference standards used in the Pivotal Study. The recommended cutoff was calculated to be 6.1 above baseline with an indeterminate zone of +/- 0.6 delta units, which is approximately twice the standard deviation of the mean of a distribution of null tests. Thus if either the 30-minute or 60-minute post breath sample differed from the baseline by more than 6.7, the result was regarded as positive for *H. pylori* according to the breath test. A delta value below 5.51 was regarded as negative for *H. pylori* and results between 5.51 and 6.70 were in the indeterminate zone.

Table 13 presents the number of patients with positive, negative, and indeterminate results using the ITT population.

Table 13: Breakdown of Positive, Negative, and Indeterminate Results Using the Cutoff of 6.1 delta (Cold Trap Study)

	N	Percent
# Evaluable Patients	398	100.0
# Patients with Positive UBT Results	228	57.3
# Patients with Negative UBT Results	158	39.7
# Patients with Indeterminate UBT Results	12	3.0

Table 14 presents the performance characteristics using the five reference standards with a cutoff of 6.1 delta using the ITT population.

Table 14: Performance Characteristics Using the Cutoff of 6.1 delta (Cold Trap Study)

Reference	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
IDE Protocol	93%	96.6%	97.8%	89.2%
CDER Protocol	94%	96.6%	97.8%	91.1%
CDRH Protocol	95.2%	96.7%	97.8%	93.0%
CLOTest™	95.6%	96.1%	97.3%	93.5%
Central Histology	94.7%	95.9%	97.3%	92.3%

Statistical Reviewer's Comment: Since the cutoff point of 6.1 delta, with corresponding indeterminate zone of 5.51 to 6.70, was determined using results from the Cold Trap Study and then applied to the Cold Trap Study, it is impossible to know how representative the performance characteristics given in Table 14 are of the true performance characteristics of the Pylori-Chek Breath Test. The only way to answer this question would be to perform a validation study of the new cutoff point and indeterminate zone.

In terms of labeling the drug/device, however, since the design of the Pylori-Chek Breath Test was modified between the time the Pivotal Study and the Cold Trap Study were conducted, it might be reasonable to conclude that the new cutoff point and indeterminate zone are the most appropriate values to include in the label.

Review of Safety

No adverse events were reported in the phase 1 study (N=79) or in the specificity study (N=172). Six patients were listed as having adverse events in the supportive (Cold Trap) study. These included mild bleching, pain in the abdomen, belching, nausea/vomiting, dizziness, and nausea/vomiting, respectively. The duration varied from 2 to 30 minutes and all patients recovered. In 4 patients it was thought that the AE was related to the product. In the pivotal study, 5 patients were reported to have an AE. These included extreme amount of gas/vomiting, emesis, cramping like pain (abdomenal pain), pancreatitis, and hypoglycemia, respectively. All patients recovered and the duration ranged from 2 minutes to 5 days (pancreatitis). Two patients had AEs thought to be

related to the study drug. The one patient with pancreatitis did not have a breath test attempted.

Reviewers' Conclusions

^{13}C-urea when used with the Pylori-Chek Breath Test Kit is safe and well tolerated. The performance characteristics of the test when using two different cut-off points and indeterminate ranges are excellent.

Improvement in the instrumentation (inclusion of a "cold trap") yielded two results:

1) A more precise measurement of the sample and a narrower indeterminate zone

2) A decrease in the number of samples with CO_2 levels lower than 50% of those in normal breath

The number of UBT results in the indeterminate zone were reduced from 4.8% in the Pivotal Study to 3.0% in the Cold Trap Study (note: this difference is not statistically significant, p=0.14). The number of samples considered to have "low CO_2" was significantly reduced from 3.9% in the Pivotal Study to 2.5% in the Cold Trap Study (p=0.02).

The problem of samples that were classified as "unable to process" was somewhat corrected in the Cold Trap Study. The number of patients with a result classified as "unable to process" due to low CO_2 in one or more samples was reduced from 11% (in the Pivotal Study) to 7% (in the Cold Trap Study) (note: this difference was statistically significant, p=0.02). The Medical Officer considers this a "significant minority" of patients which would require repeat testing.

Reviewers' Recommendations

^{13}C-urea when used in combination with the Pylori-Chek Breath Test Kit should be approved as the clinical studies show that it is safe and effective in assessing the H. pylori status for patients.

The sponsor should include the data regarding the number of patients with "unable to process" results in the package insert for the supplemental study.

The sponsor should replace the CDRH reference standard with the CDER reference standard since the CDER standard (see appendix 1) is what was used to assess the performance characteristics for the previously approved Meretek application. This will provide some degree of consistency for approved urea breath tests.

/S/ 12/1/97

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/S/ 12/1/97

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Statistical Reviewer, DB IV, CDER

Concurrence:
DivDirHFD-590/GoldbergerM /S/
StatTLHFD-725/ChakravartyA /S/ 12/1/97

cc:
HFD-590/Div File/NDA 20-900
HFZ-440/Div File/510 (k) K972352
HFD-590/Acting TLMO/HopkinsR
HFD-725/Biometrics/SillimanN
HFD-590/Dep Div Dir/AlbrechtR
HFD-590/Div Dir/GoldbergerM
HFD-725/Acting TLBiometrics/ChakravartyA
HFD-570/MO/CDRH/HarveyB
HFD-440/Micro/CDRH/DuboisD
HFD-440/Micro/CDRH/PinkosA
HFD-590/PM/CSO/AndersonR
HFD-725/Acting Div Dir/HuqueM
HFD-725/Sec/ShoresS

Appendix #1

Table 1

Classification of Infection, Evaluability, and Eradication Based on Endoscopic Tests for *H. pylori*

Pre-therapy Diagnosis				Post-therapy Diagnosis			
Test Result			Patient Status	Test Result			Patient Status
Cult	Hist	CLO		Cult	Hist	CLO	
Three Tests Available							
+	+/-	+/-	Infected	+	+/-	+/-	Infected
-	+	+	Infected	-	+	+	Infected
-	-	+	Not infected	-	-	+	Infected
-	+	-	Not infected	-	+	-	Infected
-	-	-	Not infected	-	-	-	Eradicated
Two Tests Available							
+	+	N/A	Infected	+	+	N/A	Infected
+	-	N/A	Infected	+	-	N/A	Infected
-	+	N/A	Not evaluable	-	+	N/A	Infected
-	-	N/A	Not infected	-	-	N/A	Eradicated
+	N/A	+	Infected	+	N/A	+	Infected
+	N/A	-	Infected	+	N/A	-	Infected
-	N/A	+	Not evaluable*	-	N/A	+	Infected
-	N/A	-	Not infected	-	N/A	-	Eradicated
N/A	+	+	Infected	N/A	+	+	Infected
N/A	+	-	Not evaluable	N/A	+	-	Infected
N/A	-	+	Not evaluable*	N/A	-	+	Infected
N/A	-	-	Not infected	N/A	-	-	Eradicated
One Test Available							
+	N/A	N/A	Infected	+	N/A	N/A	Infected
-	N/A	N/A	Not evaluable	-	N/A	N/A	Not evaluable
N/A	N/A	+	Not evaluable*	N/A	N/A	+	Infected
N/A	N/A	-	Not evaluable	N/A	N/A	-	Not evaluable
N/A	+	N/A	Not evaluable	N/A	+	N/A	Infected
N/A	-	N/A	Not evaluable	N/A	-	N/A	Not evaluable

N/A Indicates not evaluable or missing result

* Patients with a single positive CLOtest at baseline may be more appropriately considered infected since the specificity of this test is related to gastric colonization of other urease-producing organisms. Colonization is most likely to occur in patients achlorhydria; a uncommon condition in patients who present with acid-peptic disorders such as peptic ulcer disease. However, this has not been decided to date.